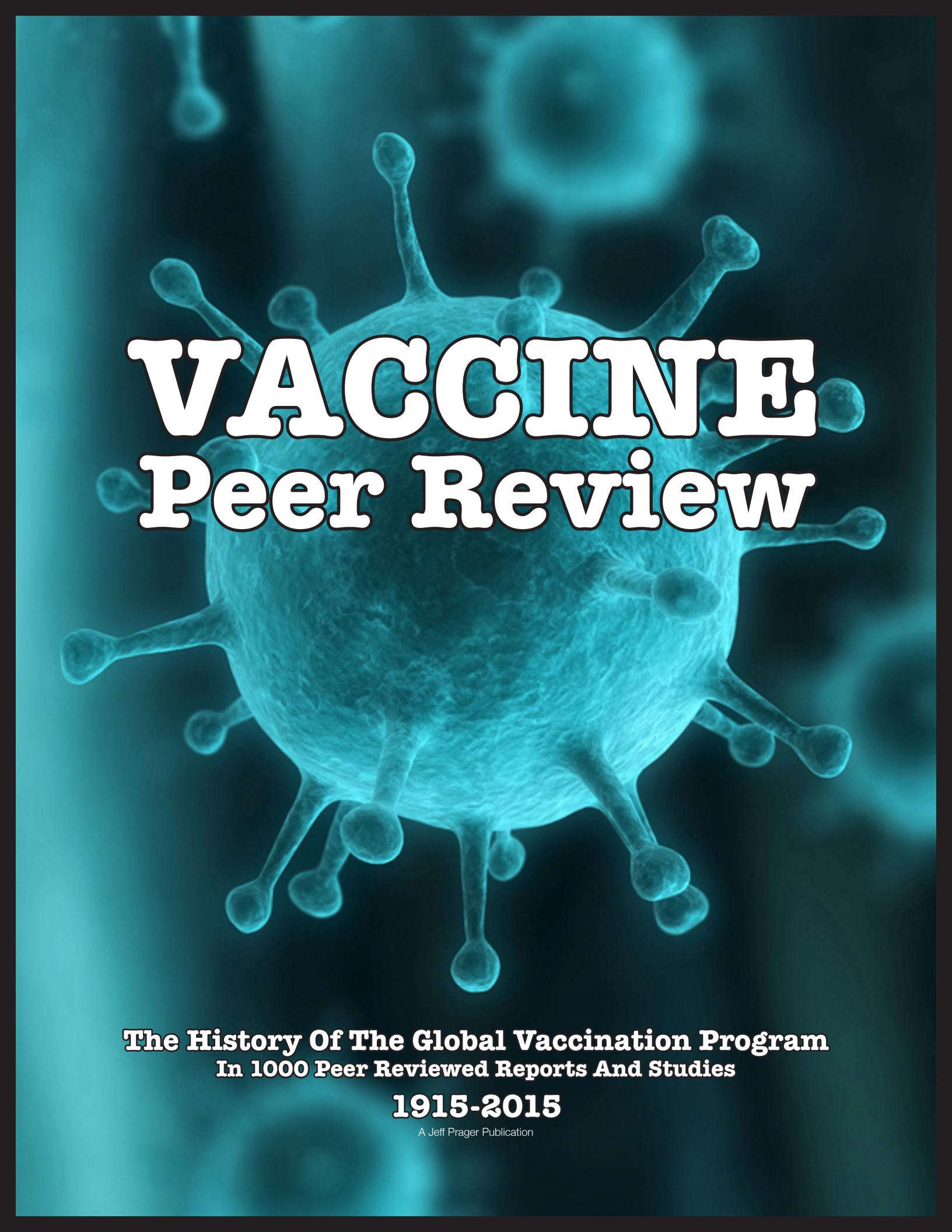


VACCINE Peer Review

The History Of The Global Vaccination Program
In 1000 Peer Reviewed Reports And Studies

1915-2015

A Jeff Prager Publication

“Dissent is crucial for the advancement of science.
Disagreement is at the heart of peer review and is important for uncovering
unjustified assumptions, flawed methodologies and problematic reasoning.”

I. de Melo-Martín and K. Intemann, Division of Medical Ethics, Department of Public Health, Weill Cornell Medical College, New York, USA

“the harm from vaccines has seriously exceeded the benefit of disease prevention”

Dr. Harold Buttram

“No batch of vaccine can be proved safe before it is given to children”

Surgeon General of the United States, Leonard Scheele, addressing an AMA convention in 1955

“The only safe vaccine is a vaccine that is never used”

Dr. James A. Shannon, National Institutes of Health

“Immune challenges during early development,
including those vaccine-induced, can lead to permanent
detrimental alterations of the brain and immune function.

Experimental evidence also shows that simultaneous administration
of as little as two to three immune adjuvants can overcome genetic
resistance to autoimmunity. In some developed countries, by the time
children are 4 to 6 years old, they will have received a total of
126 antigenic compounds along with high amounts of
aluminum adjuvants through routine vaccinations.

According to the US Food and Drug Administration, safety assessments for vaccines have often not included appropriate toxicity studies because vaccines have not been viewed as inherently toxic. Taken together, these observations raise plausible concerns about the overall safety of current childhood vaccination programs.”

From the Journal Lupus, February 2012 by Lucija Tomljenovic & CA Shaw, Neural Dynamics Research Group

Institutional Corruption of Pharmaceuticals and the Myth of Safe and Effective Drugs

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~ June 1, 2013 ~

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Abstract

Over the past 35 years, patients have suffered from a largely hidden epidemic of side effects from drugs that usually have few offsetting benefits. The pharmaceutical industry has corrupted the practice of medicine through its influence over what drugs are developed, how they are tested, and how medical knowledge is created. Since 1906, heavy commercial influence has compromised Congressional legislation to protect the public from unsafe drugs. The authorization of user fees in 1992 has turned drug companies into the FDA's prime clients, deepening the regulatory and cultural capture of the agency. Industry has demanded shorter average review times and, with less time to thoroughly review evidence, increased hospitalizations and deaths have resulted. Meeting the needs of the drug companies has taken priority over meeting the needs of patients. Unless this corruption of regulatory intent is reversed, the situation will continue to deteriorate. We offer practical suggestions including: separating the funding of clinical trials from their conduct, analysis, and publication: independent FDA leadership; full public funding for all FDA activities; measures to discourage R&D on drugs with few if any new clinical benefits; and the creation of a National Drug Safety Board.

Institutional corruption is a normative concept of growing importance that embodies the systemic dependencies and informal practices that distort an institution's societal mission. An extensive range of studies and lawsuits already documents strategies by which pharmaceutical companies hide, ignore, or misrepresent evidence about new drugs; distort the medical literature; and misrepresent products to prescribing physicians. We focus on the consequences for patients: millions of adverse reactions. After defining institutional corruption, we focus on evidence that it lies behind the epidemic of harms and the paucity of benefits.

It is our thesis that institutional corruption has occurred at three levels. First, through large-scale lobbying and political contributions, the pharmaceutical industry has influenced Congress to pass legislation that has compromised the mission of the Food and Drug Administration (FDA). Second, largely as a result of industry pressure, Congress has underfunded FDA enforcement capacities since 1906, and turning to industry-paid "user fees" since 1992 has biased funding to limit the FDA's ability to protect the public from serious adverse reactions to drugs

that have few offsetting advantages. Finally, industry has commercialized the role of physicians and undermined their position as independent, trusted advisers to patients.

Institutional Integrity: The Baseline of Corruption

If "corruption" is defined as an impairment of integrity or moral principle, then institutional corruption is an institution's deviation from a baseline of integrity. In the case of Congress, integrity demands that democratically elected representatives should be dedicated solely to the best interests of the people they represent. According to seminal essays on institutional corruption by Dennis Thompson and Larry Lessig, this baseline of integrity is corrupted because elections are not publicly funded. As a result, congressional representatives must constantly raise funds from a tiny percent of the population and respond to their priorities. This dependency corruption creates an "economy of influence," even if individual actors are well-intentioned. Lessig's examples portray how secrecy and rationalizations disguise distortions in the democratic process and mission.

The concept of institutional corruption highlights numerous distinctions — between what is legal and illegal; between good people doing bad things, not bad people doing bad things; between influence, not money, affecting decisions. These are the ends of continua, and there is a need to recognize degrees of corruption in between.

Special interests also influence members of Congress to make legal what has been illegal or else to game the rules, thereby blurring the line between legal and illegal as well as making it hard to determine the law's intent.

Just as a proper electoral democracy is devoted to the public good, health care systems are founded on the moral principles of beneficence, nonmaleficence (" first, do no harm"), respect for autonomy, and the just distribution of scarce resources. Based on these principles, health care workers are obliged to use the best medical science to relieve suffering and pain, treat illness, and address risks to health. The institutional corruption of health care consists of deviations from these principles.

The major patent-based research pharmaceutical companies also nominally commit themselves to improving health and relieving suffering. For example, Merck promises "*to provide innovative, distinctive products that save and improve lives ... and to provide investors with a superior rate of return.*" Pfizer is dedicated "*to applying science and our global resources to improve health and well-being at every stage of life.*" Pharmaceutical companies continuously emphasize how deeply society depends on their development of innovative products to improve health. But in fact, these companies are mostly developing drugs that are little better than existing products but have the potential to cause widespread adverse reactions even when appropriately prescribed.

This deviation from the principles of health care by institutions allegedly dedicated to health care is institutional corruption. We present evidence that industry has a hidden business model to maximize profits on scores of drugs with clinically minor additional benefits. Physician commitment to better health is compromised as the industry spends billions to create what Lessig calls a "gift economy" of interdependent reciprocation. New research finds that truly innovative new drugs sell themselves in the absence of such gift-economy marketing.

Regulators such as the FDA and the Environmental Protection Agency arise when unregulated competition is perceived to cause serious harm to society and government regulation is needed to address the problem. The FDA was founded to protect the public's health from the fraudulent cures peddled in the 19th century. Through a series of legislative enactments, often in response to a drug disaster, the pharmaceutical regulatory side of the FDA has acquired ever-wider responsibilities to ensure that new drugs do more good than harm. Institutional corruption consists of distortions of these responsibilities, such as approving drugs that are mostly little better than existing medications, failing to ensure sufficient testing for serious risks, and inadequately guarding the public from harmful side effects. These distortions serve commercial interests well and public health poorly.

For the past 50 years, patent-based research companies have objected to the FDA's gatekeeping function as being too rigid and too slow. They have claimed that an obsessive concern about safety has undermined patient access to drugs that could save lives or reduce the burdens of ill health. This message is increasingly being accepted by the FDA.

Flooding the Market with Drugs of Little Benefit

In response to the emphasis by pharmaceutical companies, their lobbyists, and their trade association — the Pharmaceutical Research Manufacturers of America (PhRMA) — on the high risk and cost of research and development (R&D), Congress has authorized billions in taxpayer contributions to support R&D, exemptions from market competition, and special privileges. Patents, of course, can be found in all industries, but lobbyists for the pharmaceutical industry have successfully pressured Congress to provide several forms of market protection beyond patents.

Therapeutic Value of Drugs Marketed in France, 2002-2011

The industry measures "*innovation*" in terms of new molecular entities (NMEs), but most NMEs provide at best minor clinical advantages over existing ones and may lawfully be approved by the FDA even if they are inferior to previously approved drugs. The preponderance of drugs without significant therapeutic gain dates back at least 35 years. From the mid-1970s through the mid-1990s, multiple assessments have found that only 11 to 15.6 percent of NMEs provide an important therapeutic gain. Millions of patients benefit from the one out of six drugs that are therapeutically significant advances; but most R&D dollars are devoted to developing molecularly different but therapeutically similar drugs, which tends to involve less risk and cost for manufacturers. These drugs are then sold through competition based on brand name, patent status, and newness, rather than on their therapeutic merits.

An analysis of data from the National Science Foundation by Donald Light and Joel Lexchin indicates that patent-based pharmaceutical companies — often deemed by Congress, the press, the public, and themselves to be "innovative" — in fact devote only 1.3 percent of revenues, net of taxpayer subsidies, to discovering new molecules. The 25 percent of revenues spent on promotion is about 19 times more than the amount spent on discovering new molecules. In short, the term "R&D" as used by industry primarily means "development" of variations rather than the path-breaking "research" that onlookers might like to imagine.

The independent drug bulletin, La revue Prescrire, analyzes the clinical value of every

new drug product or new indication approved in France. From 1981 to 2001, it found that about 12 percent offered therapeutic advantages.But in the following decade, 2002- 2011, as shown in Figure 1, only 8 percent offered some advantages and nearly twice that many — 15.6 percent – were judged to be more harmful than beneficial. A mere 1.6 percent offered substantial advantages. Assessments by the Canadian advisory panel to the Patented Medicine Prices Review Board and by a Dutch general practice drug bulletin have come to similar conclusions. No comparable review has been done in the United States on the 229 NMEs approved by the FDA between 2002 and 2011.

This decrease does not come from the "innovation crisis" of fewer new molecules entering trials or eventually being approved but from fewer new drugs being clinically superior. The number of products put into trials has actually increased as the number of clinically superior drugs has decreased. These facts provide evidence that companies are using patents and other protections from market competition primarily to develop drugs with few if any new therapeutic benefits and to charge inflated prices protected by their strong IP rights.

Despite the small number of clinically superior drugs, sales and profits have soared as successful marketing persuades physicians to prescribe the much more costly new products that are at best therapeutically equivalent to established drugs. Both an American and a Canadian study found that 80 percent of the increase in drug expenditures went to paying for these minor-variation new drugs, not for important advances. Companies claim that R&D costs are "unsustainable." But over the past 15 years, revenues have increased six times faster than has investment in R&D.

Almost a decade ago, Jerry Avorn, a widely respected pharmacoepidemiologist and author of a book on the risks of drugs, described how the big pharmaceutical companies exploited patents and concluded that "[l]aws designed to encourage and protect meaningful innovation had been turned into a system that rewarded trivial pseudo-innovation even more profitably than important discoveries." He also noted that efforts in Congress to introduce a "reasonable pricing clause" that would reflect large taxpayer contributions to new drugs were defeated by industry lobbyists.

An Epidemic of Harmful Side Effects

Most new drugs approved and promoted since the 1970s lack additional clinical advantages over existing drugs and — as with all drugs — they have been accompanied by harmful side effects. A systematic review of the 39 methodologically strongest studies performed in the U.S. between 1964 and 1995 examined patients who were hospitalized due to a serious adverse drug reaction (ADR) or who experienced an ADR while in the hospital.

The review found that 4.7 percent of hospital admissions were due to serious reactions from prescription drugs that had been appropriately prescribed and used. In addition, 2.1 percent of in-hospital patients who received correctly prescribed medications experienced a serious ADR, for a total of 6.8 percent of hospital patients having serious ADRs. Applying this 6.8 percent hospital ADR rate to the 40 million annual admissions in U.S. acute care hospitals indicates that up to 2.7 million hospitalized Americans each year have experienced a serious adverse reaction. Of all hospitalized patients, 0.32 percent died due to ADRs, which means that an estimated 128,000 hospitalized patients died annually, matching stroke as the 4th leading cause of death. Deaths and serious reactions outside of hospitals would significantly increase the totals.

An analysis conducted in 2011, based on a year of ADRs reported to the FDA, came to similar conclusions: Americans experienced "2.1 million serious injuries, including 128,000 patient deaths."

Other studies reveal that one in every five NMEs eventually caused enough serious harm in patients to warrant a severe warning or withdrawal from the market.

Of priority drugs that were reviewed in slightly more than half the normal time, at least one in three of them caused serious harm.

The public health impacts are even greater when milder adverse reactions are taken into account. Given estimates that about 30 ADRs occur for every one that leads to hospitalization, about 81 million side effects are currently experienced every year by the 170 million Americans who use pharmaceuticals. Groups such as pregnant women, elderly patients, and those who are taking multiple medications are especially at risk. Most of these medically minor adverse reactions are never brought to clinical attention, but even minor reactions can impair productivity or functioning, lead to falls, and cause potentially fatal motor vehicle accidents.

Contributors to More Harm and Less Benefit

Are the adverse side effects we have just been describing simply the "price of progress or an unavoidable risk of drug therapy?" In fact, evidence suggests that commercial distortions of the review process and aggressive marketing contribute to both undermining beneficence as health care's raison d'être and to the epidemic of harm to patients.

Distorting, Limiting, and Circumventing Safety Regulations

Since at least the 1890s, the public has clamored for Congress to regulate contaminated or adulterated foods and harmful or ineffective medicines (medicines that may delay truly useful treatments). At that time, lobbyists — paid from drug profits — argued that even bills to require accurate listing of secret ingredients would destroy the industry. These lobbyists had managed to have earlier bills sent to die in the Committee on Manufactures until President Roosevelt intervened to secure passage of the 1906 Food and Drug Act, which still only required that statements on labels be true and provided no budget for enforcement.

Work on what would become the 1938 food and drug law began in 1933 with a bill that would prohibit misstatements in advertising and require manufacturers to prove to the FDA that drugs were safe before being allowed to sell them. The companies' two trade associations launched "well-choreographed screams of protest" and letter-writing campaigns to mislead Congress and to distort its mission to protect its constituents from harm. Employees of drug makers wrote to Congress, arguing that requiring companies to make honest claims about safe drugs would put thousands out of work. The FDA staff wanted the legislation passed but were stopped by threats of prosecution if they campaigned for it. Then a manufacturer added diethylene glycol (antifreeze) to a sulfa drug to make a sweet-tasting elixir and children started dying. Public response trumped industry lobbyists and Congress passed the 1938 law, requiring that drugs be safe but leaving it to companies to decide how to define and test for safety.

For the next 25 years, drugs were approved within 180 days unless the FDA objected, based on the companies' tests and reports of safety. Some companies "tested" their products by sending samples out to providers for feedback, keeping no records of the results, and denying serious harms when reported by doctors. Daniel Carpenter, the author of a book considered to be a definitive work on the politics of the FDA, has detailed how the FDA staff dedicated themselves to enforcing the rules and developing better criteria for safety and efficacy. But as Malcolm Salter, at the Harvard Business School emphasizes, companies institutionalize corruption by getting legislative and administrative rules shaped to serve their interests, either directly or by crafting rules in ways they can game.

In his review of new pharmaceutical products in the 1940s and 1950s, Dr. Henry Dowling, an AMA senior officer and expert, found that companies launched 200-400 a year but only three on average were clinically useful. Physicians, swamped with far more drugs than they could know much about, relied on sales reps to brief them, entertain them, and leave an ample supply of free samples as gifts that the physicians could then give to their patients — a two-stage economy of reciprocation. In effect, through political pressure and lobbying, companies minimized the role of the FDA as the protector of public health for its first 56 years.

Following the 1962 amendments, propelled to passage by the thalidomide tragedy, the FDA commissioned the National Research Council, as part of the National Academy of Sciences, to review the effectiveness of all 2820 drugs (available in 4350 different versions) approved between 1938 to 1962. Companies were required to submit substantial evidence of effectiveness. The review concluded that seven percent of the drugs reviewed were completely ineffective for every claim they made and a further 50 percent were only effective for some of the claims made for them. Although the FDA has acted to remove many of these ineffective drugs from the market, some pre-1962 drugs are — more than 50 years later — still under-going review and are among the "several thousand drug products" that, according to a 2011 FDA guidance document, are today "marketed illegally without required FDA approval."

Regulatory capture begins with the dependency corruption of Congress, which passes the regulations and provides the funding for agencies to protect the public. While the 1962 amendments ushered in the modern era of testing for safety and efficacy before a drug can be approved, three key features of the modern drug-testing system actually work for industry profits and against the development of safe drugs that improve health.
First, three criteria used by the FDA contribute to the large number of new drugs approved with few therapeutic advantages. New drugs are often tested against placebos rather than against established effective treatments, and the use of surrogate or substitute end points, rather than actual effects on patients' health. Noninferiority trials that merely show that the product is not worse than another drug used to treat the same condition by more than a specified margin are accepted, rather than requiring superiority trials. Silvio Garattini, founder of the Mario Negri Institute for Pharmacological Research, points out that placebo and noninferiority trials violate international ethical standards and provide no useful information for prescribing.

Second, allowing companies to test their own products has led them — as rational economic actors — to design trials in ways that minimize detection and reporting of harms and maximize evidence of benefits. Furthermore, clinical trials for new drugs are designed to test primarily for efficacy and generally are not able to detect less common adverse events.

Industry-friendly rules allow companies to exclude those patients most likely to have adverse reactions, while including those most likely to benefit, so that drugs look safer and more effective than they are in practice. Approvals based on scientifically compromised trials underlie the large number of heavily marketed new drugs with few or no new therapeutic benefits to offset their under-tested risks of harm.

Third, companies have created what can be characterized as the trial-journal pipeline because companies treat trials and journals as marketing vehicles. They design trials to produce results that support the marketing profile for a drug and then hire "publication planning" teams of editors, statisticians, and writers to craft journal articles favorable to the sponsor's drug. Articles that present the conclusions of commercially funded clinical trials are at least 2.5 times more likely to favor the sponsor's drug than are the conclusions in articles discussing non-commercially funded clinical trials. Yet, journal approval is deemed to certify what constitutes medical knowledge. Published papers legitimate the pharmaceutical products emerging from the R&D pipeline and provide the key marketing materials.

Furthermore, companies are much less likely to publish negative results, and they have threatened researchers who break the code of secrecy and confidentiality about those results. Positive results are sometimes published twice — or even more often — under different guises. This further biases meta-analyses — a method of statistically combining the results of multiple studies — and clinical guidelines used for prescribing. The result is "a massive distortion of the clinical evidence."

For decades, the FDA has kept silent about these practices and about the discrepancies between the data submitted to the FDA by companies and the findings published in journal articles, to the detriment of patients but much to the benefit of the companies. In sum, testing and FDA criteria approval provide little or no information to clinicians on how to prescribe new drugs, a vacuum filled by company-shaped "evidence" that misleads physicians to prescribe drugs that are less safe and effective than indicated by evidence that the FDA possesses.

PDUFA: Conflict-of-Interest Payments

In 1992, after years of underfunding and cuts in the 1980s that contributed to drug review times ballooning from 6 to 30 months, Congress passed the Prescription Drug User Fee Act (PDUFA), authorizing the FDA to collect "user fees" from drug companies that would allow it to hire 600 more reviewers and thereby speed up drug review. Supporters claimed that fees would increase incentives for innovation and improve health; but aside from clearing the backlog of NMEs waiting for approval, industry fees have not increased innovation as measured by clinically superior drugs.

In return for paying user fees, companies required the FDA to guarantee that it would review priority applications within six months and standard applications within 12 months of submission. Shortened review times led to substantial increases in serious harms. An in-depth analysis found that each 10-month reduction in review time — which could take up to 30 months — resulted in an 18.1-percent increase in serious adverse reactions, a 10.9-percent increase in hospitalizations, and a 7.2-percent increase in deaths. Now, 20 years

later, what Carpenter calls "corrosive capture" has set in — a weakened application of regulatory tools and a cultural capture of rhetoric about saving lives by getting new drugs to patients more quickly.

For the FDA, the reduction in review time combined with the fear that missing review deadlines will jeopardize continued PDUFA funding has also led to an increase in "up against the wall" approvals as review deadlines approach. Carpenter and his colleagues found that "the probability of a drug approved in the two months before the deadline receiving a new black-box warning (the most serious safety warning that the FDA can issue) is 3.27 times greater than a drug approved at some other time" and the likelihood of a drug being withdrawn from the market because of serious adverse events is 6.92 times greater.

These detailed studies corroborate what FDA staff told the Office of the Inspector General, namely, that concerns arising near the end of the review period are not adequately addressed, that needed meetings with advisory committees are not held, and that label warnings and contraindications are hastily written. As a result, there are "tens of thousands of additional hospitalizations, adverse drug reactions, and deaths."

The 1998 withdrawal of five drugs, used by 19.8 million Americans, prompted critical reflection. Three distinguished physicians were struck by how little information had been gathered about the harmful side effects of these drugs before they were withdrawn. They attributed inaction to the FDA's lack of interest in safety, lack of funds, and to "the lack of a proactive, comprehensive and independent system to evaluate the long-term safety, efficacy, and toxicity of drugs" after FDA approval.

To compensate for the FDA's failures, they called for an independent National Drug Safety Board — akin to the National Transportation Safety Board that investigates each plane crash and holds public meetings — so that the same part of the FDA that approves drugs, the Center for Drug Evaluation and Research (CDER), would not later be asked to decide whether that drug should be restricted or withdrawn. In other words, public health would not depend on FDA officials' willingness to admit their own mistakes. Such an independent board should establish an active monitoring system and gather comparative data across a given therapeutic class so it could provide objective information and develop better strategies for addressing adverse reactions as a major cause of death.

In 1997, a year before these five withdrawals, Congress had passed PDUFA II and companies had insisted that none of the fees collected be spent on post-market surveillance or on drug-safety programs. PDUFA II, III, IV, and V and related legislation provided the FDA with steeply increasing user fees but included lower criteria for approval, mandated that an industry representative be on FDA scientific advisory committees, lowered barriers to promotional efforts by companies, and required FDA officers to consult and negotiate with industry on the agency's goals and plans.

Offsetting the harms associated with PDUFA I's shortened approval framework are several tools created in PDUFA III through V for detecting, managing, and raising awareness of risks such as the Sentinel system and the Risk Evaluation and Mitigation Strategies; but there is no clear evidence these are reducing the epidemic of harms. These tools are inadequate to counterbalance the increase in risks — let alone to improve safety.

The additional $10 million of funding provided by PDUFA III for the Office of Drug Safety and the $7.5 million provided for the FDA's advertising enforcement arm are tiny in comparison to the more than $690 million in user fees that flow to the FDA each year. In sum, PDUFA allocates user fees overwhelmingly to ensure speedy review of new drug applications while leaving safety and enforcement dependent on grossly inadequate funding, perpetuating a history of underfunding safety.

Granting priority status to more drugs further increases the number of drugs reviewed in the shortest time and the chance of a major safety issue increases from one drug in five to one in three. Between 1999 and 2008, the FDA gave priority review status to almost 47 percent (114 of 244) of new drug applications, more than four times the proportion of drugs found to have superior clinical effects by independent review groups. Reflecting the cultural and corrosive capture of the FDA, its Commissioner said recently that "an increasing number of treatments are being approved under the agency's fast-track, priority review ... to get critical and innovative medicines to market more rapidly." Quicker reviews and less evidence of clinical benefit have rewarded the hidden business model of developing still more drugs with minor benefits.

The FDA's obligation to serve the public is being corroded by pressures to serve the companies it regulates. As for post-market surveillance — "the single most important function…for protecting the public against the dangers of harmful drugs" — it is put largely in the hands of the manufacturers and the FDA Center for Drug Evaluation and Research (CDER), the part of the FDA that companies pay to review their new drug applications.

After approval, aggressive marketing of new drugs to doctors for both approved and unapproved uses before good safety information is available maximizes the number of patients exposed to risks from the roughly 25 to 40 new NMES approved annually.

Field studies find that most drug representatives do not discuss adverse side effects. Although the law requires companies to submit some marketing materials for review, Congress and the FDA allocate only a small budget and staff to review about 75,000 submissions a year for false or misleading information. Further, the small stream of letters ordering that inaccuracies be corrected is subject to a review process that delays their reaching the companies.

Marketing for unapproved or "off-label" uses worsens the balance of harm and benefit and undermines the purpose of testing to show that a drug is effective and safe for a specific use. While trying drugs for new uses is clinically important, especially for certain populations such as children and cancer patients, 75 percent of off-label prescribing is neither supported by sound evidence nor accompanied by an organized means for gathering such evidence. Companies retain leading experts to expand use, broaden clinical guidelines, and conduct small, short sham trials that companies get published and hand out to their physician-customers as "evidence."

A 15-month investigation by the Committee on Government Reform of the U.S. House of Representatives found "a growing laxity in FDA's surveillance and enforcement procedures, a dangerous decline in regulatory vigilance, and an obvious unwillingness to move forward even on claims from its own field offices." The resulting 2006 report also documented a 53.7-percent decline in warning letters. Since then, FDA leadership has shifted to talking about being a "partner" with industry to get more drugs to patients more quickly. For the reasons we explained above, the proportion of new products with clinical advantages seems to have moved from about 1 in 8 down to 1 in 12, while the proportion with serious harms has gone up from 1 in 5 towards 1 in 3 as the number of drugs given priority status increases.

Read the rest: https://app.box.com/s/5414zf7lufhtwf3czjfo9msafnoz6ht5 or: http://ethics.harvard.edu/news/institutional-corruption-and-pharmaceutical-policy

Direct from author: https://www.academia.edu/6750219/Institutional_Corruption_and_the_Myth_of_Safe_and_Effective_Drugs

Medical Veritas • 2008

The truth behind the vaccine cover-up

Russell L. Blaylock, MD

Abstract

On June 7-8, 2000 a secret conference was held at the Simpsonwood Conference Center in Norcross, Georgia to discuss a study examining the link between increasing doses of Thimerosal and neurodevelopmental disorders. The study was done using the Vaccine Safety Datalink (VSD) data-base, an official governmental data bank collecting patient vaccination information on the children from the health maintenance organizations (HMOs) being paid to participate. Attending were 51 scientists, representatives of pharmaceutical vaccine manufacturing companies and a representative of the World Health Organization; the public and the media were unlawfully excluded. The conclusions of this meeting were quite startling, since it confirmed a dose-response link between Thimerosal and neurodevelopmental disorders that held up to rigorous statistical analyses.

In their discussion, they make plain why the meeting was held in secret: the conclusions would have destroyed the public's confidence in the vaccine program, and more importantly, their faith in vaccine authorities. When the results of this study were published three years later in the journal Pediatrics, the "problem" had been fixed, in that by adding another set of data from a third HMO, reorganizing the criteria for inclusion and restructuring the patient groupings, a less than statistically significant link was demonstrated. In my analysis I discuss the more outrageous statements made during the meeting and how accepted experts in the field of mercury neurotoxicity were excluded from the meeting.

I was asked to write a paper on some of the newer mechanisms of vaccine damage to the nervous system, but in the interim I came across an incredible document that should blow the lid off the cover-up being engineered by the pharmaceutical companies in conjunction with powerful governmental agencies.

continued on page 725-726

“There is a great deal of evidence to prove that immunization of children does more harm than good”

Dr. J. Anthony Morris, former Chief Vaccine Control Officer, FDA

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Introduction

Vaccines are not the product of altruistic and generous or benevolent action on the part of the manufacturers. Gardasil alone sells for well over 100 dollars per injection. As a consequence, each of us at birth immediately represents thousands of dollars worth of income across the over 188 injections we'll receive in a lifetime—according to the complete recommended US vaccination schedule—starting with 128 antigen, adjuvant and excipient injections before reaching adulthood.

Vaccines are sold under an extremely clever marketing strategy that encompasses not only a "must-have" scenario for each of us but included with that is absolutely no liability for harm. What do you suppose motivated the vaccine manufacturers to work so exceedingly hard through public and governmental processes to establish a "lawsuit-free zone" for vaccines? Was it to avoid any chance at all of legal challenges? The extraordinary harm you'll read about here is directly related to seeking that discharge of legal responsibility for damage. Many of us won't remember that years ago the lawsuits were mounting and the vaccine business was about to come to an end.

This collection of reports reveals the gruesome and stark reality that lies hidden behind what is actually "open-source and public" medical literature that, for reasons unknown, the general public will rarely see. Perhaps the difficulty in finding representative material is an obstacle. Maybe the complexities surrounding the issue are an impediment to fruitful searches. This PDF was created for these reasons. Admittedly, this is a large collection of data that can't be examined properly in a weekend. Yet the totality of the data is what's so very important. If one person told us that repeatedly injecting aluminum, mercury, antigens or excipients could be dangerous we might question the theory but when 100s of professionals make a medically supported claim, we should listen closely, don't you think?

The vaccine industry is rife with corruption and fraud and that's about the only thing that isn't actually printed. The human damage and the collateral toll from vaccination is carefully recorded and this collection discloses some of that harm. While there may be 1000 peer reviewed reports here, I can assure you that there are 1000s more just the same. This collection provides the reader with the peer review that is less complex and easier to understand. Some of you, hopefully, will research the more complex issues further on your own using terms, authors and subject matter found here.

If you take the time to read all of the reports collected here you'll come to understand certain uncomfortable realities. For example, that all of the 350-plus vaccines currently in use are nothing more than population-wide experiments. The pre-licensing trials are so short and with small cohorts and they use only very healthy, robust people, that they can't gain any knowledge at all regarding adverse events in the general population. It's common knowledge within the industry that a vaccine isn't tested and that adverse events are virtually unknown, until after it's been used for some time in large segments of the population. Several years to a decade or more later they may find that there are serious problems related to a particular vaccine. This is what happened with Thimerosal. The scientific evidence came in decades later that autism, neurological disorders and other human diseases were promoted by and often caused by Thimerosal. You'll read peer reviewed reports here from respected journals about the epidemic human damage and the cover-up. In fact, if not for the cover-up we might have been able to reduce or even eventually halt the autism epidemic. Instead, the issue has been concealed from the public and Thimerosal was quietly replaced with aluminum.

Thimerosal was not "removed" from vaccines. All Thimerosal-containing vaccines (TCVs) were used up and the new lots of vaccine were made with a new adjuvant.

Various aluminum salts, adjuvants used in many vaccines, may be even more insidious than Thimerosal. Numerous authors from around the world believe so. A new disease, encompassing nearly 100 different disorders and affecting as many as 50 million people in the US, has been named and studied. ASIA, autoimmune/inflammatory syndrome induced by adjuvants, was officially named by the medical research community in 2013. To paraphrase one of the authors within these pages, we've reached a point in time where the damage from vaccines has exceeded the hoped for protection from disease. To paraphrase further, childhood illnesses like chicken pox, measles, mumps and others are "challenge viruses" that strengthen the immune system and we've removed a significant and very important immune fortifying evolutionary step from humankind by vaccinating.

Misleading advertising campaigns with deceptive and often times unproven claims accompanied by well organized sham-marketing strategies have completely misled the average consumer who buys vaccines like lattes. The resulting tragedy is a series of epidemics of disease and disorder that translates into nothing short of the very definition of the word "pandemic."

Across the globe the vaccination programs have traded several childhood diseases for nearly 100 new disorders many of which were virtually unknown just a century ago. Measles, mumps, rubella, chicken pox and other tolerable, "*immune system fortifying*" childhood illnesses have been replaced by epidemics, and I'm not using that word lightly. Epidemics of Autistic Spectrum Disorder (ASD), Guillain-Barre Syndrome (GBS), Macrophagic Myofasciitis (MMF), Multiple Sclerosis (MS), Alzheimers Disease (AD), Learning Disabilities (ADHD), Arthritis, Inflammatory Bowel Disease, Crohn's Disease (CD), Autoimmune And Inflammatory Syndrome Induced By Adjuvants (ASIA), Hodgkin and non-Hodgkin lymphomas, Allergies, Asthma and nearly 100 more diseases and disorders are all reaching epidemic proportions. They're all caused by vaccines.

Yet the greatest human epidemic of the 20th and 21st centuries will be the enormous spectrum of neurological and biological symptoms and complications associated with autism, ADHD and learning disabilities. Taken together, these neuro-bio-disorders affect one in 6 children in the USA and they are directly related to the US vaccine schedule.

The material collected herein will inform the reader that vaccines cause disorders that increase the profits on tablet and capsule style drugs substantially and that vaccines are not safe, nor are they effective. The collateral damage currently being caused by what the reader will come to know as a very primitive and largely unknown and unproven science, is beyond imaginable and beyond description. It requires 100s of pages of text to accurately describe the full gamut of human damage caused by the global vaccination programs and that's exactly what we've collected here.

The reports within these pages were written by many celebrated, accomplished and esteemed authors who are well known within their fields, independent authors whose integrity hasn't been compromised by influence or wealth. Represented here are hundreds of prominent and duly recognized medical professionals and specialists, scientists, clinicians and researchers from around the world, people such as Dr. Christopher Exley, one of the worlds leading experts on Aluminum, and whose sense of humor in the face of extraordinary, planet-wide adversity, is a welcomed respite. I hope you'll become acquainted with Dr. Jose Dorea, Dr. CA Shaw, Dr. Harold Buttram, Dr. Joachim Mutter, Dr. Russell Blaylock and Dr. Lucija Tomljenovic and their varied, prescient and wholly honest writing styles. There are many others. These are just some of my favorites. Look for them and read what they have to say and your understanding of vaccination will grow accordingly. After all, they're writing to you.

These issues are so critically important to these professionals that they write about them repeatedly. You can literally hear their voices in their writing. Many of the 100s of authors within these pages may be risking career advancement to expose the truth— that the harm from vaccines has seriously exceeded the benefit of disease prevention—yet none of these authors have compromised their morals. Please, listen to them.

Preface

Most of the ingredients in vaccines—including aluminum, mercury, formaldehyde, B2 glycoprotein, Triton X-100®, Polysorbate or Tween 80®, 60 and 20, 2-Phenoxyethanol, etc.—are neurotoxins, toxic to cells, cell structure and neurons. Vaccines are designed such that "tissue damage" is a necessary component of antibody creation to acquire some level of assumed immunity. Tissue damage, cell death or apoptosis are required aspects of vaccination success. The key is to cause tissue damage without damaging the person herself. After 100 years of vaccination science we are still as yet unable to achieve that goal. Vaccine damage is ubiquitous.

There are low-responders and non-responders the medical profession fails to discuss publicly and inform us about. Within every country-population cohort—people that will respond to vaccination with low or zero recognizable titers and whose immune system simply will not "take" to the vaccine—make up a normal and expected percentage of the population. Non- and low-responders can be responsible for outbreaks of disease just as fully vaccinated individuals can acquire and spread the illnesses they were vaccinated for. Vaccination is never, ever 100% and comes with no guarantees of protection or immunity to disease nor guarantees against serious harm or death.

Historically, the innate immune system was at the forefront of disease defense and it mobilized epithelial barriers (referring to the skin and the thin tissue covering the body's surface and lining the alimentary canal and other hollow structures of the ears, eyes, nose and throat), special lymphocytes called " natural killer (NK)" cells, plasma proteins and other immune system components. Vaccination bypasses the innate immune system and directly affects only the humoral immune system (referring to antibodies in body fluids as distinct from cells).

Decades of bypassing the innate immune system along with removal of common and tolerable childhood "challenge" diseases—mumps, chicken pox, measles, etc.—has caused a reversal in the way our bodies fight viral and bacterial infection. Evolutions first line of defense and the faster, stronger primary system, the innate immune system, has been relegated to second place with vaccination causing the slower acting humoral immune system to occupy the first line of defense. The result of repeated vaccination to perturb the human immune system into developing antibodies to less than 2 dozen different tolerable childhood ailments—antibodies which have never been proven to be markers of immunity—has manifest as 100 or more human disorders after little more than 100 years of vaccination. The epidemic of disease we can now see surrounding us is staggering. The reasons for these epidemics of disease are outlined herein and are supported not by any individual report or study but by the totality of the collected evidence.

I sincerely hope that the material represented here helps you to
better understand a very important aspect of life in this 21st century.

The link below accesses a collection of 44 full-length reports in PDF format that are
free to download and that are also included herein in shorter abstract form:

https://app.box.com/s/xa75ta0j9jbe05e615gd5xto9ff1mz4a

“It is now universally recognized that we have a steadily growing epidemic of childhood autism, learning disabilities, and other developmental disorders, with comparable increases in asthma and allergies.”

Medical Veritas International Inc • 2007

Reminiscences of America’s children in the 1930s as compared with today, and the possible role of vaccines in causing retrogressive changes

Editorial

by Harold Buttram, MD, FAACP
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Abstract

It is now universally recognized that we have a steadily growing epidemic of childhood autism, learning disabilities, and other developmental disorders, with comparable increases in asthma and allergies. By any measure now available, these conditions were rare during the 1930s and 1940s. If this trend is to be reversed, we must seek for causes.

As largely disclosed during the U.S. Congressional Hearings on issues of vaccine safety, which took place from 1999 to December, 2004, there are gross deficiencies in vaccine safety testing. Because of this lack, we have no means of identifying or proving adverse reactions when they do occur.

Almost totally lacking until now, the great need is for definitive before-and-after tests specifically designed to search for adverse effects of vaccines on the neurological and immune systems as well as genetics of our children, and in findings adverse effects to make appropriate safety modifications in vaccine programs. Over the years there have been a scattering of before-and-after vaccine tests showing that there can be harm to the immune and central nervous systems, bringing suspicion on vaccines as an underlying cause of current childhood epidemics. However, these have always been of limited scale, seldom if ever with adequate follow-up.

In the opinion of this observer, until the safety of vaccine programs can be assured by such testing, any further mandating of childhood vaccines will remain morally and ethically untenable.

http://www.medicalveritas.com/images/00166.pdf

Lucija Tomljenovic, PhD

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Regarding H.527

Distinguished Members of the Vermont House,

The argument of forcing a parent to vaccinate their child in the name of the "greater good argument" is flawed both scientifically and ethically. Firstly, all drugs are associated with some risks of adverse reactions. Because vaccines represent a special category of drugs which are by and large given to healthy individuals, and for prophylaxis against diseases to which an individual may never be exposed, the margin of tolerance for side effects is very narrow (in fact, the U.S. Food and Drug Administration (FDA) concurs with this point [1]) and careful assessment of risks versus benefits essential in deciding whether one should be vaccinated or not. Removing the "philosophical exemption" as a means to opt out from vaccination will put vulnerable but otherwise healthy individuals at risk of serious adverse reactions to vaccinations. Such an outcome should be of concern since cases of permanent neurodevelopmental disabilities and deaths following vaccination in children with underlying genetic and other susceptibilities have been firmly established in scientific literature [2-4]. Please consider carefully whether you wish to be responsible for such potential outcomes should you facilitate this legislation to come to pass.

Secondly, medical ethics demand that vaccination should be carried out with the participant's full and informed consent. This necessitates an objective disclosure of the known or foreseeable vaccination benefits and risks. The way in which pediatric vaccines are often promoted by various health authorities indicates that such disclosure is rarely given from the basis of best available knowledge but rather, largely unproven and/or untenable assumptions on both, vaccine safety and effectiveness. I shall herein elaborate on these arguments.

Is Vaccine Safety Evidence "Rock Solid"?

The statement by Dr Chen that "the science behind vaccination safety is rock solid" is factually inaccurate and contradicts a large body of scientific literature published on this subject [3-35]. As with any medication, vaccines can carry risks of adverse reactions (ADRs). However, in spite of the widespread notion that vaccines are largely safe and serious adverse complications are extremely rare, a close scrutiny of the scientific literature does not support this view [10-12]. For example, to date the clinical trials that could adequately address vaccine safety issues have not been conducted (i.e., comparing health outcomes in vaccinated versus non-vaccinated children). The lack of such controlled trials may be because historically, vaccines have been assumed safe [12]. There is also a view that conducting such trials would be extraordinarily difficult or unethical; the first is simply not correct, the second is not a scientific issue per se.

It is also often assumed that vaccines face a tougher safety standard than most pharmaceutical products. However, according to the U.S. FDA, "Historically, the non-clinical safety assessment for preventive vaccines has often not included toxicity studies in animal models. This is because vaccines have not been viewed as inherently toxic" [1]. This is a startling admission from an Agency which according to its own mission statement is "responsible for protecting the public health by assuring the safety, efficacy, and security of human and veterinary drugs"[36]. Essentially, what the FDA workshop [1] revealed is that not only are vaccines not adequately evaluated for toxicity but also, that the reason for such an oversight rested on a belief rather than scientific evidence. Science is not a religion in which dogmatic statements of faith can replace adequately powered, controlled, longitudinal vaccine safety studies in animals and people. Furthermore, such assumptions of safety, in the absence of actual experimental data, are not only dangerous but have historically hampered serious scrutiny of potential vaccine harms.

To illustrate a recent example of grave consequences that resulted from pushing a poorly tested vaccine to young children, note that there have been a large numbers of major ADRs from seasonal influenza vaccines. Consequently, they have been suspended for use in children under five years of age in Australia. In a series of Rapid Responses addressing this issue, published in British Medical Journal, titled "Adverse events following influenza vaccination in Australia-should we be surprised?" Collignon (Director of Infectious Diseases & Microbiology at Australian National University) and colleagues from the Cochrane Collaboration review panel concluded: "There is poor evidence on how well influenza vaccines prevent any influenza complications in children and other age groups. There is good evidence that influenza vaccines study reports cherry pick results and achieve spurious notoriety. Exposing human beings to uncertain effects is a risky business" [25].The authors also noted that worldwide, the recommendations from public health authorities regarding influenza vaccination has been "misguided"[26].

It important to note that even those in the scientific community who are strong proponents of vaccinations have come to question the scientific legitimacy of "one-size fits all" vaccination practices [37]. For example, Poland (Editor in Chief of the journal Vaccine and co-author of "The age-old struggle against the antivaccinationists" [38]) and colleagues rightly ask whether "with the advances coming from the new biology of the 21st Century", it is time to consider "how might new genetic and molecular biology information inform vaccinology practices of the future?" [37]. In light of this question Poland et al. conclude that "one-size fits all" approach for all vaccines and all persons should be abandoned. According to Poland, this conclusion applies to both vaccine efficacy, as well as safety [37]. Regarding the latter, the widely held view that serious vaccine-related ADRs are rare needs revision, as current worldwide vaccination policies indeed operate on "one-size fits all" assumption. This assumption persists despite the fact that historically, vaccine trials have routinely excluded vulnerable individuals with a variety of pre-existing conditions (i.e., premature birth, personal or family history of developmental delay or neurologic disorders including epilepsy/seizures, hypersensitivity to vaccine constituents etc. [39-43]). Because of such selection bias, the occurrence of serious ADRs resulting from vaccinations may be considerably underestimated. As mentioned previously, such an outcome should be of concern in view of documented evidence of permanent neurodevelopmental disabilities and deaths following vaccination in children with underlying genetic and other susceptibilities [2-4]. Poland et al.'s current data may thus have far broader implications for understanding vaccines, not only in terms of efficacy and the desired immune response, but also in terms of safety. Indeed, vulnerable populations will neither have the same antibody response nor the same level of tolerance to serious ADRs as non-vulnerable populations [37,44].

The Quality of Existing Vaccine Safety Data

A further obfuscation of the actual rate of serious vaccine-associated ADRs may also be due to methodological inadequacy of existing vaccine trials (i.e, the frequent exclusion of individuals with potential pre-existing susceptibilities to vaccine-associated ADRs) [12], and due to the fact that the vast majority of such trials use an aluminum adjuvant-containing placebo or another aluminum-containing vaccine as the "control group" [45]. That aluminum is a demonstrated neurotoxin has been known for over 100 years [46] and in this context, it is becoming clear to a number of investigators that its use as a placebo control is scientifically untenable [45,47].

Furthermore, with regard to the studies which allegedly demonstrably show no link between autism and vaccines, it has to be emphasized that once such studies undergo proper expert scrutiny, the "evidence" against the link becomes rather flimsy. In reviewing the published literature on measles- mumps-rubella (MMR) vaccine (139

studies), the respected Cochrane Collaboration review panel concluded that, “The design and reporting of safety outcomes in MMR vaccine studies, both pre- and post-marketing, are largely inadequate” [48]. Moreover, none of the 31 studies that were included in the review met the Cochrane Collaboration’s methodological criteria. More specifically, referring to the 2001 Fombonne and Chakrabarti study [49] which was widely regarded by medical health authorities as most persuasive in disproving the link between the MMR vaccine and autism, the Cochrane Collaboration commented the following: “The number and possible impact of biases in this study was so high that interpretation of the results is impossible” [48]. Although the Cochrane Review on the safety of MMR concluded that there was no credible link between MMR vaccination and autism and Crohn’s disease, as pointed out earlier, the majority of the studies included in the evaluation were methodologically inadequate. The question thus is what “credible” or “rock solid” evidence can be derived from inadequate studies?

Demonstrated Toxicity of Vaccine Constituents

Vaccines contain known neurotoxins (i.e., mercury, aluminum, formaldehyde), potent adjuvants designed to hyperstimulate the immune system, as well as various antigenic compounds [10,50] albeit all in relatively small amounts. Thus a typical vaccine formulation contains all the necessary biochemical components to induce both autoimmune as well as neuoroimmune disorders. The question is not whether these compounds are in vaccines or if they are toxic, rather if in such concentrations alone or combined, they can harm the nervous and other systems. Experimental evidence indeed shows that some of these constituents (mercury and aluminum) can cause long-term neurological impairments in animal models when individually administered in vaccine-relevant human exposures [7,51-57].

Furthermore, data also demonstrate that over-stimulating the host’s immune system by repeated immunization with immune antigens and/or adjuvants inevitably leads to autoimmunity even in genetically non-susceptible animals [58,59]. Specifically, simultaneous administration of as little as two to three immune adjuvants can overcome genetic resistance to autoimmunity [59]. Yet in spite of these observations, according to the current U.S. immunization schedule by the time children are 4 to 6 years old, they will have received a total of 126 antigenic compounds along with high amounts of Al adjuvants [10].

Given the scarcity of evidence of safety of the combined pediatric schedule and the fact that administration of only a few vaccines in human adults can lead to brain dysfunction and a variety of autoimmune conditions [8,16,17,19], the concerns about the overall safety of current childhood vaccination programs are scientifically plausible and thus require urgent consideration [10].

Full Report with References

http://www.vaxchoicevt.com/wp-content/uploads/2012/04/Lucija-Tomljenovic-PhD-letter.pdf

https://app.box.com/s/ev8bhi6vb3rofhrkavum3v3hpt2xlil9

http://vaccinechoicecanada.com/wp-content/uploads/Forced-Vaccinations-For-the-Greater-Good-Tomljenovic.pdf

“According to the Autism Society of America, autism is now considered to be an epidemic.”

Journal Of Toxicology And Environmental Health Part B, Critical Review • November 2006

Evidence of toxicity, oxidative stress, and neuronal insult in autism

Author information

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Abstract

According to the Autism Society of America, autism is now considered to be an epidemic. The increase in the rate of autism revealed by epidemiological studies and government reports implicates the importance of external or environmental factors that may be changing. This article discusses the evidence for the case that some children with autism may become autistic from neuronal cell death or brain damage sometime after birth as result of insult; and addresses the hypotheses that toxicity and oxidative stress may be a cause of neuronal insult in autism. The article first describes the Purkinje cell loss found in autism, Purkinje cell physiology and vulnerability, and the evidence for postnatal cell loss. Second, the article describes the increased brain volume in autism and how it may be related to the Purkinje cell loss. Third, the evidence for toxicity and oxidative stress is covered and the possible involvement of glutathione is discussed. Finally, the article discusses what may be happening over the course of development and the multiple factors that may interplay and make these children more vulnerable to toxicity, oxidative stress, and neuronal insult.

http://www.ncbi.nlm.nih.gov/pubmed/17090484

Medical Veritas • 2005

Vaccination and autoimmunity: reassessing evidence

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Abstract

The autoimmune risks of vaccines seem frequently overlooked. Whereas most available vaccinations are supposed to produce long-lasting immunity, the fact that they can also produce long-term detrimental immune effects seems to be ignored as evidenced by the short duration of safety studies during development. Likewise, whereas it seems natural to simply rely on surrogate markers, such as antibodies, to demonstrate vaccine efficacy, the levels of evidence required to acknowledge adverse effects is far higher. Reports to the Vaccine Adverse Event Reporting System (VAERS) are deemed more conclusive when reassuring than when suggesting significant toxicity. As a result of these blatant biases in clinical and/or epidemiological research, experts on autoimmunity and vaccine critics are limited to demonstrating theoretical mechanisms because evidence in practice is lacking.

Known as the bias of the selective assessment, this unbalance in the demonstration of the benefits as compared to the risks is the bête noire of evidence-based medicine. Therefore, when readjusted to the demonstrative level normally viewed as sufficient in clinical research in general and in vaccine science specifically, the corpus of data on the autoimmune hazards of vaccines appears certainly more impressive than generally recognized and calls for further research, for an overall reassessment of the benefit/risk ratio of vaccines including multiple vaccinations. Because vaccines are now aimed at preventing diseases which may be quite rare, the Hippocratic principle of prudence is more than ever a very topical issue.

Many other examples of poor methodology, selective assessment or dissimulation of data could be given. This suggests that research and development on vaccines are still at the zero- level of evidence-based medicine (EBM).

As assessed with the same units of measure used with other drugs, some vaccines and specifically the hepatitis B vaccine have an unacceptable benefit/risk ratio, especially in countries where the diseases they claim to control are not endemic.

For obvious reasons of profit, the threats to the scientific and medical ethics of our job have reached a worrying level: it is the personal responsibility of each of us to resist – and to support those who are the most under pressure.

http://www.know-vaccines.org/PDF/VaccinationAutoimmunity.pdf

“The autoimmune risks of vaccines seem frequently overlooked. Many other examples of poor methodology, selective assessment or dissimulation of data could be given. This suggests that research and development on vaccines are still at the zero-level of evidence-based medicine (EBM) ... It is the personal responsibility of each of us to resist”

Pace Environmental Law Review, vol. 28, no. 2 • 2011

Unanswered Questions
A Review of Compensated Cases of Vaccine-Induced Brain Injury

by Mary Holland, Louis Conte, Robert Krakow and Lisa Colin

Executive Summary

In 1986, Congress created the Vaccine Injury Compensation Program (VICP) under the National Childhood Vaccine Injury Act (1986 Law). This Program has original jurisdiction for children's claims of vaccine injury. Because almost all children receive multiple vaccinations for daycare and school, it is critically important that the Program provides fundamental fairness, due process and transparency.

This empirical investigation, published in a peer-reviewed law journal, examines claims that the VICP compensated for vaccine-induced encephalopathy and seizure disorder. The VICP has compensated approximately 2,500 claims of vaccine injury since the inception of the program. This study found 83 cases of acknowledged vaccine-induced brain damage that include autism, a disorder that affects speech, social communication and behavior. In 21 published cases of the Court of Federal Claims, which administers the VICP, the Court stated that the petitioners had autism or described autism unambiguously. In 62 remaining cases, the authors identified settlement agreements where Health and Human Services (HHS) compensated children with vaccine-induced brain damage, who also have autism or an autism spectrum disorder.

Parents reported the existence of autism in telephone interviews and supplied supplemental materials including medical diagnoses, school records, and completed, standard autism screening questionnaires to verify their reports. In 39 of the 83 cases, or 47% of the cases of vaccine injury reviewed, there is confirmation of autism or autism spectrum disorder beyond parental report.

This finding of autism in compensated cases of vaccine injury is significant. U.S. government spokespeople have been asserting no vaccine-autism link for more than a decade. This finding calls into question the decisions of the Court of Federal Claims in the Omnibus Autism Proceeding in 2009 and 2010 and the statement of Health and Human Services on its website that "HHS has never concluded in any case that autism was caused by vaccination."

Using publicly available information, the investigation shows that the VICP has been compensating cases of vaccine-induced brain damage associated with autism for more than twenty years. This investigation suggests that officials at HHS, the Department of Justice and the Court of Federal Claims may have been aware of this association but failed to publicly disclose it.

The study calls on Congress to thoroughly investigate the VICP, including a medical investigation of compensated claims of vaccine injury. This investigation calls on Congress to get answers to these critically important unanswered questions.

http://www.ebcala.org/unanswered-questions

"Using publicly available information, the investigation shows that the Vaccine Injury Compensation Program (VICP) has been compensating cases of vaccine-induced brain damage associated with autism for more than twenty years. This investigation suggests that officials at HHS, the Department of Justice and the Court of Federal Claims may have been aware of this association but failed to publicly disclose it."

“This eBook is free because the truth should always be free”

~ Jeff Prager

Chapter One
The Business Of Manufacturing Biologics
1969 - 2015

If the global vaccination programs are causing epidemic incidents of death and disease, and they are, then it's our responsibility to do something about it and revealing it using respected, independent peer review is a critically important component of that exposure. Here we provide basic insight into the highly complex and tricky business of manufacturing injectable products. Laboratory creation of safe injectable's is a dirty business fraught with risk and unpredictable circumstances at every turn. Viruses mutate and new viruses appear out of nowhere to sully the product. Most, if not all, vaccine lots are contaminated. Enteroviruses, pestiviruses, DNA and RNA fragments, bovine and porcine viruses and other components of the virus manufacturing process remain in the final product. We're told there's no harm related to injecting these vagrant particles but the truth is, there's absolutely no scientific data to support that claim. Mutating viruses with the high potential for undiscovered contamination will eventually win over man in his misguided attempt to repeatedly vaccinate every living human being. We're each faced with almost 200 vaccines in our lifetime—128 antigen, adjuvant and excipient injections by adulthood if the vaccine schedule is followed—and that extraordinary volume of repeatedly injected material is now causing devastating population-wide effects. The increase in disease and disorder is readily apparent to anyone that looks. This chapter describes the dirty business of biological manufacturing.

“A cell line (MDCK) of dog kidney origin grows on a glass surface as a mosaic of epithelium with many multicellular hemispherical vesicles. The cells lining the blisters actively secrete into the cyst cavities. Suspensions of these cells injected intravenously in the chick embryo produce brain metastases resembling adenocarcinoma.”

Science • January 1969

Secretory activity and oncogenicity of a cell line (MDCK) derived from canine kidney

A cell line (MDCK) of dog kidney origin grows on a glass surface as a mosaic of epithelium with many multicellular hemispherical vesicles. The cells lining the blisters actively secrete into the cyst cavities. Suspensions of these cells injected intravenously in the chick embryo produce brain metastases resembling adenocarcinoma.

[Editors Note: The MDCK (NBL-2) (ATCC® CCL-34™) cell line has been used since 1958 to produce influenza and other vaccines]

http://www.sciencemag.org/content/163/3866/472.long

MDCK cell line:

http://www.atcc.org/products/all/CCL-34.aspx

“The phage contamination of virus vaccines and its possible consequences need further investigations.”

Journal of Biological Standardization
Volume 3, Issue 3, July 1975
Pages 307–308

Bacteriophage contamination in live poliovirus vaccine

by Hedda Milch†, F. Fornosi†

Abstract

Bacteriophages lytic for Escherichia coli strains were isolated from two lots of oral poliomyelitis vaccine. From one ultracentrifuged sample bacteriophages of four different plaque patterns were demonstrable with E. coli C 3000 (2·8 × 102 PFU/ml) and E. coli (1·1 × 102 PFU/ml) as indicator strains. The phage contamination of virus vaccines and its possible consequences need further investigations.

Purchase Price - $31.50

http://www.sciencedirect.com/science/article/pii/0092115775900347

“The determination of the total 5,224 base-pair DNA sequence of the virus SV40 has enabled us to locate precisely the known genes on the genome.”

Nature • May 1978

Complete nucleotide sequence of SV40 DNA

Fiers W, Contreras R, Haegemann G, Rogiers R, Van de Voorde A,
Van Heuverswyn H, Van Herreweghe J, Volckaert G, Ysebaert M.

Abstract

The determination of the total 5,224 base-pair DNA sequence of the virus SV40 has enabled us to locate precisely the known genes on the genome. At least 15.2% of the genome is presumably not translated into polypeptides. Particular points of interest revealed by the complete sequence are the initiation of the early t and T antigens at the same position and the fact that the T antigen is coded by two non-contiguous regions of the genome; the T antigen mRNA is spliced in the coding region. In the late region the gene for the major protein VP1 overlaps those for proteins VP2 and VP3 over 122 nucleotides but is read in a different frame. The almost complete amino acid sequences of the two early proteins as well as those of the late proteins have been deduced from the nucleotide sequence. The mRNAs for the latter three proteins are presumably spliced out of a common primary RNA transcript. The use of degenerate codons is decidedly non-random, but is similar for the early and late regions. Codons of the type NUC, NCG and CGN are absent or very rare.

https://www.ncbi.nlm.nih.gov/pubmed/205802

“Preservatives in multidose vaccine vials do not prevent short-term bacterial contamination.”

Pediatrics • February 1985

Outbreaks of group A streptococcal abscesses following diphtheria-tetanus toxoid-pertussis vaccination

Stetler HC, Garbe PL, Dwyer DM, Facklam RR,
Orenstein WA, West GR, Dudley KJ, Bloch AB.

Abstract

Two outbreaks of group A streptococcal abscesses following receipt of diphtheria-tetanus toxoid-pertussis (DTP) vaccine from different manufacturers were reported to the Centers for Disease Control (CDC) in 1982. The clustering of the immunization times of cases, the isolation of the same serotype of Streptococcus from all cases in each outbreak, and the absence of reported abscesses associated with receipt of the same lots of vaccine in other regions of the country, suggest that each outbreak was probably caused by contamination of a single 15-dose vial of vaccine. The preservative thimerosal was present within acceptable limits in unopened vials from the same lot of DTP vaccine in each outbreak. Challenge studies indicate that a strain of Streptococcus from one of the patients can survive up to 15 days in DTP vaccine at 4 degrees C. Contamination of vials during manufacturing would have required survival of streptococci for a minimum of 8 months. Preservatives in multidose vaccine vials do not prevent short-term bacterial contamination. Options to prevent further clusters of streptococcal abscesses are discussed. The only feasible and cost-effective preventive measure now available is careful attention to sterile technique when administering vaccine from multidose vials.

http://www.ncbi.nlm.nih.gov/pubmed/3881728

Lancet • April 1987

Possible Role Of Pestiviruses In Microcephaly

Author Information

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Abstract

“The background of this suggestion was that, first, although usually a pathogen in cattle and sheep, pestivirus infection can occur in children (Yolken et al. 1989). Second, an association has been reported between pestivirus exposure and microcephaly in newborns (Potts et al. 1987), which might be due to a generalized reduction in white matter bulk. Third, dysmyelination (Potts et al. 1985, Anderson et al. 1987b), frank brain damage (Hewicker-Trautwein and Trautwein 1994), and hypothyroxinemia (Anderson et al. 1987a) are characteristics of perinatal pestivirus infection in lamb models, are found in preterm infants (Leviton and Gilles 1996, Reuss et al. 1997), and are associated with each other among preterm infants (Den Ouden et al. 1996, Leviton et al. 1999). “

Report available for purchase

http://www.thelancet.com/journals/lancet/article/PIIS0140-6736(87)90311-4/abstract

“... an association has been reported between pestivirus exposure and microcephaly in newborns, which might be due to a generalized reduction in white matter bulk. Third, dysmyelination, frank brain damage and hypothyroxinemia are characteristics of perinatal pestivirus infection in lamb models, are found in preterm infants, and are associated with each other among preterm infants ...”

“Vaccine produced on contaminated cells may in turn be contaminated,

leading to seroconversion or disease in the vaccine.”

Developments In Biological Standardization • 1991

Bovine viral diarrhea virus contamination of nutrient serum, cell cultures and viral vaccines

Author information

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Abstract

Bovine viral diarrhea virus (BVDV) infection is common in the bovine population. Infection in utero leads to virus and antibody contamination of the fetal bovine serum used in cell cultures. These contaminants can interfere with diagnosis of viral infection. The high frequency of virus and antibody detection in individual animal or small pool samples suggests that any large pool of unscreened sera will be contaminated. Infection of cell cultures with BVDV can lead to interference with the growth of other viruses. Vaccine produced on contaminated cells may in turn be contaminated, leading to seroconversion or disease in the vaccine. The safety, purity, and efficacy of viral vaccines require BVDV testing of ingredients, cell substrates and final product. Methods for detection of BVDV in nutrient serum, cell cultures, seed viruses, and viral vaccines, and the frequency of their detection at the National Veterinary Services Laboratories are discussed.

http://www.ncbi.nlm.nih.gov/pubmed/1665461

Developments In Biological Standardization • 1991

Viral contamination of fetal bovine serum used for tissue culture: risks and concerns

Author information

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Abstract

Four viral contaminants have been routinely detected in unprocessed and commercial lots of fetal bovine serum: bacteriophage, infectious bovine rhinotracheitis, parainfluenza-3 and bovine viral diarrhea virus (BVDV). Of those, BVDV is consistently present in a majority of commercial lots of fetal bovine serum. Methods for BVDV detection and removal are reviewed. The tentative role of an unclassified pestivirus in microcephaly of infants has been reported. Its significance remains uncertain.

http://www.ncbi.nlm.nih.gov/pubmed/1665460

“Four viral contaminants have been routinely detected in unprocessed and commercial lots of fetal bovine serum: bacteriophage, infectious bovine rhinotracheitis, parainfluenza-3 and bovine viral diarrhea virus (BVDV). Of those, BVDV is consistently present in a majority of commercial lots of fetal bovine serum. Methods for BVDV detection and removal are reviewed. The tentative role of an unclassified pestivirus in microcephaly of infants has been reported. Its significance remains uncertain.”

Journal Of Clinical Microbiology • June 1994

Evidence of pestivirus RNA in human virus vaccines

Author information

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Abstract

We examined live virus vaccines against measles, mumps, and rubella for the presence of pestivirus RNA or of pestiviruses by reverse transcription PCR. Pestivirus RNA was detected in two measles-mumps-rubella combined vaccines and in two monovalent vaccines against mumps and rubella. Nucleotide sequence analysis of the PCR products indicated that a modified live vaccine strain used for immunization of cattle against bovine viral diarrhea is not responsible for the contamination of the vaccines.

http://www.ncbi.nlm.nih.gov/pubmed/?term=8077414

“Pestivirus RNA was detected in two measles-mumps-rubella combined vaccines and in two monovalent vaccines against mumps and rubella.”

“Sixty-one % of the neoplastic patients positive for SV40 sequences

had an age excluding exposure to SV40-contaminated polio vaccines, suggesting a contagious transmission of SV40.”

Cancer Research • October 1996

SV40 early region and large T antigen in human brain tumors, peripheral blood cells, and sperm fluids from healthy individuals

Author information

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Abstract

SV40 T antigen (Tag) coding sequences were detected by PCR amplification followed by Southern blot hybridization in human brain tumors and tumor cell lines, as well as in peripheral blood cells and sperm fluids of healthy donors. SV40 early region sequences were found in 83% of choroid plexus papillomas, 73% of ependymomas, 47% of astrocytomas, 33% of glioblastoma multiforme cases, 14% of meningiomas, 50% of glioblastoma cell lines, and 33% of astrocytoma cell lines and in 23% of peripheral blood cell samples and 45% of sperm fluids from normal individuals. None of the 13 normal brain tissues were positive for SV40 DNA, nor were seven oligodendrogliomas, two spongioblastomas, one neuroblastoma, one meningioma, or four neuroblastoma cell lines. Expression of SV40 early region was found by reverse transcription PCR, and SV40-specific Tag was detected by indirect immunofluorescence in glioblastoma cell lines. DNA sequence analysis, performed in four positive samples, confirmed that the amplified PCR products belong to the SV40 early region. Sixty-one % of the neoplastic patients positive for SV40 sequences had an age excluding exposure to SV40-contaminated polio vaccines, suggesting a contagious transmission of SV40. The possible role of SV40 Tag in the etiopathogenesis of human brain tumors and the spread of SV40 by horizontal infection in the human population are discussed.

http://www.ncbi.nlm.nih.gov/pubmed/8841004

Biologicals • December 1996

Application of PCR for detection of mycoplasma DNA and pestivirus RNA in human live viral vaccines

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Abstract

PCR techniques were applied for the detection of mycoplasma DNA and pestivirus RNA to 43 lots of live viral vaccines (measles, mumps, rubella, and oral poliomyelitis) produced by six manufacturers in Japan. Although mycoplasma DNA was not detected in any of the vaccines tested, pestivirus RNA was detected in 12 lots (28%). The incidence of contamination among the four viral vaccines was in the range of 20 to 37%, and the incidence among the six manufacturers varied from 0 to 56%.

http://www.ncbi.nlm.nih.gov/pubmed/9088554

“The incidence of contamination among the four viral vaccines was in the range of 20 to 37%, and the incidence among the six manufacturers varied from 0 to 56%.”

“These issues have received relatively little attention hitherto but are likely to achieve greater prominence as development of such preparations proceeds.”

Developments In Biological Standardization • 1996

Reasons for instability of bacterial vaccines

Author information

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Abstract

Stability problems in relation to bacterial vaccines vary widely between different types of product. Killed whole cell bacterial vaccines including pertussis, cholera and typhoid vaccines generally show a high degree of stability of potency. Reversion to toxicity may occur in incompletely inactivated pertussis vaccines. Live attenuated vaccines such as BCG and Ty21a typhoid vaccines lose potency through loss of viability when exposed to adverse conditions. Both vaccines are susceptible to ultra violet radiation but Ty21a also has low thermal stability. Its fragility is probably a consequence of multiple mutations affecting structural and metabolic factors. Diphtheria and tetanus toxoids generally show high stability of potency. Reversion to toxicity may occur if the toxoiding process is inadequate. Decline in potency may result from exposure to adverse conditions, such as freezing, that affect the interaction with the adjuvant. Similar problems may be encountered with purified subunit vaccines such as acellular pertussis preparations. Some components, in particular pertussis toxin and filamentous haemagglutinin, show inherent low stability and degrade on storage at refrigerator temperatures unless stabilized by a protein cross-linking agent. Bacterial proteases carried over from the cell cultures may also be responsible for degradation of purified components. Purified bacterial polysaccharides usually show high stability if freeze-dried under appropriate conditions. Catalytic degradation may occur however, if the stabilizers are of inadequate purity. Polysaccharide-protein conjugates such as Haemophilus influenzae b (Hib) polyribosylribityl phosphate-protein conjugates show high thermal stability if freeze dried. In the liquid state, such conjugates tend to degrade by hydrolysis of the polysaccharide chains. Combined vaccines may present special stability problems because of the interaction of the various components in the liquid state. It can be difficult to freeze-dry some components of such vaccines, particularly aluminium hydroxide-adsorbed diphtheria-tetanus-pertussis (DTP) components. Slow release vaccines based on polyglycolide-factolide microspheres may show suboptimal stability of encapsulated antigen under both in vitro conditions as a result of gradual acidification through polymer hydrolysis. Vaccines based on the use of live recombinant strains to express heterologous protective antigens may present special stability problems. Apart from the carrier strains, heterologous genes carried on plasmids may be subject to spontaneous deletion under adverse conditions. These issues have received relatively little attention hitherto but are likely to achieve greater prominence as development of such preparations proceeds.

http://www.ncbi.nlm.nih.gov/pubmed/8854008

Monaldi Archives For Chest Disease • April 1998

Simian virus 40 and human cancer

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Abstract

Deoxyribonucleic acid (DNA) oncoviruses can induce neoplastic transformation by interfering with proliferative proteins. Simian virus 40 (SV40) has been shown to induce brain tumors, osteosarcoma, lymphoid tumors and malignant mesothelioma in hamsters and SV40-like DNA sequences corresponding to the Rb-pocket binding domain of SV40 T-antigen (Tag) have been detected in the same human tumors. Since only a small percentage of people exposed to asbestos fibers develop a malignant mesothelioma, SV40 has been suspected to co-operate with the fibers in the neoplastic transformation or even to itself induce the onset of malignant mesothelioma in patients without expositive history. The mechanism that seems to be involved in the SV40-induced carcinogenesis process is mediated by interaction of Tag, both with p53 and Rb proteins, leading to their functional inactivation that is responsible for the removal of their inhibitory cell cycle effect which determines the increase of the number of cells entering the G1-S phase. Up to now the source of SV40 human infections has not yet been completely identified even though administration from 1957-1965 of SV40 contaminated polio vaccines is highly suspected. Horizontal infection by sexual transmission has been also hypothesized. Due to the important public health implications further investigations are required in order to establish both the source and the carcinogenetic role of simian virus 40 in humans.

http://www.ncbi.nlm.nih.gov/pubmed/9689809

“Up to now the source of SV40 human infections has not yet been completely identified even though administration from 1957-1965 of SV40 contaminated polio vaccines is highly suspected. Horizontal infection by sexual transmission has been also hypothesized.”

Monaldi Archives Of Chest Disease • April 1998

The biological activities of simian virus 40 large-T antigen and its possible oncogenic effects in humans

Author information

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Abstract

Simian virus 40 (SV40) is an oncogenic virus which induces tumors in hamsters and transforms human cells in tissue culture. Between 1955 and 1963, polio vaccines and adenovaccines were contaminated with SV40; therefore, millions of people were exposed to this oncogenic virus. The SV40 proteins responsible for in vivo oncogenesis and in vitro cell transformation are encoded by the early region of the virus. These proteins are called T (tumor) antigens (Tags), because animals with tumors induced by SV40 have antibodies against these viral proteins. Recently, we and other research laboratories have found SV40 in specific types of human tumors: mesothelioma, ependymoma and choroid plexus tumors, osteosarcoma and sarcoma. The same tumor types will develop in hamsters which have been injected systemically with SV40. SV40 causes cell transformation in tissue culture and tumors in animals, because SV40 Tag binds and inactivates the cellular tumor suppressor gene products, Rb and p53. We found that SV40 Tag binds p53 and Rb in human mesotheliomas, possibly contributing to the malignant phenotype.

http://www.ncbi.nlm.nih.gov/pubmed/9689808

“Between 1955 and 1963, polio vaccines and adenovaccines were contaminated with SV40; therefore, millions of people were exposed to this oncogenic virus.”

Monaldi Archives For Chest Diseases • April 1998

The detection of simian virus 40 in human tumors by polymerase chain reaction

Author information

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Abstract

Simian virus (SV) 40 is a deoxyribonucleic acid (DNA) virus that induces mesotheliomas, ependymomas, bone tumors, and lymphomas in hamsters. In recent years SV40 sequences have been detected in approximately 60% of mesotheliomas and ependymomas, in 33% of bone tumors and sarcomas, and in 13% of lymphomas. Because the amount of human specimens available for molecular studies is usually minimal, the method most commonly used to demonstrate SV40 in human specimens is the polymerase chain reaction (PCR). PCR is a highly sensitive and useful technique. In the PCR reaction, different sets of primers are used for targeting different regions of DNA. The regions of the SV40 genome targeted by PCR include the large T-antigen, the small t-antigen, the origin of replication, and viral protein-1 capsid protein. The use of these different sets of primers to test human tumor specimens for SV40 produce a different percentage of positive results. This is because these experiments revealed that some primers are more specific than others which may also detect sequences belonging to other DNA papovaviruses. Therefore, the combined use of different sets of primers is recommended when it is important to distinguish SV40 from other related papovaviruses such as BK and JC, which can also be occasionally present in human cells. Furthermore, these experiments demonstrated that polymerase chain reaction analyses for simian virus 40 can be performed better and easier when using deoxyribonucleic acid extracted from fresh and/or frozen tissue. Deoxyribonucleic acid from paraffin embedded specimens should not be used routinely for simian virus 40 testing because of the high risk of obtaining false negative results. However, these paraffin derived deoxyribonucleic acids can be used reliably in molecular laboratories specialized in these type of analyses. This paper describes the methods that we have developed to test simian virus 40 in human specimens.

http://www.ncbi.nlm.nih.gov/pubmed/?term=9689810

“This paper describes the methods that we have developed to test simian virus 40 in human specimens.”

BioDrugs • July 1998

Practical considerations in converting from plasma-derived to recombinant hepatitis B vaccines

Author information

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Abstract

Plasma-derived and recombinant vaccines have been developed to prevent hepatitis B virus infections. Both types of vaccine perform very well with respect to safety, immunogenicity and protective efficacy. The protection afforded by both types of vaccine is satisfactory for at least 5 to 10 years after vaccination, and a further booster dose is not necessary during this period. However, the plasma-derived vaccine is costly to produce and there is an unjustified but prevalent fear that it may be contaminated by potential pathogens. The supply of human plasma for production of the plasma-derived vaccine cannot be assured once use of hepatitis B vaccines becomes universal. It is therefore inevitable that the recombinant vaccine will replace the plasma-derived vaccine. If necessary, both vaccines can be used in combination. Future directions for hepatitis B vaccine development include: determination of the need for incorporation of pre-S gene products to enhance immunogenicity; defining a practical strategy to combat the problem of escape mutants after vaccination; and development of combination vaccines containing other inactivated antigens to allow complete immunisation against several diseases with a minimal number of injections.

http://www.ncbi.nlm.nih.gov/pubmed/?term=18020583

“the plasma-derived vaccine is costly to produce and there is an unjustified but prevalent fear that it may be contaminated by potential pathogens. The supply of human plasma for production of the plasma-derived vaccine cannot be assured once use of hepatitis B vaccines becomes universal.”

Journal Of The National Cancer Institute • January 1999

Cell and molecular biology of simian virus 40: implications for human infections and disease

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Abstract

Simian virus 40 (SV40), a polyomavirus of rhesus macaque origin, was discovered in 1960 as a contaminant of polio vaccines that were distributed to millions of people from 1955 through early 1963. SV40 is a potent DNA tumor virus that induces tumors in rodents and transforms many types of cells in culture, including those of human origin. This virus has been a favored laboratory model for mechanistic studies of molecular processes in eukaryotic cells and of cellular transformation. The viral replication protein, named large T antigen (T-ag), is also the viral oncoprotein. There is a single serotype of SV40, but multiple strains of virus exist that are distinguishable by nucleotide differences in the regulatory region of the viral genome and in the part of the T-ag gene that encodes the protein's carboxyl terminus. Natural infections in monkeys by SV40 are usually benign but may become pathogenic in immunocompromised animals, and multiple tissues can be infected. SV40 can replicate in certain types of simian and human cells. SV40-neutralizing antibodies have been detected in individuals not exposed to contaminated polio vaccines. SV40 DNA has been identified in some normal human tissues, and there are accumulating reports of detection of SV40 DNA and/or T-ag in a variety of human tumors. This review presents aspects of replication and cell transformation by SV40 and considers their implications for human infections and disease pathogenesis by the virus. Critical assessment of virologic and epidemiologic data suggests a probable causative role for SV40 in certain human cancers, but additional studies are necessary to prove etiology.

http://www.ncbi.nlm.nih.gov/pubmed/9923853

"Critical assessment of virologic and epidemiologic data suggests a probable causative role for SV40 in certain human cancers, but additional studies are necessary to prove etiology."

“These data suggest that there may be an increased incidence of certain cancers among the 98 million persons exposed to contaminated polio vaccine in the U.S.”

Anticancer Research • May 1999

Cancer risk associated with simian virus 40 contaminated polio vaccine

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Abstract

BACKGROUND

The presence of SV40 in monkey cell cultures used in the preparation of the polio vaccine from 1955 through 1961 is well documented. Investigations have consistently demonstrated the oncogenic behavior of SV40 in animal models. Early epidemiologic studies were inadequate in demonstrating an increase in cancer incidence associated with contaminated vaccine. Recently, investigators have provided persuasive evidence that SV40 is present in human ependymomas, choroid plexus tumors, bone tumors, and mesotheliomas, however, the etiologic role of the virus in tumorigenesis has not been established.

MATERIALS AND METHODS

Using data from SEER, we analyzed the incidence of brain tumors, bone tumors, and mesotheliomas from 1973-1993 and the possible relationship of these tumors with the administration of the SV40 contaminated vaccine.

RESULTS

Our analysis indicates increased rates of ependymomas (37%), osteogenic sarcomas (26%), other bone tumors (34%) and mesothelioma (90%) among those in the exposed as compared to the unexposed birth cohort.

CONCLUSIONS

These data suggest that there may be an increased incidence of certain cancers among the 98 million persons exposed to contaminated polio vaccine in the U.S.; further investigations are clearly justified.

http://www.ncbi.nlm.nih.gov/pubmed/10472327

Cancer Research • December 1999

Unique strains of SV40 in commercial poliovaccines from 1955 not readily identifiable with current testing for SV40 infection

Author information

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Abstract

SV40 was first identified as a contaminant of poliovaccines used from 1955 until 1963. Recently, SV40 has been detected in several human tumors. The virus detected in human tumors often contained only one 72-bp enhancer in the regulatory region, in contrast to the SV40 originally isolated from poliovaccines, which contained two 72-bp enhancers. The origin of viruses with one 72-bp enhancer in humans was unknown, because it was thought that these viruses were not present in poliovaccines. It was also thought that all poliovaccine vials produced from 1955 until 1963 had been discarded, thus the possibility that one 72-bp virions contaminated those vials could not be tested. We unexpectedly obtained what appear to be the last available vials of poliovaccine produced in 1955. In these vials, we detected and sequenced SV40 containing only one 72-bp enhancer in the regulatory region. The tissue culture cytopathic test currently used in the United States to screen oral poliovaccines was designed to detect rapidly proliferating SV40 virions containing two 72-bp enhancers. We found that this test is not sensitive enough to detect low amounts of the slow-replicating SV40 virions containing one 72-bp enhancer. This virus was easily detected in the same cells by immunostaining and PCR. Twelve current vials of poliovaccines tested uniformly negative for SV40, suggesting that the precaution of preparing poliovaccines from kidneys obtained from monkeys bred in isolated colonies prevented SV40 contamination. Our data demonstrate that humans were exposed to SV40 viruses with both one 72-bp enhancer and two 72-bp enhancers SV40 through contaminated vaccines. Our data also suggest that instead of cytopathic tests, immunohistochemical and/or molecular studies should be used to screen poliovaccines for SV40 to completely eliminate the risk of occasional contamination.

https://www.ncbi.nlm.nih.gov/pubmed/10626798

“SV40 was first identified as a contaminant of poliovaccines used from 1955 until 1963. Recently, SV40 has been detected in several human tumors.”

"... in litigation involving the Lederle oral polio vaccine,

the manufacturer's internal documents failed to reveal such removal in all of the seeds."

Anticancer Research • November 2000

Oral polio vaccine and human cancer: a reassessment of SV40 as a contaminant based upon legal documents

Author information

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Abstract

To date, the scientific literature and research examining SV40 and cancer-related diseases has been based upon an assumption that SV40 was not present in any poliovirus vaccine administered in the United States and was removed from the killed polio vaccine by 1963. The basis for this presumption has been that the regulations for live oral polio vaccine required that SV40 be removed from the seeds and monovalent pools ultimately produced in the manufacturing process. The Division of Biologic Standards permitted an additional two tissue culture passages--from three to five--in order to allow manufacturers the ability to remove this contaminant from the oral poliovirus vaccines then awaiting licensure. The confirmation of the removal by one drug manufacturer, Lederle, has been made public at an international symposium in January 1997, where its representatives stated that all of Lederle's seeds had been tested and screened to assure that it was free from SV40 virus. However, in litigation involving the Lederle oral polio vaccine, the manufacturer's internal documents failed to reveal such removal in all of the seeds. The absence of confirmatory testing of the seeds, as well as testimony of a Lederle manager, indicate that this claim of removal of SV40 and the testing for SV40 in all the seeds cannot be fully substantiated. These legal documents and testimony indicate that the scientific community should not be content with prior assumptions that SV40 could not have been in the oral polio vaccine. Only further investigation by outside scientific and independent researchers who can review the test results claimed in the January 1997 meeting and who can conduct their own independent evaluations by testing all the seeds and individual mono-valent pools will assure that SV40 has not been present in commercially sold oral poliovirus vaccine manufactured by Lederle.

http://www.ncbi.nlm.nih.gov/pubmed/11205211

Journal Of Veterinary Medical Science • July 2001

Genotypes of pestivirus RNA detected in live virus vaccines for human use

Author information

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Abstract

Live virus vaccines for human use, 29 monovalent vaccines against measles, mumps, rubella or polio, eight polyvalent vaccines against measles-mumps-rubella and one bacterial polyvalent vaccine against Streptococcus pneumoniae, were tested by reverse transcriptase-nested PCR for the presence of petivirus or pestivirus RNA. Twenty-four samples were selected from European manufacturers, ten were from U.S.A. and four from Japan. Five (13.1%) out of 38 tested samples were positive for pestivirus RNA. Three vaccines (rubella and two measles) were from Europe and two (mumps and rubella) from Japan. The 5'-untranslated genomic region of the contaminant pestivirus RNA were amplified by reverse transcription-PCR and sequenced. Analyses based on primary nucleotide sequence homology and on secondary structures, characteristic to genotypes, revealed that the cDNA sequences belonged to bovine viral diarrhea virus (BVDV). A cDNA sequence, detected from one measles sample, belonged to BVDV-1b genotype. Pestiviral cDNA detected from the Japanese mumps and rubella vaccine samples, belonged to the BVDV genotypes 1a and 1c, respectively. Analysis on two cDNA sequences detected from measles and rubella vaccine samples from Europe showed their appurtenance to a new genotype, BVDV-1d. These findings indicate that contamination by animal pestivirus may occur in biological products for human use.

http://www.ncbi.nlm.nih.gov/pubmed/11503899

"Twenty-four samples were selected from European manufacturers, ten were from U.S.A. and four from Japan. Five (13.1%) out of 38 tested samples were positive for pestivirus RNA. Three vaccines (rubella and two measles) were from Europe and two (mumps and rubella) from Japan."

Vaccine • October 2001

What are the limits of adjuvanticity?

Author information

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Abstract

Vaccines developed traditionally following empirical approaches have often limited problems of immunogenicity, probably due to the low level of purity of the active component(s) they contain. The application of new technologies to vaccine development is leading to the production of purer (e.g. recombinant) antigens which, however, tend to have a poorer immunogenicity as compared to vaccines of the previous generation. The search for new vaccine adjuvants involves issues related to their potential limits. Since the introduction of aluminium salts as vaccine adjuvants more than 70 years ago, only one adjuvant has been licensed for human use. The development of some of these new vaccine adjuvants has been hampered by their inacceptable reactogenicity. In addition, some adjuvants work strongly with some antigens but not with others, thus, limiting their potentially widespread use. The need to deliver vaccines via alternative routes of administration (e.g. the mucosal routes) in order to enhance their efficacy and compliance has set new requirements in basic and applied research to evaluate their efficacy and safety. Cholera toxin (CT) and labile enterotoxin (LT) mutants given along with intranasal or oral vaccines are strong candidates as mucosal adjuvants. Their potential reactogenicity is still matter of discussions, although available data support the notion that the effects due to their binding to the cells and those due to the enzymatic activity can be kept separated. Finally, adjuvanticity is more often evaluated in terms of antigen-specific antibody titers induced after parenteral immunization. It is known that, in many instances, antigen-specific antibody titers do not correlate with protection. In addition, very little is known on parameters of cell-mediated immunity which could be considered as surrogates of protection. Tailoring of new adjuvants for the development of vaccines with improved immunogenicity/efficacy and reduced reactogenicity will represent one of the major challenges of the ongoing vaccine-oriented research.

http://www.ncbi.nlm.nih.gov/pubmed/11587808

“Vaccines developed traditionally following empirical approaches have often limited problems of immunogenicity, probably due to the low level of purity of the active component(s) they contain.”

American Journal Of Health-System Pharmacy • February 2002

Implications of prion-induced diseases for animal-derived pharmaceutical products

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Abstract

The implications of prion-induced diseases for the use of medications that theoretically could harbor the infectious pathogens are discussed. Prions have been identified as protein particles that lack nucleic acids. There is evidence that prions cause the transmissible neurodegenerative diseases known as transmissible spongiform encephalopathies. Of these diseases, bovine spongiform encephalopathy (BSE) and the human spongiform encephalopathy to which it has been linked, new variant Creutzfeldt-Jakob disease (CJD), have generated the most attention. The first cases of new variant CJD appeared in Britain in the mid-1990s. Ingestion of prion-infected beef remains the only known cause of new variant CJD. No cases of BSE or new variant CJD have been documented in the United States. The time from exposure to the development of clinical sequelae appears to be about 10 years. The median duration of illness is 14 months, and the outcome is invariably death. There is no treatment; currently the only available approach is prevention. There is no reliable method of predicting the number of new cases that might occur because of lack of definitive information on the efficiency of transmission from animals to humans and the number of people currently infected and at risk for infection. The infectivity of medications and plasma fractionation products containing material from cattle with BSE is unknown, but the risk is believed to be very low. No cases of such transmission have been identified. Guidelines to keep the risk of transmission via medications low have been promulgated by FDA, and further research is warranted. There have been no reports of medications or plasma fractionation products being contaminated with the prions that cause new variant CJD. Ongoing vigilance and research are appropriate, however.

http://www.ncbi.nlm.nih.gov/pubmed/?term=11862637

“The infectivity of medications and plasma fractionation products containing material from cattle with BSE is unknown, but the risk is believed to be very low.”

“This analysis confirmed higher concentrations of endotoxin

in whole-cell DTP vaccines compared with DTaP or DT vaccines.

As high concentrations of endotoxin may be correlated with a higher incidence of adverse events ...”

Annals Of Pharmacotherapeutics • May 2002

Clinical implications of endotoxin concentrations in vaccines

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Abstract

BACKGROUND

A previous study suggested that high concentrations of endotoxin may be present in whole-cell diphtheria/tetanus/pertussis (DTP) vaccine, and the scientific literature contains many studies examining the reactivity of whole-cell DTP vaccine. The medical and scientific communities have previously reported that the presence of endotoxin in commercial vaccines may have negative effects on vaccine recipients.

OBJECTIVE

To determine the endotoxin concentrations in whole-cell DTP, acellular DTP(DTaP), and DT vaccines and determine the clinical experience with each vaccine.

METHODS

To study the endotoxin concentrations in vaccines, the Limulus amebocyte lysate (LAL) assay was used. The vaccines analyzed with the LAL assay were whole-cell DTP vaccine lots manufactured by Connaught, Lederle, the Michigan and Massachusetts Departments of Health, and Wyeth; DTaP vaccine lots manufactured by Merieux and Takeda; and DT vaccine lots manufactured by Wyeth and Lederle. The incidence of adverse reactions following whole-cell DTP, DTaP, and DT vaccines were determined based on analysis of the Vaccine Adverse Events Reporting System (VAERS) database.

RESULTS

The results of the LAL assay showed that whole-cell DTP vaccines contained considerably more endotoxin than either DTaP or DT vaccines. The VAERS showed that statistically significantly more adverse reactions were associated with whole-cell DTP vaccine than DTaP or DT vaccines.

CONCLUSIONS

This analysis confirmed higher concentrations of endotoxin in whole-cell DTP vaccines compared with DTaP or DT vaccines. As high concentrations of endotoxin may be correlated with a higher incidence of adverse events, the switch from whole-cell DTP to DTaP for routine vaccinations in the US seems well justified.

http://www.ncbi.nlm.nih.gov/pubmed/?term=11978151

Anticancer Research • November 2002

SV40 in human tumors: new documents shed light on the apparent controversy

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Abstract

BACKGROUND
Presently there are over 61 reports from 49 different laboratories that have detected SV40 in human mesothelioma, lymphoma, brain and bone tumors, versus three reports (two from Dr. Shah's laboratory who performed his study under contract from Dr. Strickler at the Viral Epidemiology Branch (VEB) National Cancer Institute (USA) that have failed to detect SV40 in some of these same tumor types. To address whether the negative reports were caused by lack of sensitivity of the technique used in Shah's laboratory, or whether the positive reports were caused by contamination within the greater number of laboratories reporting SV40 detection, two multi-center studies were conducted. The first study, Testa et al., 1998, confirmed the presence of SV40 in mesothelioma. The second study, Strickler et al., produced irregular results indicating that: (a) though never reporting SV40 detection to date, Dr. Shah's laboratory reported the most sensitive technique of all participating laboratories; (b) all participating laboratories essentially agreed the DNA extracts provided under contract to the VEB were negative; (c) all participating laboratories agreed one-half of the negative controls prepared by the VEB contract laboratory were positive due to contamination by the contract laboratory. In addition, (d) the authors concluded the laboratories previously detecting SV40 in human tissue specimens were not reporting contamination. Scientists in the field have since debated how these seemingly contradictory results were produced.

MATERIALS
During the course of litigation representing patients with SV40-positive tumors, the author obtained correspondence among members of the VEB multi-center study and sworn testimony by Dr. Shah that address some of the incongruities of the study.

RESULTS
Dr. Shah's laboratory technique used in 1996 was apparently not sufficiently sensitive to detect SV40 in human tumors. When this became apparent, during unilateral pre-trial testing of positive controls by Dr. Shah, the study coordinator of the VEB, Dr. Strickler, apparently compromised the blinded nature of the study and allowed Dr. Shah to modify and improve his technique. When one of the participating laboratories questioned irregularities in the data from Dr. Shah's laboratory and directly questioned Dr. Strickler, the study organizer, about the potential irregularity, Dr. Strickler and Dr. Shah offered letters stating that such irregularities had not occurred and re-confirmed that they had not deviated from the standard protocol.

CONCLUSION
The facts indicating that Dr. Shah's laboratory technique was not sufficiently sensitive to detect SV40 were not made available to the other laboratories participating in the study and were not published. Instead, according to Dr. Shah's testimony, Dr. Strickler, the VEB multi-center study coordinator, compromised the masked positive controls and knowingly permitted Dr. Shah to re-test and adjust his technique during pre-trial testing. The actual negative pre-trial test results were never published alongside the published trial results indicating Dr. Shah's laboratory had the most sensitive technique to detect SV40 among the nine participating laboratories.

http://www.ncbi.nlm.nih.gov/pubmed/12552945

"When one of the participating laboratories questioned irregularities in the data from Dr. Shah's laboratory and directly questioned Dr. Strickler, the study organizer, about the potential irregularity, Dr. Strickler and Dr. Shah offered letters stating that such irregularities had not occurred and re-confirmed that they had not deviated from the standard protocol."

[it was found that they had lied]

Biologicals • December 2002

Detection and characterization of pestivirus contaminations in human live viral vaccines

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Abstract

In view of the use of potentially contaminated foetal calf serum (FCS) in cell cultures pestiviruses may be present in live viral vaccines. Thirty-six lots of human live viral vaccines produced by three manufacturers were tested for the presence of pestiviruses. Bovine viral diarrhoea virus (BVDV) RNA was detected in 33% of the vaccine lots. All positive results were caused by the mumps component of a single manufacturer. Partial sequences of the 5' untranslated region of BVD viral RNA were determined. The sequences were closely related to that of the NADL strain of BVDV. The amount of BVDV RNA in the vaccines was determined by real-time RT-PCR using the LightCycler. Between 3.3*10(2) and 6.2*10(5) RNA copies per dose were found to be present in the vaccine samples.Additionally, culture tests were done with FCS and human diploid cells used in the vaccine production of the manufacturer whose vaccines were positive by PCR. All attempts to detect virus antigen in MRC-5 human diploid cells or to infect these cells with BVDV failed. This suggests that BVDV RNA detected in human live viral vaccines represents passive carry over of BVDV from contaminated FCS rather than active virus replication in human diploid cells. Our results indicate that contamination with BVDV of FCS used in vaccine production does not appear to be of immediate concern to human health. Furthermore, our results indicate that gamma-irradiation of FCS destroys BVDV particles and is also effective in preventing the presence of BVDV RNA in the vaccines.

http://www.ncbi.nlm.nih.gov/pubmed/12421586

"This suggests that BVDV RNA detected in human live viral vaccines represents passive carry over of BVDV from contaminated foetal calf serum rather than active virus replication in human diploid cells. Our results indicate that contamination with BVDV of foetal calf serum used in vaccine production does not appear to be of immediate concern to human health."

Institute of Medicine (US) Immunization Safety Review Committee • 2002

Immunization Safety Review: SV40 Contamination of Polio Vaccine and Cancer

Washington, DC National Academies Press

Editors
Stratton K, Almario DA, McCormick MC.

Excerpt

Some of the polio vaccine administered from 1955–1963 was contaminated with a virus, called simian virus 40 (SV40). The virus came from the monkey kidney cell cultures used to produce the vaccine. Most, but not all, of the contamination was in the inactivated polio vaccine (IPV). Once the contamination was recognized, steps were taken to eliminate it from future vaccines. Researchers have long wondered about the effects of the contaminated vaccine on people who received it. Although SV40 has biological properties consistent with a cancer-causing virus, it has not been conclusively established whether it might have caused cancer in humans. Studies of groups of people who received polio vaccine during 1955–1963 provide evidence of no increased cancer risk. However, because these epidemiologic studies are sufficiently flawed, the Institute of Medicine's Immunization Safety Review Committee concluded that the evidence was inadequate to conclude whether or not the contaminated polio vaccine caused cancer. In light of the biological evidence supporting the theory that SV40-contamination of polio vaccines could contribute to human cancers, the committee recommends continued public health attention in the form of policy analysis, communication, and targeted biological research.

http://www.ncbi.nlm.nih.gov/pubmed/?term=25057632

Full Report

http://www.ncbi.nlm.nih.gov/books/NBK221113/

“ In light of the biological evidence supporting the theory that SV40-contamination of polio vaccines could contribute to human cancers, the committee recommends continued public health attention in the form of policy analysis, communication, and targeted biological research.”

Leukemia & Lymphoma • 2003

Association between SV40 and non-Hodgkin's lymphoma

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Abstract

Millions of people worldwide were inadvertently exposed to live simian virus 40 (SV40) between 1955 and 1963 through immunization with SV40-contaminated polio vaccines. Although the prevalence of SV40 infections in humans is not known, numerous studies suggest that SV40 is a pathogen resident in the human population today. SV40 is a potent DNA tumor virus that is known to induce primary brain cancers, bone cancers, mesotheliomas, and lymphomas in laboratory animals. SV40 oncogenesis is mediated by the viral large tumor antigen (T-ag), which inactivates the tumor suppressor proteins p53 and pRb. During the last decade, independent studies using different molecular biology techniques have shown the presence of SV40 DNA, T-ag, or other viral markers in primary human brain and bone cancers and malignant mesotheliomas. Evidence suggests that there may be geographic differences in the frequency of these virus-positive tumors. Recent large independent controlled studies have shown that SV40 T-ag DNA is significantly associated with human non-Hodgkin's lymphoma (NHL). In our study, we analyzed systemic NHL from 76 HIV-1-positive and 78 HIV-1-negative patients, and nonmalignant lymphoid samples from 79 HIV-1-positive and 107 HIV-1-negative patients without tumors; 54 colon and breast carcinoma samples served as cancer controls. We used polymerase chain reaction (PCR) followed by Southern blot hybridization and DNA sequence analysis to detect DNAs of polyomaviruses and herpesviruses. SV40-specific DNA sequences were detected in 64 (42%) of 154 NHL, none of 186 nonmalignant lymphoid samples, and none of 54 control cancers. For NHL from HIV-1-positive patients, 33% contained SV40 DNA and 39% Epstein Barr virus (EBV) DNA, whereas NHLs from HIV-1-negative patients were 50% positive for SV40 and 15% positive for EBV. Few tumors were positive for both SV40 and EBV. Human herpesvirus type 8 was not detected. SV40 sequences were found most frequently in diffuse large B cell and follicular-type lymphomas. We conclude that SV40 is significantly associated with some types of NHL and that lymphomas should be added to the types of human cancers associated with SV40.

http://www.ncbi.nlm.nih.gov/pubmed/15202523

"Millions of people worldwide were inadvertently exposed to live simian virus 40 (SV40) between 1955 and 1963 through immunization with SV40-contaminated polio vaccines. We conclude that SV40 is significantly associated with some types of non-Hodgkins Lymphoma and that lymphomas should be added to the types of human cancers associated with SV40."

Cancer Epidemiological Biomarkers And Prevention • May 2003

Serum antibodies to JC virus, BK virus, simian virus 40, and the risk of incident adult astrocytic brain tumors

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Abstract

Genomic sequences of the human polyomaviruses, JC virus (JCV) and BK virus (BKV), and simian virus 40 (SV40) have been reported from several types of human brain tumors, but there have been no population-based seroepidemiologic studies to evaluate the association between polyomavirus infection and brain tumors. We conducted a case-control study, nested within a prospective cohort, to investigate the association between antibodies to JCV, BKV, and SV40, as measured in serum collected 1-22 years before diagnosis and incident primary malignant brain tumors. Brain tumor cases (n = 44) and age-, gender-, and race-matched controls (n = 88) were identified from participants of two specimen banks in Washington County, Maryland. IgG antibodies to the capsid proteins of JCV and BKV were assessed using ELISAs. SV40-neutralizing antibodies were measured using plaque neutralization assays. Similar to the general population, the prevalence of JCV and BKV infection was high in our study population (77 and 85%, respectively). Antibodies to SV40 were less prevalent (11%). The odds ratio for subsequent brain tumor development was 1.46 [95% confidence interval (CI), 0.61-3.5] for JCV, 0.66 for BKV (95% CI, 0.22-1.95), and 1.00 for SV40 (95% CI, 0.30-3.32). Given the high prevalence of JCV and BKV infections and the millions who were potentially exposed to SV40 through contaminated polio vaccines, future studies should attempt to replicate these findings.

http://www.ncbi.nlm.nih.gov/pubmed/12750243

“Given the high prevalence of JCV and BKV infections and the millions who were potentially exposed to SV40 through contaminated polio vaccines, future studies should attempt to replicate these findings.”

American Journal Of Medicine • June 2003

Simian virus 40 in human cancers

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Abstract

BACKGROUND
Many studies have reported the presence of simian virus 40 (SV40) deoxyribonucleic acid (DNA) or protein in human brain tumors and bone cancers, malignant mesothelioma, and non-Hodgkin's lymphoma. However, the small samples and lack of control groups in some reports have made it difficult to assess their reliability.

METHODS
Studies were included in this analysis if they met the following criteria: original studies of patients with primary brain tumors and bone cancers, malignant mesothelioma, or non-Hodgkin's lymphoma; the investigation of SV40 was performed on primary cancer specimens; the analysis included a control group; and the same technique was used for cases and controls. Included reports were published from 1975 to 2002.

RESULTS
Thirteen studies fulfilled the criteria for the investigation of primary brain cancers (661 tumors and 482 control samples). Specimens from patients with brain tumors were almost four times more likely to have evidence of SV40 infection than were those from controls (odds ratio [OR] = 3.9; 95% confidence interval [CI]: 2.6 to 5.8). The association was even stronger for mesothelioma (OR = 17; 95% CI: 10 to 28; based on 15 studies with 528 mesothelioma samples and 468 control samples) and for bone cancer (OR = 25; 95% CI: 6.8 to 88; based on four studies with 303 cancers and 121 control samples). SV40 DNA was also more frequent in samples from patients with non-Hodgkin's lymphoma (OR = 5.4; 95% CI: 3.1 to 9.3; based on three studies with 301 cases and 578 control samples) than from controls.

CONCLUSION
These results establish that SV40 is associated significantly with brain tumors, bone cancers, malignant mesothelioma, and non-Hodgkin's lymphoma. Studies are needed to assess current prevalence of SV40 infections.

http://www.ncbi.nlm.nih.gov/pubmed/12798456

"These results establish that SV40 is associated significantly with brain tumors, bone cancers, malignant mesothelioma, and non-Hodgkin's lymphoma."

Oncogene • August 2003

New developments about the association of SV40 with human mesothelioma

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Abstract

Simian virus 40 (SV40) has been detected in human tumors in over 40 different laboratories. Many of these reports linked SV40 to human mesotheliomas. The Vaccine Safety Committee of the Institute of Medicine (IOM), National Academy of Sciences, USA, recently reviewed the evidence associating polio vaccines and/or SV40 with human tumors. The IOM conclusions about polio vaccines and human cancer were: (1) 'the evidence is inadequate to accept or reject a causal relation between SV40-containing polio vaccines and cancer' because the 'epidemiological studies are sufficiently flawed'; (2) 'the biological evidence is of moderate strength that SV40 exposure from the polio vaccines is related to SV40 infection in humans'. The epidemiological studies were considered flawed because it was not possible to distinguish reliably among exposed and nonexposed cohorts. Concerning SV40, the IOM concluded that (1) 'the evidence is strong that SV40 is a transforming virus; (2) the evidence is of moderate strength that SV40 exposure could lead to cancer in humans under natural conditions' (IOM, 2002). Similar conclusions were reached at an International consensus meeting on SV40 and human tumors held at the University of Chicago in 2001. G Klein and C Croce, who chaired the final panel that reviewed all the published evidence linking SV40 to human tumors, stated that 'the presence of SV40 in human tumors has been convincingly demonstrated' (Klein et al., 2002). In addition, a workshop organized by the Biological Carcinogenesis Branch of the National Cancer Institute, Bethesda, MD, chaired by J Pagano, has reached similar conclusions (Wong et al., 2002). Therefore, three independent scientific panels have all agreed that there is compelling evidence that SV40 is present in some human cancers and that SV40 could contribute to the pathogenesis of some of them. It should be noted that the presence of SV40 in mesothelioma and other human tumor types has been challenged by a research team that has consistently reported negative findings (Strickler et al., 2001). However, a member of this research team has recently acknowledged - in sworn testimony -sensitivity problems and possible irregularities that raise concerns about these negative reports (MacLachlan, 2002). These revelations, together with the conclusions of the three independent panels mentioned above, appear to bring to an end the apparent controversy about the presence of SV40 in human mesotheliomas and brain tumors.

http://www.ncbi.nlm.nih.gov/pubmed/12910254

"Therefore, three independent scientific panels have all agreed that there is compelling evidence that SV40 is present in some human cancers and that SV40 could contribute to the pathogenesis of some of them."

[foetal calf serum is used in vaccine production]

Biologicals • September 2003

Bovine viral diarrhoea virus antigen in foetal calf serum batches and consequences of such contamination for vaccine production

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Abstract

A protocol to test foetal calf serum (FCS) for contamination with bovine viral diarrhoea virus (BVDV) is described. Following this protocol, which combines cell culture methods and detection of pestivirus RNA, seven batches of FCS were tested. Infectious BVDV was detected in four of those batches. One of the remaining batches contained a relatively high number of non-infectious BVDV particles. A sample of this batch was formulated with aluminium hydroxide and aluminium phosphate as adjuvant into an experimental vaccine preparation. This product was injected twice into BVDV seronegative cattle with a 4 week interval. Blood samples taken 4 weeks after the second application were negative for BVDV specific antibodies. Our data stress that detection of BVDV RNA is not sufficient for a complete risk assessment on FCS. Discrimination between infectious and non-infectious BVDV is essential. This can only be achieved by cell culture methods.

http://www.ncbi.nlm.nih.gov/pubmed/12935809

“Our data stress that detection of BVDV RNA is not sufficient for a complete risk assessment on Foetal Calf Serum. Discrimination between infectious and non-infectious BVDV is essential. This can only be achieved by cell culture methods.”

Veterinaria Italiana • January 2004

Genotypes of Pestivirus RNA detected in anti-influenza virus vaccines for human use

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Abstract

Nine polyvalent human influenza virus vaccines were tested by reverse transcriptase-polymerase chain reaction (RT-PCR) for the presence of pestivirus RNA. Samples were selected from manufacturers in Europe and the USA. Three samples of the nine vaccines tested (33.3%) gave positive results for pestivirus RNA. The 5'-untranslated genomic region sequence of the contaminant pestivirus RNA was analysed based on primary nucleotide sequence homology and on secondary sequence structures characteristic to genotypes. Two sequences belonged to Pestivirus type-1 (bovine viral diarrhoea virus [BVDV]) species, genotypes BVDV-1b and BVDV-1e. These findings confirm previous reports, suggesting an improvement in preventive measures against contamination of biological products for human use.

http://www.ncbi.nlm.nih.gov/pubmed/?term=20437384

Full Report (In Italian)

http://www.izs.it/vet_italiana/2004/40_1/7.pdf

"Samples were selected from manufacturers in Europe and the USA.

Three samples of the nine vaccines tested (33.3%) gave positive results for pestivirus RNA."

Virology • January 2004

Simian virus 40 infection in humans and association with human diseases: results and hypotheses

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Abstract

Simian virus 40 (SV40) is a monkey virus that was introduced in the human population by contaminated poliovaccines, produced in SV40-infected monkey cells, between 1955 and 1963. Epidemiological evidence now suggests that SV40 may be contagiously transmitted in humans by horizontal infection, independent of the earlier administration of SV40-contaminated poliovaccines. This evidence includes detection of SV40 DNA sequences in human tissues and of SV40 antibodies in human sera, as well as rescue of infectious SV40 from a human tumor. Detection of SV40 DNA sequences in blood and sperm and of SV40 virions in sewage points to the hematic, sexual, and orofecal routes as means of virus transmission in humans. The site of latent infection in humans is not known, but the presence of SV40 in urine suggests the kidney as a possible site of latency, as it occurs in the natural monkey host. SV40 in humans is associated with inflammatory kidney diseases and with specific tumor types: mesothelioma, lymphoma, brain, and bone. These human tumors correspond to the neoplasms that are induced by SV40 experimental inoculation in rodents and by generation of transgenic mice with the SV40 early region gene directed by its own early promoter-enhancer. The mechanisms of SV40 tumorigenesis in humans are related to the properties of the two viral oncoproteins, the large T antigen (Tag) and the small t antigen (tag). Tag acts mainly by blocking the functions of p53 and RB tumor suppressor proteins, as well as by inducing chromosomal aberrations in the host cell. These chromosome alterations may hit genes important in oncogenesis and generate genetic instability in tumor cells. The clastogenic activity of Tag, which fixes the chromosome damage in the infected cells, may explain the low viral load in SV40-positive human tumors and the observation that Tag is expressed only in a fraction of tumor cells. “Hit and run” seems the most plausible mechanism to support this situation. The small tag, like large Tag, displays several functions, but its principal role in transformation is to bind the protein phosphatase PP2A. This leads to constitutive activation of the Wnt pathway, resulting in continuous cell proliferation. The possibility that SV40 is implicated as a cofactor in the etiology of some human tumors has stimulated the preparation of a vaccine against the large Tag. Such a vaccine may represent in the future a useful immunoprophylactic and immunotherapeutic intervention against human tumors associated with SV40.

http://www.ncbi.nlm.nih.gov/pubmed/?term=15015494

“Simian virus 40 (SV40) is a monkey virus that was introduced in the human population by contaminated poliovaccines, produced in SV40-infected monkey cells, between 1955 and 1963. Epidemiological evidence now suggests that SV40 may be contagiously transmitted in humans by horizontal infection, independent of the earlier administration of SV40-contaminated poliovaccines.”

Medical Hypotheses • 2005

Multiple sclerosis and hepatitis B vaccination: could minute contamination of the vaccine by partial hepatitis B virus polymerase play a role through molecular mimicry?

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Abstract

Reports of multiple sclerosis developing after hepatitis B vaccination have led to the concern that this vaccine might be a cause of multiple sclerosis in previously healthy subjects. Some articles evidenced that minor Hepatitis B virus (HBV) polymerase proteins could be produced by alternative transcriptional or translational strategies. Their detection is very difficult because they are in minute concentration and probably enzymatically inactive, however, it was shown that they could be exposed on the outside of the virus particles and also be immunogenic. In addition, HBV polymerase shares significant amino acid similarities with the human myelin basic protein. We hypothesise that some of the apparent adverse reactions to the vaccine could be due to a process called of molecular mimicry, the HBV polymerase, which could be a contaminant in the recombinant or plasma-derived vaccines, could act as autoantigens and induce autoimmune demyelinating diseases such as multiple sclerosis.

http://www.ncbi.nlm.nih.gov/pubmed/15908138

“We hypothesise that some of the apparent adverse reactions to the vaccine could be due to a process called of molecular mimicry, the Hepatitus B Virus polymerase, which could be a contaminant in the recombinant or plasma-derived vaccines, could act as autoantigens and induce autoimmune demyelinating diseases such as multiple sclerosis.”

Cancer Research • November 2005

Some oral poliovirus vaccines were contaminated with infectious SV40 after 1961

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Abstract

Some polio vaccines prepared from 1954 to 1961 were contaminated with infectious SV40. It has been assumed that all polio vaccines were SV40 free in the United States after 1961 and in other countries after 1962. Following a WHO requirement that was prompted by the detection of SV40 in some human tumors, we conducted a multilaboratory study to test for SV40 polio vaccines prepared after 1961. Vaccine samples from 13 countries and the WHO seed were initially tested by PCR. The possible presence of intact and/or infectious SV40 DNA in PCR-positive samples was tested by transfection and infection of permissive CV-1 cells. All results were verified by immunohistochemistry, cloning, and sequencing. All the vaccines were SV40 free, except for vaccines from a major eastern European manufacturer that contained infectious SV40. We determined that the procedure used by this manufacturer to inactivate SV40 in oral poliovirus vaccine seed stocks based on heat inactivation in the presence of MgCl2 did not completely inactivate SV40. These SV40-contaminated vaccines were produced from early 1960s to about 1978 and were used throughout the world. Our findings underscore the potential risks of using primary monkey cells for preparing poliovirus vaccines, because of the possible contamination with SV40 or other monkey viruses, and emphasize the importance of using well-characterized cell substrates that are free from adventitious agents. Moreover, our results indicate possible geographic differences in SV40 exposure and offer a possible explanation for the different percentage of SV40-positive tumors detected in some laboratories.

http://www.ncbi.nlm.nih.gov/pubmed/16288015

“It has been assumed
that all polio vaccines were SV40 free in the United States
after 1961 and in other countries after 1962.

These SV40-contaminated vaccines were produced
from early 1960s to about 1978 and were used throughout
the world. Our findings underscore the potential risks of
using primary monkey cells for preparing poliovirus
vaccines, because of the possible contamination with SV40
or other monkey viruses, and emphasize the importance
of using well-characterized cell substrates that are
free from adventitious agents.”

Brain Research Reviews • December 2005

Human polyomaviruses and brain tumors

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Abstract

Polyomaviruses are DNA tumor viruses with small circular genomes. Three polyomaviruses have captured attention with regard to their potential role in the development of human brain tumors: JC virus (JCV), BK virus (BKV), and simian vacuolating virus 40 (SV40). JCV is a neurotropic polyomavirus that is the etiologic agent of progressive multifocal leukoencephalopathy (PML), a fatal demyelinating disease of the central nervous system occurring mainly in AIDS patients. BKV is the causative agent of polyomavirus-associated nephropathy (PVN) which occurs after renal transplantation when BKV reactivates from a latent state during immunosuppressive therapy to cause allograft failure. SV40, originating in rhesus monkeys, gained notoriety when it entered the human population via contaminated polio vaccines. All three viruses are highly oncogenic when injected into the brain of experimental animals. Reports indicate that these viruses, especially JCV, are associated with brain tumors and other cancers in humans as evidenced from the analysis of clinical samples for the presence of viral DNA sequences and expression of viral proteins. Human polyomaviruses encode three non-capsid regulatory proteins: large T-antigen, small t-antigen, and agnoprotein. These proteins interact with a number of cellular target proteins to exert effects that dysregulate pathways involved in the control of various host cell functions including the cell cycle, DNA repair, and others. In this review, we describe the three polyomaviruses, their abilities to cause brain and other tumors in experimental animals, the evidence for an association with human brain tumors, and the latest findings on the molecular mechanisms of their actions.

http://www.ncbi.nlm.nih.gov/pubmed/15982744

“In this review, we describe the three polyomaviruses, [SV40, JC virus (JCV) and BK virus (BKV)] their abilities to cause brain and other tumors in experimental animals, the evidence for an association with human brain tumors, and the latest findings on the molecular mechanisms of their actions.”

Developments In Biologicals (Basel) • 2006

Vaccine cell substrates: bovine and porcine virus considerations

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Abstract

The use of materials of animal origin to supplement cell cultures used in vaccine production, viral diagnostic testing, or materials testing may lead to contamination of the vaccines, with seroconversion or disease in the vaccinated animals, and possible misdiagnosis of diagnostic samples or incorrect test results. The methods used by the Center for Veterinary Biologics to monitor serum and cell cultures are described. Considerations for the use of animal origin materials, especially bovine and porcine, as substrates or additives, plus the possibility of crossovers to humans are discussed.

http://www.ncbi.nlm.nih.gov/pubmed/16566453

“The use of materials of animal origin to supplement cell cultures used in vaccine production, viral diagnostic testing, or materials testing may lead to contamination of the vaccines, with seroconversion or disease in the vaccinated animals, and possible misdiagnosis of diagnostic samples or incorrect test results.”

Archives de Pediatrie • February 2006

Pharmacovigilance of vaccines

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Abstract

Safety of vaccines must be excellent to make vaccine's strategy acceptable, since it usually has a deferred individual benefit but immediate adverse drug reactions (ADRs). Pharmacovigilance of vaccines after their marketing is crucial because, prior to its availability on the market, the size of clinical trials is insufficient to identify rare or deferred adverse effects. The Pharmacovigilance is based on "spontaneous reporting" of ADRs to the Pharmacovigilance Regional Centre (PVRC) which establishes a relationship between each drug taken by the patient and the ADRs occurrence (imputability). This method is crucial to generate alerts, but under-estimates the real frequency of ADRs (1 to 10% of severe ADRs are reported). Thus pharmacoepidemiology studies are necessary to confirm the alerts identified by spontaneous reporting. ADRs can be specific, related to the antigen of an attenuated alive virus vaccine (lymphocyte meningitis after anti-mumps vaccine) or non-specific, related to a component different from the antigen (aluminium hydroxide involved in the "macrophagic myofasciitis", allergic reactions to neomycin, latex, egg or gelatine). Importance of Pharmacovigilance of vaccines is illustrated. Data, especially case-control studies, about the relationship between multiple sclerosis and hepatitis B vaccine are summarised. Data about the relationship between Crohn's disease or autism and MMR vaccine are analysed. As vaccines are used in healthy people, their safety must be excellent to be accepted. To monitor them after their marketing is the unique way to detect rare ADRs. This surveillance is made through reporting of ADRs to the PVRC. However, an active and intensive surveillance of ADRs as the one set up from the marketing of Prevenar should be systematic.

http://www.ncbi.nlm.nih.gov/pubmed/16343870

"Pharmacovigilance
of vaccines after their marketing
is crucial because, prior to its availability on the market,
the size of clinical trials is insufficient to identify
rare or deferred adverse effects."

Developments In Biology, Basel • March 2006

Polio vaccines, SV40 and human tumours, an update on false positive and false negative results

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Abstract

Simian virus 40 (SV40) has been detected in different human tumours in numerous laboratories. The detection of SV40 in human tumours has been linked to the administration of SV40-contaminated polio vaccines from 1954 until 1963. Many of these reports linked SV40 to human mesothelioma. Some studies have failed to detect SV40 in human tumours and this has caused a controversy. Here we review the current literature. Moreover, we present evidence showing how differences in the sensitivities of methodologies can lead to a very different interpretation of the same study. The same 20 mesothelioma specimens all tested negative, 2/20 tested positive or 7/20 tested positive for SV40 Tag by simply changing the detection method on the same immuno-precipitation/western blot membranes. These results provide a simple explanation for some of the apparent discordant results reported in the literature.

http://www.ncbi.nlm.nih.gov/pubmed/16566440

“we present evidence showing how differences in the sensitivities of methodologies can lead to a very different interpretation of the same study.”

Cancer Investigation • April 2006

High prevalence of SV40 infection in patients with nodal non-Hodgkin's lymphoma but not acute leukemia independent of contaminated polio vaccines in Taiwan

Author information

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Abstract

Recent studies have linked simian virus 40 (SV40) to non-Hodgkin's lymphoma (NHL), especially in countries in which people were exposed to contaminated polio vaccines prior to 1963. In Taiwan, nearly all children were not exposed to contaminated polio vaccine during this period; the relationship between SV40 infection and hematological malignancies is unclear and deserves to be studied. Using PCR amplification of SV40 large T antigen DNA, confirmed by Southern blot hybridization and sequence analysis, 91 frozen lymph nodes from NHL patients were examined. Thirteen (14.3 percent) showed positive for SV40. All other test samples, including diagnostic bone marrow from patients with acute leukemia, peripheral blood from 10 relatives of SV40 positive-patients and 91 age-matched normal volunteers, and 5 reactive hyperplastic lymphoid tissues, showed negative. These results may reflect that human-to-human transmission of SV40 is independent of contaminated polio vaccines; and SV40 is possibly associated with the development of NHL in Taiwan ($p = 0.0001$). Prospective studies are needed to determine the prevalence of SV40 infections in our and other human populations and to explore the means of transmission of the virus.

http://www.ncbi.nlm.nih.gov/pubmed/16809147

"These results may reflect that human-to-human transmission of SV40 is independent of contaminated polio vaccines; and SV40 is possibly associated with the development of non-Hodgkin's lymphoma in Taiwan ..."

Journal of Public Health Management & Practice • July 2006

The Legal Environment Underlying Influenza Vaccine Allocation and Distribution Strategies

Hodge, James G. Jr JD, LLM; O'Connell, Jessica P. JD/MPH

Abstract

In the fall of 2004, the United States faced a national shortage of influenza vaccine after a major vaccine manufacturer was unable to produce millions of doses of the vaccine due to potential contamination. Many public and private sector entities had far fewer doses of influenza vaccine to allocate than they had anticipated. In response, federal, state, and local public health officials, private vaccine distributors, and healthcare providers collaborated to distribute available doses of influenza vaccine. However, the existing legal framework through which allocations were made is murky. This article examines major legal issues regarding allocation strategies involving limited supplies of influenza vaccines, addressing in particular (1) existing legal requirements for allocating and distributing influenza vaccines among public health authorities and healthcare providers at the federal, state, and local levels; (2) the legal capacity of public health authorities to acquire existing vaccine supplies from healthcare providers; and (3) specific legal responses implemented by states in response to the 2004–2005 influenza vaccine shortage.

"In the fall of 2004, the United States faced a national shortage of influenza vaccine after a major vaccine manufacturer was unable to produce millions of doses of the vaccine due to potential contamination."

http://journals.lww.com/jphmp/pages/articleviewer.aspx?year=2006&issue=07000&article=00007&type=abstract

Proceedings Of The National Academy Of Science USA • September 2006

Crocidolite asbestos and SV40 are co-carcinogens in human mesothelial cells and in causing mesothelioma in hamsters

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ABSTRACT

Only a fraction of subjects exposed to asbestos develop malignant mesothelioma (MM), suggesting that additional factors may render some individuals more susceptible. We tested the hypothesis that asbestos and Simian virus (SV40) are cocarcinogens. Asbestos and SV40 in combination had a costimulatory effect in inducing ERK1/2 phosphorylation and activator protein-1 (AP-1) activity in both primary Syrian hamster mesothelial cells (SHM) and primary human mesothelial cells (HM). Ap-1 activity caused the expression and activation of matrix metalloprotease (MMP)-1 and MMP-9, which in turn led to cell invasion. Experiments using siRNA and chemical inhibitors confirmed the specificity of these results. The same effects were observed in HM and SHM. Experiments in hamsters showed strong cocarcinogenesis between asbestos and SV40: SV40 did not cause MM, asbestos caused MM in 20% of hamsters, and asbestos and SV40 together caused MM in 90% of hamsters. Significantly lower amounts of asbestos were sufficient to cause MM in animals infected with SV40. Our results indicate that mineral fibers and viruses can be cocarcinogens and suggest that lower amounts of asbestos may be sufficient to cause MM in individuals infected with SV40.

Full Report: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC1599923/

“Our results indicate that mineral fibers and viruses can be cocarcinogens and suggest that lower amounts of asbestos may be sufficient to cause malignant mesothelioma in individuals infected with SV40.”

Inhalation Toxicology • November 2006

The role of SV40 in malignant mesothelioma and other human malignancies

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Abstract

SV40 is a DNA tumor virus thrust upon human populations primarily as a contaminant in various vaccine preparations. Some estimates suggest that millions of people are currently infected with the virus. The virus causes primary brain tumors, bone tumors, lymphomas, and mesotheliomas when injected into some rodent models. It has also been detected in a similar spectrum of human tumors. However, epidemiological studies have failed to conclusively demonstrate a higher incidence of disease in affected populations. To date, over 60 reports from 49 different laboratories have shown SV40 sequences in tissues from human cancer patients. Six studies, however, have failed to detect evidence of virus in similar tissues. Some have suggested that SV40 may act as a cocarcinogen with asbestos to cause mesothelioma formation, or that it may be responsible for the 10-20% of mesotheliomas with no reported history of asbestos exposure. This report briefly covers the historical evidence for SV40 carcinogenesis and then covers experiments now underway to better understand the role of SV40 in human mesotheliomas.

https://www.ncbi.nlm.nih.gov/pubmed/16920674

“Some have suggested that SV40 may act as a co-carcinogen with asbestos ‘to cause mesothelioma formation, or that it may be responsible for the 10-20% of mesotheliomas with no reported history of asbestos exposure.”

“The use of materials of animal origin to supplement cell cultures used in vaccine production, viral diagnostic testing, or materials testing may lead to contamination of the vaccines ...”

Developments In Biologicals (Basel) • 2006

Vaccine cell substrates: bovine and porcine virus considerations

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Abstract

The use of materials of animal origin to supplement cell cultures used in vaccine production, viral diagnostic testing, or materials testing may lead to contamination of the vaccines, with seroconversion or disease in the vaccinated animals, and possible misdiagnosis of diagnostic samples or incorrect test results. The methods used by the Center for Veterinary Biologics to monitor serum and cell cultures are described. Considerations for the use of animal origin materials, especially bovine and porcine, as substrates or additives, plus the possibility of cross-overs to humans are discussed.

http://www.ncbi.nlm.nih.gov/pubmed/16566453

Cellular And Molecular Life Sciences • April 2007

SV40 association with human malignancies and mechanisms of tumor immunity by large tumor antigen

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Abstract

SV40 was discovered as a contaminate of poliovirus vaccine lots distributed to millions of individuals in the United States between 1955 and 1963 while contaminated vaccine batches were later circulated worldwide. After SV40 was observed to cause in vitro animal and human cell transformations and in vivo tumor formations in animals, the search for a connection between the virus and human malignancies has continued to the present day. Different molecular methods have been used to detect SV40 gene products in a variety of human cancers, though SV40 causality in these tumor types has yet to be established. These data, however, are not without controversial issues related to inconclusive SV40 serological and epidemiological evidence alongside tools and methodologies that may contribute to false-positive results in human specimens. This review will also explore how vaccination against SV40 protein products may be used to help prevent and treat individuals with SV40-expressing cancers.

http://www.ncbi.nlm.nih.gov/pubmed/17260087

“SV40 was discovered as a contaminate of poliovirus vaccine lots distributed to millions of individuals in the United States between 1955 and 1963 while contaminated vaccine batches were later circulated worldwide.”

Immunology Letters • June 2007

Mycoplasma contamination and viral immunomodulatory activity: dendritic cells open Pandora's box

Author information

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Abstract

During in vitro investigations on the interaction of classical swine fever virus (CSFV)--an immunosuppressive viral pathogen--with monocyte-derived dendritic cells (MoDC) a soluble factor with a strong anti-proliferative activity for T lymphocytes was found. This activity, with an inhibitory dilution 50% (ID(50)) of 10(3)-10(7), was induced after virus infection of monocytes differentiating into DC. UV--inactivation of the supernatants and blocking experiments with a monoclonal antibody against the E2 envelope protein of CSFV initially indicated a virus-dependency. However, further investigations including filtration and centrifugation experiments as well as antibiotic treatment demonstrated the involvement of mycoplasma. This was confirmed by a Hoechst 33258 staining, PCR and mycoplasma cultures--Mycoplasma hyorhinis was identified as the contaminant. Elucidation of a mycoplasma presence occurred under conditions in which the original virus stocks prepared in SK6 cells were negative for mycoplasma using the above tests. Moreover, conventional passage of the virus on the SK6 cells used for this purpose did not reveal any mycoplasma. It was the passage of virus in MoDC rather than SK6 cells that was required to expose the contamination. Three passages of the anti-proliferative supernatants on MoDC cultures increased the ID(50) 10(3)-fold; only when these MoDC-derived supernatants were employed was the mycoplasma contaminant also detectable on SK6 cells. In conclusion, these data demonstrate that regular testing of cell lines and virus stocks for mycoplasma does not necessarily identify their presence, and that application of passage in MoDC cultures could prove an aid for identifying initially undetectable levels of mycoplasma contamination.

http://www.ncbi.nlm.nih.gov/pubmed/?term=17532055

"... these data demonstrate that regular testing of cell lines and virus stocks for mycoplasma does not necessarily identify their presence ..."

Cellular And Molecular Life Sciences • July 2007

Oncogenic potentials of the human polyomavirus regulatory proteins

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Abstract

The polyomaviruses BK, JC and SV40 are common in the human population. Their DNA genomes encode large T-antigen, small t-antigen, agnoprotein, and the capsid proteins VP1-3. Studies with these viruses have contributed extensively to the understanding of processes such as replication, transcriptional and posttranscriptional regulation, and cell cycle control. All three viruses can transform human cells in vitro, can induce tumours in animal models, and are strongly association with certain human cancers. It is generally assumed that large T-antigen is the major protein involved in neoplastic processes and that large T-antigen predominantly exerts its effect through deregulation of the tumour suppressors p53 and the retinoblastoma family members. However, additional properties of large T-antigen as well as the other viral proteins contribute to oncogenic processes. This review presents the different mechanisms by which the polyomavirus proteins can induce transformation and discusses which mechanisms may be operational in polyomavirus-positive cancers.

https://www.ncbi.nlm.nih.gov/pubmed/17483871

“This review presents the different mechanisms by which the polyomavirus proteins can induce transformation and discusses which mechanisms may be operational in polyomavirus-positive cancers.”

"... determining the origin of the SV40 sequences detected in human tumors might be difficult."

Virology • January 2008

Recovery of strains of the polyomavirus SV40 from rhesus monkey kidney cells dating from the 1950s to the early 1960s

Keith Pedena, Li Shenga, Romelda Omeira, Maureen Yacobuccia,
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Abstract

From stocks of adenovirus and poliovirus prepared in primary rhesus macaque kidney cells and dating from 1956 to 1961, the time when SV40 contaminated some poliovirus vaccine lots, we have recovered ten isolates of SV40. Of these ten isolates, based on the C-terminal region of T antigen, five novel strains of SV40 have been identified. Additionally, three pairs of isolates were found to be the same strain: one pair was strain 777, one pair was strain 776 archetype, and the third pair represented a novel strain. All strains had identical protein sequences for VP2 and VP3. There were two variants of agnoprotein and the small t antigen and three variants of VP1. These results, and those of others, suggest that a limited number of SV40 strains might exist in rhesus macaques in the United States, and thus determining the origin of the SV40 sequences detected in human tumors might be difficult.

Full Report: http://www.sciencedirect.com/science/article/pii/S0042682207004321

Journal Of Pharmaceutical And Biomedical Analysis • February 2008

Strategy for identification of leachables in packaged pharmaceutical liquid formulations

Author information

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Abstract

Drug stability is one of the key properties to be monitored in pharmaceutical drug development. Drug degradation products, impurities and/or leachables from the drug product and packages may have significant impacts on drug efficacy, safety profile and storage conditions. In the registration stability samples of an ophthalmic pharmaceutical drug product, an unknown compound was found at a level of 0.19% by HPLC analysis. Subsequent liquid chromatography/mass spectrometry (LC/MS) analysis with electrospray ionization (ESI) indicated that the unknown was not related to the drug substance and was most likely a leachable. Identification of this unknown leachable was needed to evaluate the impact on drug safety. Through systematic extraction of various components or component combination of the packaging materials, and subsequently LC/MS analysis, the unknown was found to be a leachable coming from the varnish applied to the label. In general, using LC/MS alone is not sufficient to elucidate the structure of a complete unknown. Gas chromatography/mass spectrometry (GC/MS) was then conducted with a chemical ionization (CI) source to determine the retention time and mass of the compound of interest. Both CI and ESI sources generated the same protonated molecular ion [M+H] and similar fragmentation ions, which provides a good correlation of the unknown eluted in the liquid chromatogram and in the gas chromatogram. GC/MS with electron impact (EI) was then conducted to obtain the EI mass spectrum of this unknown. It was identified as monomethyl derivative of mephenesin through the NIST library search. The identification strategy utilized electrospray LC/MS and GC/MS with chemical and electron ionization sources which provided complimentary information for structure elucidation of this unknown compound. This combination approach in conjunction with systematic extraction was necessary for the determination of the source of this unknown in the pharmaceutical drug stability studies.

http://www.ncbi.nlm.nih.gov/pubmed/?term=18180126

“Drug degradation products, impurities and/or leachables from the drug product and packages may have significant impacts on drug efficacy, safety profile and storage conditions.”

International Journal Of Nanomedicine • June 2008

Drug delivery and nanoparticles: Applications and hazards

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Abstract

The use of nanotechnology in medicine and more specifically drug delivery is set to spread rapidly. Currently many substances are under investigation for drug delivery and more specifically for cancer therapy. Interestingly pharmaceutical sciences are using nanoparticles to reduce toxicity and side effects of drugs and up to recently did not realize that carrier systems themselves may impose risks to the patient. The kind of hazards that are introduced by using nanoparticles for drug delivery are beyond that posed by conventional hazards imposed by chemicals in classical delivery matrices. For nanoparticles the knowledge on particle toxicity as obtained in inhalation toxicity shows the way how to investigate the potential hazards of nanoparticles. The toxicology of particulate matter differs from toxicology of substances as the composing chemical(s) may or may not be soluble in biological matrices, thus influencing greatly the potential exposure of various internal organs. This may vary from a rather high local exposure in the lungs and a low or neglectable exposure for other organ systems after inhalation. However, absorbed species may also influence the potential toxicity of the inhaled particles. For nanoparticles the situation is different as their size opens the potential for crossing the various biological barriers within the body. From a positive viewpoint, especially the potential to cross the blood brain barrier may open new ways for drug delivery into the brain. In addition, the nanosize also allows for access into the cell and various cellular compartments including the nucleus. A multitude of substances are currently under investigation for the preparation of nanoparticles for drug delivery, varying from biological substances like albumin, gelatine and phospholipids for liposomes, and more substances of a chemical nature like various polymers and solid metal containing nanoparticles. It is obvious that the potential interaction with tissues and cells, and the potential toxicity, greatly depends on the actual composition of the nanoparticle formulation. This paper provides an overview on some of the currently used systems for drug delivery. Besides the potential beneficial use also attention is drawn to the questions how we should proceed with the safety evaluation of the nanoparticle formulations for drug delivery. For such testing the lessons learned from particle toxicity as applied in inhalation toxicology may be of use. Although for pharmaceutical use the current requirements seem to be adequate to detect most of the adverse effects of nanoparticle formulations, it can not be expected that all aspects of nanoparticle toxicology will be detected. So, probably additional more specific testing would be needed.

Full Report: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2527668/

“for pharmaceutical use the current requirements seem to be adequate to detect most of the adverse effects of nanoparticle formulations, it can not be expected that all aspects of nanoparticle toxicology will be detected.”

Collegium Antropologicum • June 2008

The role of polio-vaccine in pleural mesothelioma— an epidemiological observation

Author information

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Abstract

From the Croatian Cancer Registry (period 1991-1997) 194 malignant pleural mesothelioma patients were collected. According to participation in polio vaccination mass campaign in 1961 that covered the entire Croatian population aged 3 months to 20 years, mesothelioma patients were divided in vaccinated (N=58), and non-vaccinated (N=136) subjects. Significantly higher percentage of those with a history of occupational exposure to asbestos was found in vaccinated (79%) compared to non-vaccinated group (63%). This is the opposite to what would be expected if potential SV40 contamination of polio vaccine used had a causative role in the development of the tumour. On the other hand, shorter latency period reflected by very high percentage of 45-year-old or younger mesothelioma patients in vaccinated group (15 out of 58), with all of them having a history of occupational asbestos exposure, raises a question for a possible enhancing effect of the vaccine used to asbestos exposure, if it was contaminated with SV40.

http://www.ncbi.nlm.nih.gov/pubmed/18756898

“... raises a question for a possible enhancing effect of the vaccine used to asbestos exposure ...”

Vaccine • June 2008

A quantitative risk assessment of exposure to adventitious agents in a cell culture-derived subunit influenza vaccine

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Abstract

A risk-assessment model has demonstrated the ability of a new cell culture-based vaccine manufacturing process to reduce the level of any adventitious agent to a million-fold below infectious levels. The cell culture-derived subunit influenza vaccine (OPTAFLU), Novartis Vaccines and Diagnostics) is produced using Madin-Darby canine kidney (MDCK) cells to propagate seasonal viral strains, as an alternative to embryonated chicken-eggs. As only a limited range of mammalian viruses can grow in MDCK cells, similar to embryonated eggs, MDCK cells can act as an effective filter for a wide range of adventitious agents that might be introduced during vaccine production. However, the introduction of an alternative cell substrate (for example, MDCK cells) into a vaccine manufacturing process requires thorough investigations to assess the potential for adventitious agent risk in the final product, in the unlikely event that contamination should occur. The risk assessment takes into account the entire manufacturing process, from initial influenza virus isolation, through to blending of the trivalent subunit vaccine and worst-case residual titres for the final vaccine formulation have been calculated for >20 viruses or virus families. Maximum residual titres for all viruses tested were in the range of 10(-6) to 10(-16) infectious units per vaccine dose. Thus, the new cell culture-based vaccine manufacturing process can reduce any adventitious agent to a level that is unable to cause infection.

http://www.ncbi.nlm.nih.gov/pubmed/18485545

“... the ability of a new cell culture-based vaccine manufacturing process to reduce the level of any adventitious agent to a million-fold below infectious levels.”

“Two tetanus outbreaks in 1901 — from contaminated diphtheria antitoxin in St. Louis, Missouri,

and contaminated smallpox vaccine in Camden, New Jersey — raised public concern about pharmaceutical safety.”

Perspectives In Biology And Medicine • Spring 2008

The first pharmacoepidemiologic investigations: national drug safety policy in the United States, 1901-1902

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Abstract

The pharmaceutical industry developed in the late 19th century as a consequence of both scientific and commercial innovations, such as the development of diphtheria antitoxin and the commercialization of smallpox vaccine. Two tetanus outbreaks in 1901 — from contaminated diphtheria antitoxin in St. Louis, Missouri, and contaminated smallpox vaccine in Camden, New Jersey — raised public concern about pharmaceutical safety. In St. Louis, errant manufacturing processes were found to be the source of the outbreak. In Camden, investigation identified contaminated vaccine from one manufacturer as the cause. These investigations, the first known pharmacoepidemiologic studies, were widely reported. They formed the basis for the 1902 Biologics Control Act, which focused on the safety of biologics produced and sold by the pharmaceutical industry and established a precedent of federal regulation of this industry. That power, welcomed by manufacturers to restore the public’s trust in their products, was enhanced in the 1906 Food and Drug Act, which created the Food and Drug Administration.

http://www.ncbi.nlm.nih.gov/pubmed/18453724

Virology • December 2008

SV40 DNA replication: From the A gene to a nanomachine

Author Information

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Abstract

Duplication of the simian virus 40 (SV40) genome is the best understood eukaryotic DNA replication process to date. Like most prokaryotic genomes, the SV40 genome is a circular duplex DNA organized in a single replicon. This small viral genome, its association with host histones in nucleosomes, and its dependence on the host cell milieu for replication factors and precursors led to its adoption as a simple and powerful model. The steps in replication, the viral initiator, the host proteins, and their mechanisms of action were initially defined using a cell-free SV40 replication reaction. Although our understanding of the vastly more complex host replication fork is advancing, no eukaryotic replisome has yet been reconstituted and the SV40 paradigm remains a point of reference. This article reviews some of the milestones in the development of this paradigm and speculates on its potential utility to address unsolved questions in eukaryotic genome maintenance.

Full Report: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2718763/

“Duplication of the simian virus 40 genome is the best understood eukaryotic DNA replication process to date.”

BMJ • March 2009

Suspected contamination leads to recall of meningitis C vaccine

Caroline White

Two batches of meningitis C vaccine distributed to general practices across England have been recalled by the medicines watchdog amid fears that they may have been contaminated. The manufacturer, Novartis Vaccines, raised the alarm last week after routine sampling of a shipment of doses from the same two batches air freighted to the United States showed contamination with Staphylococcus aureus. The sterility of the solvent, aluminium hydroxide, which is used to mix the vaccine, had been compromised.

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http://www.bmj.com/content/338/bmj.b896.long

“The sterility of the solvent, aluminium hydroxide, which is used to mix the vaccine, had been compromised.”

Pharmacoepidemiological Drug Safety • March 2010

Safety assessment of recalled Haemophilus influenzae type b (Hib) conjugate vaccines United States, 2007-2008

Author information

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Abstract

PURPOSE

On 13 December 2007, Merck & Co., Inc. voluntarily recalled 1.2 million doses of Haemophilus influenzae type b (Hib) vaccines that had been distributed since April 2007 for concerns regarding potential Bacillus cereus contamination. Enhanced postrecall surveillance was conducted to detect vaccine-associated B. cereus infections.

METHODS

We reviewed reports involving recalled Hib vaccines received by the Vaccine Adverse Event Reporting System (VAERS) during 1 April 2007-29 February 2008. For each reported death, autopsy review sought evidence of B. cereus infections. For each specified outcome, the proportional reporting ratios (PRRs) were calculated to compare the recalled Hib vaccines with the manufacturer's nonrecalled Hib vaccines in the VAERS databases. On 20 December 2007, we used the Epidemic Information Exchange (Epi-X) to solicit nongastrointestinal vaccine-associated B. cereus infections, and requested B. cereus isolates for genotyping to compare with the manufacturing facility isolate.

RESULTS

VAERS received 75 reports involving recalled Hib vaccines; none described a confirmed B. cereus infection. Comparative analyses did not reveal disproportionate reporting of specified outcomes for recalled Hib vaccines. The Epi-X posting triggered one report of vaccine-associated B. cereus bacteremia from a child who received a nonrecalled Hib vaccine manufactured by Merck; the genotypes of isolates from the patient and the manufacturing facility differed.

CONCLUSIONS

No evidence of vaccine-associated B. cereus infection had been found in recipients of recalled Hib vaccines. Conducting laboratory surveillance through Epi-X was feasible and may enhance public health response capacities for future vaccine safety emergencies.

http://www.ncbi.nlm.nih.gov/pubmed/20084617

"On 13 December 2007, Merck & Co., Inc. voluntarily recalled 1.2 million doses of Haemophilus influenzae type b (Hib) vaccines that had been distributed since April 2007 ..."

Journal Of Virology • April 2010

Isolation of an Infectious Endogenous Retrovirus in a Proportion of Live Attenuated Vaccines for Pets

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Abstract

The genomes of all animal species are colonized by endogenous retroviruses (ERVs). Although most ERVs have accumulated defects that render them incapable of replication, fully infectious ERVs have been identified in various mammals. In this study, we isolated a feline infectious ERV (RD-114) in a proportion of live attenuated vaccines for pets. Isolation of RD-114 was made in two independent laboratories using different detection strategies and using vaccines for both cats and dogs commercially available in Japan or the United Kingdom. This study shows that the methods currently employed to screen veterinary vaccines for retroviruses should be reevaluated.

http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2838105/?tool=pubmed

“ In this study, we isolated a feline infectious ERV (RD-114) in a proportion of live attenuated vaccines for pets. Isolation of RD-114 was made in two independent laboratories using different detection strategies and using vaccines for both cats and dogs commercially available in Japan or the United Kingdom. This study shows that the methods currently employed to screen veterinary vaccines for retroviruses should be reevaluated.”

Veterinary Microbiology • April 2010

Atypical ‘HoBi’-like pestiviruses— recent findings and implications thereof

Author information

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Abstract

In 2004, an atypical pestivirus named D32/00_’HoBi’, isolated from foetal calf serum (FCS) originating from Brazil, was described (Schirrmeier et al., 2004). A few years later, a closely related virus (Th/04_KhonKaen) was detected in serum from a calf in Thailand, indicating that this group of atypical pestiviruses already is spread in cattle populations in various regions of the world. At the Friedrich-Loeffler-Institute, Insel Riems, Germany, FCS batches are regularly tested for pestivirus contamination, in general with positive PCR results, and in some cases the contaminants have been typed as ‘HoBi’-like. At the National Veterinary Institute (SVA) in Uppsala, Sweden, a recent event with contaminated FCS ruined much of the ongoing cell culture work. From the FCS and the contaminated cells we were able to amplify and sequence nucleic acid from three different pestivirus strains, including BVDV-1, -2 and ‘HoBi’-like; this in a commercial FCS that had been tested free from pestivirus by the manufacturer. In this short communication we review the current status of atypical ‘HoBi’-like pestiviruses, describe recent findings and discuss the implications thereof.

http://www.ncbi.nlm.nih.gov/pubmed/?term=19857934

“From the Fetal Calf Serum and the contaminated cells we were able to amplify and sequence nucleic acid from three different pestivirus strains, including BVDV-1, -2 and ‘HoBi’-like; this in a commercial FCS that had been tested free from pestivirus by the manufacturer.”

Biologicals • May 2010

Endogenous retroviruses as potential hazards for vaccines

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Abstract

Retroviruses are classified as exogenous or endogenous according to their mode of transmission. Generally, endogenous retroviruses (ERVs) are not pathogenic in their original hosts; however, some ERVs induce diseases. In humans, a novel gammaretrovirus was discovered in patients with prostate cancer or chronic fatigue syndrome. This virus was closely related to xenotropic murine leukemia virus (X-MLV) and designated as xenotropic murine leukemia virus-related virus (XMRV). The origin and transmission route of XMRV are still unknown at present; however, XMRV may be derived from ERVs of rodents because X-MLVs are ERVs of inbred and wild mice. Many live attenuated vaccines for animals are manufactured by using cell lines from animals, which are known to produce infectious ERVs; however, the risks of infection by ERVs from xenospecies through vaccination have been ignored. This brief review gives an overview of ERVs in cats, the potential risks of ERV infection by vaccination, the biological characteristics of RD-114 virus (a feline ERV), which possibly contaminates vaccines for companion animals, and the methods for detection of infectious RD-114 virus.

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“Many live attenuated vaccines for animals are manufactured by using cell lines from animals, which are known to produce infectious ERVs; however, the risks of infection by ERVs from xenospecies through vaccination have been ignored. This brief review gives an overview of ERVs in cats, the potential risks of ERV infection by vaccination, the biological characteristics of RD-114 virus (a feline ERV), which possibly contaminates vaccines for companion animals, and the methods for detection of infectious RD-114 virus.”

BMJ • May 2010

Australia suspends seasonal flu vaccination of young children

by Melissa Sweet

Australia has extended a suspension of vaccination of children aged 5 years and under against seasonal flu, pending further investigations into an apparent spike in febrile convulsions associated with the vaccine.

A temporary suspension was first announced on 23 April, after concerns emerged in Western Australia about an increase in the number of young children presenting to hospitals with febrile convulsion after receiving the trivalent seasonal flu vaccine.

The federal government's chief medical officer, Jim Bishop, announced on 30 April that more time was needed to complete epidemiological and scientific investigations.

"Given the ongoing and incomplete scientific and clinical case review, the moratorium on the use of seasonal influenza vaccine in children 5 years and less will continue," he said.

Figures released by the national Department of Health and Ageing show that 77 cases of febrile convulsion in children aged 5 or under and associated with the vaccination have recently been reported to the Therapeutic Goods Administration.

Of these, 57 were in Western Australia, the only Australian state to provide free seasonal flu vaccination for all children aged 6 months to 4 years. It introduced the vaccination programme in 2008 after the highly publicised deaths of three young children with flu and because of concerns that this age group has the highest hospitalisation rates for flu. About 35% of children under 5 in Western Australia are estimated to have received at least one dose of flu vaccine in 2008 and 2009, but it is not yet known how many have been vaccinated this season, Paul Armstrong of the state's health department told the BMJ.

A range of experts have said that it is unclear whether the cases of fever relate to a specific batch or product or to inclusion of the pandemic vaccine in a trivalent vaccine. Three companies market seasonal flu vaccines in Australia. They contain the components recommended by the Australian Influenza Vaccine Committee for the 2010 season (A/H1N1, A/H3N2, and B) (www.tga.gov.au/committee/aivc.htm).

The TGA is continuing to recommend the pandemic vaccine (active only against H1N1) for adults and children (www.tga.gov.au/alerts/medicines/fluvaccine.htm).

Other possibilities being investigated are whether febrile illness has increased more broadly this winter or whether the Western Australian programme has uncovered an increased risk among young children in particular.

Peter Richmond, a paediatrician in Perth, told ABC television this week that the association of fevers with the vaccination was striking (www.abc.net.au/7.30/content/2010/s2885203.htm). "This year has been something that I've never seen in 20 years as a paediatrician," he said. "We have had a large number of children presenting to their doctors who were previously well who received the flu vaccine, and they had a very sudden onset of this high fever. And obviously for parents of young children it was very scary, and unfortunately some of these children actually had febrile convulsions."

Professor Bishop told the BMJ he had an "open mind" about whether there was a real increase in side effects. "In the meantime it is prudent and safe to proceed cautiously," he said.

An industry funded group, the Influenza Specialist Group, has said that Queensland's government is also working closely with a local coroner regarding the death of a 2 year old girl who was found dead in her cot several hours after receiving a seasonal flu vaccine in early April (www.influenzaspecialistgroup.org.au/news-recent/143-seasonal-flu-vaccination-and-in-children-5-years-and-under-). Professor Bishop said that this case had not been reported to the Therapeutic Goods Administration.

A statement from the Department of Health and Ageing said that batch testing of the vaccine by the Therapeutic Goods Administration and other independent experts had so far shown the vaccine to be satisfactory, while testing by the major flu vaccine manufacturer CSL had found no abnormalities in its product. Further testing and experiments are planned.

Meanwhile, Julie Leask, a senior research fellow at the National Centre for Immunisation Research & Surveillance, said that public confidence in flu vaccination is likely to suffer, resulting in reduced vaccination coverage across all ages.
Peter Collignon, an infectious diseases specialist at the Australian National University, Canberra, said that the situation showed the need for better surveillance and evaluation of flu vaccination. "We're in a situation now where the government can't tell us how many doses of the vaccine have been given out or how many people have side effects," he said.

Dr Armstrong said that the vaccination programme would resume in Western Australia only when it was clear that it was safe to do so. He said, "The first thing we need to do is to work out [whether there] is a problem and what the magnitude is, and then to work out what the problem is; we don't know that at the moment."

http://www.ncbi.nlm.nih.gov/pubmed/20442237

BMJ • May 2010
Australia suspends seasonal flu vaccination of young children

Adverse events following influenza vaccination in Australia— should we be surprised?

There have been large numbers of major adverse reactions to this year's seasonal influenza vaccine in Australia, and the vaccine has been suspended for use in children aged five and under [1,2]. These reactions have occurred across the country and involved multiple batches of vaccine [2]. In the state of Western Australia where the problem was first detected, reports suggest that of the 20,000 to 30,000 children vaccinated, more than 250 had adverse reactions and 55 had febrile convulsions before vaccination was suspended in young children [2]. Assuming all convulsions were in children, about one child in every 500 vaccinated had a febrile convulsion. Across Australia, media accounts indicate that more than 400 adverse reactions [3] including 77 cases of febrile convulsion [1] have been reported by regulators. While attention remains focused on reactions in very young children, reports suggest only one-third of the reactions may have occurred in children under five [4].

Although this situation has triggered considerable controversy in Australia, the story has attracted little to no media attention in the US and Europe. Similarly, the media has paid little attention to a US H1N1 federal vaccine safety advisory committee which recently reported detecting signals for Guillain-Barre syndrome (GBS), Bell's palsy, and thrombocytopenia in the monovalent H1N1 (swine flu) vaccine [5]. The same monovalent H1N1 antigen component under review in the US is scheduled to be added to the US trivalent seasonal vaccine and is contained in the Australian trivalent seasonal vaccine and will be given to children, pregnant women and adults [6].

Data from a previous Australian study of H1N1 vaccine show that a large percentage of children developed fevers following vaccination — in children less than 3 years, between three and six in every ten vaccinated, depending on dose [7,8]. The data also show a dose response effect — the larger the vaccine dose, the more severe the harms. There was also an age relationship: children under the age of three developed fevers at more than twice the rate of older children [7,8]. The study was however underpowered to detect febrile convulsions at the current rates in Australia, with only 162 children below the age of three. The size problem was further aggravated by stratification by age group and antigen dose.

Presumably the vaccine manufacturer CSL, which sponsored the trial, and Australia's regulatory body, the Therapeutic Goods Administration (TGA), which used this data in approving the vaccine for children, were aware of these important findings. But authors of the study published earlier this year did not discuss the high incidence of fever associated with vaccination [7]; data were instead only reported in online-only supplementary tables [8].

Overall, the percentages of children under three who developed a fever after vaccination appear very high; thirty five per cent with the 15 ug dose and 62% after a 30 ug dose [7,8]. Of those that received a 7.5 ug dose in the seasonal influenza vaccine, 23% develop a fever of >38 degrees Celsius [6].

The large number of children suffering harms — and subsequent suspension of the vaccine — challenges the assumption that regulators are ensuring the safety and efficacy of all marketed therapeutics. Should we be surprised that these problems have occurred with influenza vaccine, a vaccine used for over 60 years, said to have "an established record of safety in all age groups"? [9]

There are actually relatively little data on the effects of vaccinating young children against influenza [10]. Some manufacturers have even withheld data from public scrutiny amidst general indifference [10,11]. Evidence from all comparative influenza vaccine studies shows that harms, when they are investigated, are not reported consistently and systematically [10,11].

As pandemic vaccines are provided to governments and not individuals and manufacturers are indemnified for damages caused to users [12-14], there seem to be few incentives for investigation of harms.

Last winter, the likelihood that a child without risk factors would die from swine flu was less than one in a million [15]. When such a high proportion of children develop moderate to severe febrile reactions to the influenza vaccine, it's likely that more harm than good will occur by vaccinating the entire population.

If such a large proportion of children develop high fevers, it is also likely that a substantial number will develop febrile convulsions as a result of vaccination. It is thus surprising the vaccine was approved for this age group. It is also surprising that more explicit warnings about the high risk of adverse reactions were not given to parents when their children were being vaccinated. Passive surveillance (as in Australia and elsewhere) is a relatively weak mechanism to detect and evaluate post-vaccination adverse events [16].

Unlike most drugs, vaccines are used on a population basis triggered by public health policy. As such, evidence of their safety and efficacy needs to be extraordinarily rigorous and evaluation methods and data should be open to independent scrutiny. We need much better and larger studies on both safety and efficacy before we roll out influenza vaccine programs to all populations, especially to children who appear to have much higher rates of adverse reactions. Finally, decisions to use a vaccine in a population must consider its safety profile, but principally its effectiveness. There is poor evidence on how well influenza vaccines prevent any influenza complications in children [10] and other age groups. There is good evidence that influenza vaccines study reports cherry pick results and achieve spurious notoriety [17]. Exposing human beings to uncertain effects is a risky business.

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"The large number of children suffering harms — and subsequent suspension of the vaccine — challenges the assumption that regulators are ensuring the safety and efficacy of all marketed therapeutics. Should we be surprised that these problems have occurred with influenza vaccine, a vaccine used for over 60 years, said to have "an established record of safety in all age groups"?

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As pandemic vaccines are provided to governments and not individuals and manufacturers are indemnified for damages caused to users, there seem to be few incentives for investigation of harms."

Journal Of Virology • June 2010

Viral Nucleic Acids in Live-Attenuated Vaccines: Detection of Minority Variants and an Adventitious Virus †

Author Information

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Highly effective, safe, and relatively inexpensive, live-attenuated viruses protect against numerous human and animal viral infections. Attenuation is achieved by genetically adapting viruses for replication in a different host species or under nonphysiological conditions, such that viruses lose their pathogenic potential in their original host species while remaining sufficiently antigenic to induce lasting protective immunity. Live-attenuated vaccines are highly efficacious due to the physiologic presentation of native antigen to the host's immune system and include the earliest human vaccine developed by serial passages of rabies virus in rabbits. In very rare instances, one attenuated viral vaccine, the oral poliovirus vaccine (OPV), can accumulate mutations as well as recombine with other coinfecting enteroviruses and revert to a pathogenic state (18, 24). Attenuated live vaccines also carry a potential risk of contamination with adventitious viruses introduced during the attenuation process, from the cell lines used, and/or from the animal sera or other biologics often used in cell cultures. Very early Theiler's yellow fever attenuated virus was once "stabi- lized" with human plasma thought to contain hepatitis B virus, resulting in many cases of hepatitis (5, 28). Some early Sabin poliovirus vaccines were contaminated with the simian virus 40 (SV40) polyomavirus from the monkey cells used to amplify polioviruses. While carcinogenic in rodents, SV40 has no epidemiologic association with human cancers (10). Avian leuko- sis virus (ALV) and endogenous avian virus (AEV) have been reported in attenuated vaccines grown in chicken embryo fi- broblasts (CEF), but extensive testing has also ruled out hu- man infections (14, 15). Vaccine-associated ALV and AEV are thought to originate from endogenous retroviruses in the chicken germ line (14, 15, 17).

Because the chemical inactivation used in the manufacture of killed-virus vaccines is also likely to inactivate adventitious viruses, we focused on eight live-attenuated viruses, OPV (Biopolio), rubella (Meruvax-II), measles (Attenuvax), yellow fever (YF-Vax), human herpesvirus 3 (HHV-3) (Varivax), rotavirus (Rotarix and Rotateq), and multivalent measles/ mumps/rubella (MMR-II), to resequence the attenuated viruses and test for the presence of adventitious viruses after viral particle purification, massively parallel pyrosequencing, and viral sequence similarity searches. Vaccine nucleic acids were also analyzed using a panmicrobial microarray.

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† The authors have paid a fee to allow immediate free access to this article.

Full Report: http://jvi.asm.org/content/84/12/6033.full.pdf

"In very rare instances, one attenuated viral vaccine, the oral poliovirus vaccine (OPV), can accumulate mutations as well as recombine with other coinfecting enteroviruses and revert to a pathogenic state."

“Recently discovered contamination of 2 rotavirus vaccines by pig viruses is unlikely to pose a human health threat, according to the US Food and Drug Administration (FDA).”

Journal Of The American Medical Association (JAMA) • July 2010
Medical News and Perspectives

FDA: Benefits of Rotavirus Vaccination Outweigh Potential Contamination Risk

by Bridget M. Kuehn

Recently discovered contamination of 2 rotavirus vaccines by pig viruses is unlikely to pose a human health threat, according to the US Food and Drug Administration (FDA). The agency recommended in May that physicians resume use of one vaccine, Rotarix, and continue use of the other vaccine, RotaTeq.

On March 22, the FDA had recommended that physicians suspend the use of Rotarix after the agency learned that academic researchers made the unexpected finding that the vaccine contained DNA from porcine circovirus 1 (PCV1), a virus that is common in US swine but not associated with illness in pigs or humans (Victoria JG et al. J Virol. 2010;84[12]:6033-6040). This finding was confirmed by scientists from the FDA and the vaccine’s maker, GlaxoSmithKline.

http://jama.jamanetwork.com/article.aspx?articleid=186166

Expert Review Of Vaccines • October 2010

MF59; as a vaccine adjuvant: a review of safety and immunogenicity

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Abstract

Approximately 70 years passed between the licensing of alum salts as vaccine adjuvants and that of MF59, an oil-in-water emulsion, is currently licensed for use in the elderly as an adjuvant in seasonal influenza vaccines. Its mechanism of action is not fully understood, but enhancement of the interaction between the antigen and the dendritic cell seems to be involved. When used with seasonal influenza vaccines, an increase occurs in the hemagglutination inhibition antibody titers against some, but not all, seasonal vaccine influenza strains. The adjuvant effect is more pronounced when MF59 is combined with novel influenza antigens such as H9 and H5. The use of the adjuvant is associated with an increase in the frequency of local and systemic early post-vaccine adverse events (3-7 days), but no increase in adverse events was observed thereafter. Currently, MF59 is under evaluation as an adjuvant with other antigens such as pandemic influenza antigens and cytomegalovirus antigens.

http://www.ncbi.nlm.nih.gov/pubmed/20923265

“Currently, MF59 [squalene] is under evaluation as an adjuvant with other antigens such as pandemic influenza antigens and cytomegalovirus antigens.”

Toxicology • December 2010

Interindividual variations in the efficacy and toxicity of vaccines

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Abstract

A number of currently available vaccines have shown significant differences in the magnitude of immune responses and toxicity in individuals undergoing vaccination. A number of factors may be involved in the variations in immune responses, which include age, gender, race, amount and quality of the antigen, the dose administered and to some extent the route of administration, and genetics of immune system. Hence, it becomes imperative that researchers have tools such as genomics and proteomics at their disposal to predict which set of population is more likely to be non-responsive or develop toxicity to vaccines. In this article, we briefly review the influence of pharmacogenomics biomarkers on the efficacy and toxicity of some of the most frequently reported vaccines that showed a high rate of variability in response and toxicity towards hepatitis B, measles, mumps, rubella, influenza, and AIDS/HIV.

http://www.ncbi.nlm.nih.gov/pubmed/19837123

“A number of currently available vaccines have shown significant differences in the magnitude of immune responses and toxicity in individuals undergoing vaccination.”

“When Eric Delwart couldn’t find the right email addresses online to contact GlaxoSmithKline ...”

Nature Medicine • 2010

Vaccine contamination prompts safety review

Megan Scudellari

When Eric Delwart couldn’t find the right email addresses online to contact GlaxoSmithKline (GSK) in early February, he posted a good old-fashioned letter to the Belgian headquarters of the pharma giant to inform the company that one of its vaccines was contaminated with a pig virus. Months earlier, Delwart, a viral…

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http://www.nature.com/nm/journal/v16/n5/full/nm0510-493.html

Vaccine • April 2011

Plaque purification as a method to mitigate the risk of adventitious-agent contamination in influenza vaccine virus seeds

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Abstract

At present, the seed viruses for the manufacture of licensed seasonal inactivated influenza vaccines in the United States are derived from primary egg isolates as a result of concerns associated with adventitious agents. According to the prevailing view, the passage of influenza viruses through eggs serves as a filtering step to remove potential contaminating viruses. We have investigated the feasibility of addressing adventitious-agent risk by subjecting influenza virus to a plaque-purification procedure using MDCK cells. SV40 and canine adenovirus-1 (representing viruses for which MDCK cells are non-permissive and permissive, respectively) were used as challenge viruses to model agents of concern that might be co-isolated along with the influenza virus. By mixing influenza virus strain A/PR/8/34 with varying amounts of each challenge virus and then performing a plaque assay for influenza virus using MDCK cells, we have attempted to determine the efficiency by which the challenge virus is removed. Our data suggest that substantial removal can be achieved even after a single round of plaque purification. If cell-derived isolates were deemed to be acceptable following a plaque-purification procedure, the manufacture of seasonal influenza vaccine would be facilitated by: (1) the expansion of the repertoire of viruses from which seed virus candidates could be generated for licensed egg-derived vaccines as well as for vaccines manufactured in mammalian cells; and (2) the mitigation of adventitious-agent risk associated with the seed virus, and hence the elimination of the need to passage seed viruses in eggs for vaccines manufactured in mammalian cells.

http://www.ncbi.nlm.nih.gov/pubmed/21354480

“At present, the seed viruses for the manufacture of licensed seasonal inactivated influenza vaccines in the United States are derived from primary egg isolates as a result of concerns associated with adventitious agents. According to the prevailing view, the passage of influenza viruses through eggs serves as a filtering step to remove potential contaminating viruses.”

Vaccine • October 2011

Investigations of porcine circovirus type 1 (PCV1) in vaccine-related and other cell lines

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Abstract

Porcine circovirus type 1 (PCV1) is highly prevalent in swine and was recently reported in some rotavirus vaccines. Since animal-derived raw materials, such as cells, trypsin, and serum, can be a major source of introducing virus contamination in biological products, we have investigated PCV1 in several cell lines obtained from ATCC that have broad use in research, diagnostics, or vaccine development. It is expected that these cell lines have been exposed to bovine and porcine viruses during their establishment and passage history due to the use of serum and trypsin that was not qualified according to current testing guidances or processed using new virus-inactivation methods. This study showed that Vero, MRC-5, and CEFs, which represent cell substrates used in some U.S. licensed vaccines, and other cell lines used in investigational vaccines, such as MDCK, HEK-293, HeLa, and A549, were negative for PCV1 using a nested PCR assay; some were also confirmed negative by infectivity analysis. However, MDBK cells, which are used for some animal vaccines, contained PCV1 sequences, although no virus was isolated. Although the results showed that PCV infection may not have occurred under previous culture conditions, the recent cases of vaccine contamination emphasizes the need for continued efforts to reduce the likelihood of introducing viruses from animal-derived materials used in product manufacture.

http://www.sciencedirect.com/science/article/pii/S0264410X1101173X

[click Science Direct]

“Although the results showed that Porcine Circovirus infection may not have occurred under previous culture conditions, the recent cases of vaccine contamination emphasizes the need for continued efforts to reduce the likelihood of introducing viruses from animal-derived materials used in product manufacture.”

Expert Review Of Respiratory Medicine • October 2011

Simian virus 40 transformation, malignant mesothelioma and brain tumors

Author information

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Abstract

Simian virus 40 (SV40) is a DNA virus isolated in 1960 from contaminated polio vaccines, that induces mesotheliomas, lymphomas, brain and bone tumors, and sarcomas, including osteosarcomas, in hamsters. These same tumor types have been found to contain SV40 DNA and proteins in humans. Mesotheliomas and brain tumors are the two tumor types that have been most consistently associated with SV40, and the range of positivity has varied about from 6 to 60%, although a few reported 100% of positivity and a few reported 0%. It appears unlikely that SV40 infection alone is sufficient to cause human malignancy, as we did not observe an epidemic of cancers following the administration of SV40-contaminated vaccines. However, it seems possible that SV40 may act as a cofactor in the pathogenesis of some tumors. In vitro and animal experiments showing cocarcinogenicity between SV40 and asbestos support this hypothesis.

Full Report: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3241931/

“it seems possible that SV40 may act as a cofactor in the pathogenesis of some tumors. In vitro and animal experiments showing cocarcinogenicity between SV40 and asbestos support this hypothesis.”

Journal of Public Health Management & Practice • November 2011

Using an Immunization Information System to Facilitate a Vaccine Recall in New York City 2007

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Abstract

Background

In December 2007, Merck & Co, Inc, initiated a voluntary recall of 10 lots of PedvaxHIB, and 2 lots of COMVAX when the potential of contamination was identified during routine testing of the manufacturing equipment. Merck recommended that providers stop vaccinating children using these vaccine lots.

Objective

To describe how the New York City (NYC) Immunization Information System was used in the effort to recall vaccines.

Methods

Immediately following Merck's announcement, NYC's Bureau of Immunization used the New York Citywide Immunization Registry (CIR) to (a) fax and e-mail all pediatric facilities a letter informing them of the recall and asking that they immediately remove recalled vaccines from their refrigerators; (b) identify facilities that had used the recalled lots, on the basis of data reported to the CIR, and contact them individually by phone; and (c) monitor the success of the recall by examining the number of recalled doses administered and reported to the CIR before and after the recall.

Results

The alert was faxed and e-mailed to 1928 pediatric facilities informing them of the recall. In addition, the Bureau of Immunization identified 105 facilities that had reported doses of vaccine from the recalled lots to the CIR and called to ask them to check their refrigerators for remaining supplies and discontinue use of this vaccine. The number of doses with the affected lot numbers reported to the CIR decreased sharply following CIR recall notification. Furthermore, the Centers for Disease Control and Prevention and Merck reported the return of nearly 50% of publicly and privately purchased vaccines from the recalled lots that had been distributed to NYC providers.

Conclusion

Immunization Information Systems can be effective tools for quickly identifying providers in possession of recalled vaccine lots, particularly when lot numbers are well reported, and for facilitating rapid vaccine recall in support of vaccine safety.

"In December 2007, Merck & Co, Inc, initiated a voluntary recall of 10 lots of PedvaxHIB, and 2 lots of COMVAX when the potential of contamination was identified during routine testing of the manufacturing equipment. Merck recommended that providers stop vaccinating children using these vaccine lots."

http://journals.lww.com/jphmp/pages/articleviewer.aspx?year=2011&issue=11010&article=00014&type=abstract

“Because the product is itself a virus,

traditional viral clearance steps are generally not included in the manufacturing process ...”

PDA Journal Of Pharmaceutical Science And Technology • November 2011

Application of Risk Assessments in the Design of the Overall Viral Control Strategy Used during the Manufacture and Testing of Live Virus Vaccines

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Abstract

CONFERENCE PROCEEDING

Proceedings of the PDA/FDA Adventitious Viruses in Biologics: Detection and Mitigation Strategies Workshop in Bethesda, MD, USA; December 1-3, 2010 Guest Editors: Arifa Khan (Bethesda, MD), Patricia Hughes (Bethesda, MD) and Michael Wiebe (San Francisco, CA) It is important to include a risk assessment process in the overall viral control strategy used during the manufacture and testing of live virus vaccines. Because the product is itself a virus, traditional viral clearance steps are generally not included in the manufacturing process, and there is normally no inactivation step in the manufacturing process either. The risk assessment is therefore necessary to identify potential sources for entry of adventitious agents into the vaccine, and to develop a strategy to minimize or eliminate the sources through which adventitious agents can enter the vaccine. The risk assessment can also be used to tailor the biosafety testing that is performed on raw materials, vaccine seeds, vaccine bulk materials, and final product. Biosafety testing is normally designed to ensure the detection of both known and unknown adventitious agents, but the results of the risk assessment can be used to put in place a biosafety testing strategy designed to maximize the detection of an adventitious agent that is potentially likely to be present in the vaccine. The risk assessment therefore enables the development of a comprehensive viral control strategy and provides a higher level of assurance that the vaccine will be free from contamination by adventitious agents.

http://www.ncbi.nlm.nih.gov/pubmed/22294607

J Neurology, Neurosurgery And Psychiatry • 2012

Contamination with gangliosides in brain-derived rabies vaccine may trigger Guillain–Barré syndrome

Author Information

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Abstract

Guillain–Barré syndrome (GBS) is an autoimmune-mediated peripheral neuropathy typically occurring after microbial infections such as Campylobacter jejuni enteritis. It can also occur following vaccinations such as the 1976 swine flu vaccine in the USA.1 GBS is divided into demyelinating and axonal subtypes. There is now good evidence that gangliosides or similar components trigger the development of axonal GBS.2 Axonal GBS associated with IgG anti-GM1 or anti-GD1a antibodies after bovine brain ganglioside administration have been recorded in several patients. Sensitisation of rabbits with bovine brain gangliosides or isolated GM1 produced a replica of axonal GBS. Based on these findings, it has been suggested that C jejuni components mimic human gangliosides GM1 and GD1a, and C jejuni infection induces the production of autoantibodies against the gangliosides that are expressed in the peripheral nerves, resulting in the limb weakness seen in GBS. By contrast, the mechanism by which certain vaccines elicit the development of GBS remains unresolved, although there have been studies to suggest that the 1976 swine flu vaccine could elicit anti-GM1 antibodies in mice and that the GM1 epitope was present in the influenza haemagglutinin.3 It is important to understand the pathogenesis of postvaccination GBS to allow safer vaccines to be developed.

http://jnnp.bmj.com/content/83/4/467.extract

“There is now good evidence that gangliosides or similar components trigger the development of axonal Guillain–Barré syndrome (GBS).”

Biologicals • January 2012

A need for careful evaluation of endotoxin contents in acellular pertussis-based combination vaccines

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Abstract

Two batches each of diphtheria-tetanus-acellular pertussis vaccine (DTaP) and that combined with inactivated polio vaccine purchased from foreign markets were tested by mouse body weight decreasing (BWD) toxicity test and Limulus amaebocyte lysate (LAL) test. Three out of the four imported vaccine batches showed the levels of BWD toxicity even comparable to that of DT-whole cell pertussis vaccine. BWD toxicity test is based on endotoxin dose-dependent weight loss of mice and has been used for controlling endotoxin in DTaP. Although of the strong BWD toxicity of the imported vaccines, there was no marked difference in LAL test results between the imported vaccines and Japanese DTaP. However, one imported DTaP batch showed very strong interference with LAL activity of spiked lipopolysaccharide (LPS). The batch interfered not only with LAL activity but also with pyrogenicity and prostaglandin E2 induction activity. However, the pyrogenicity of the spiked LPS could be recovered from the precipitated fraction of the batch by treating with phosphate buffer to suggest the possibility of recovering in vivo toxicity. As an adequate in vitro test method could not be identified for controlling the safety of the interfering batch, an appropriate in vivo test would be required for testing such vaccines.

http://www.sciencedirect.com/science/article/pii/S1045105611001977

“However, the pyrogenicity of the spiked LPS could be recovered from the precipitated fraction of the batch by treating with phosphate buffer to suggest the possibility of recovering in vivo toxicity. As an adequate in vitro test method could not be identified for controlling the safety of the interfering batch, an appropriate in vivo test would be required for testing such vaccines.”

Pharmacoepidemiology And Drug Safety • April 2012

Vaccine discontinuation and switching following regulatory interventions in response to rotavirus vaccine contamination with porcine circovirus DNA fragments

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Abstract

PURPOSE

The Food and Drug Administration temporarily suspended monovalent rotavirus vaccine (RV1) use following discovery of contamination with porcine circovirus fragments and subsequently announced similar contamination of the pentavalent rotavirus vaccine (RV5) but recommended continued use of the product. We assessed the utilization of these vaccines in relation to the announcements.

METHODS

Using claims submitted to a commercial health insurer for administration of RV1 and RV5, we estimated the number of administrations of the vaccines and the extent of switching between RV1 and RV5. Procedure codes on submitted claims identified vaccine administrations among infants ≤ 1 year old through 16 June 2010. Among infants who received a first dose of vaccine before the corresponding announcement, and whose second dose was anticipated following the announcement, we estimated the number who received no second dose of rotavirus vaccine.

RESULTS

There were 31 178 RV1 initiators and 514 357 RV5 initiators. We observed a 93% reduction in RV1 doses in the month following the recommended suspension of use, coupled with extensive switching to RV5 (90% of subsequent doses) and a reduction in second RV1 doses (from 35.5% incomplete to 40.9%). There was a 15% increase in number of RV5 administrations following announcement of its contamination, with little switching to RV1 but with a possible decrease in completion.

CONCLUSIONS

Recommended suspension of RV1 use led to a substantial decrease in use and extensive switching to RV5. The announcement that RV5 was similarly contaminated, but without a corresponding recommendation to suspend use, had little effect on use.

http://www.ncbi.nlm.nih.gov/pubmed/22290786

“The Food and Drug Administration temporarily suspended monovalent rotavirus vaccine (RV1) use following discovery of contamination with porcine circovirus fragments and subsequently announced similar contamination of the pentavalent rotavirus vaccine (RV5) but recommended continued use of the product.”

Biologicals • July 2012

Investigation of porcine circovirus contamination in human vaccines

Author Information

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Javier Martina, Philip Minora, Silke Schepelmanna,

Abstract

DNA from porcine circovirus type 1 (PCV1) and 2 (PCV2) has recently been detected in two vaccines against rotaviral gastroenteritis from manufacturers A and B. We investigated if PCV1 sequences are present in other viral vaccines. We screened seeds, bulks and final vaccine preparations from ten manufacturers using qRT-PCR. We detected 3.8 × 103 to 1.9 × 107 PCV1 DNA copies/milliliter in live poliovirus seeds for inactivated polio vaccine (IPV) from manufacturer A, however, following inactivation and purification, the finished IPV was PCV1-negative. PCV1 DNA was not detectable in live polio preparations from other vaccine producers. There was no detectable PCV1 DNA in the measles, mumps, rubella and influenza vaccines analysed including material supplied by manufacturer A. We confirmed that the PCV1 genome in the rotavirus vaccine from manufacturer A is near full-length. It contains two mutations in the PCV cap gene, which may result from viral adaptation to Vero cells. Bulks of this vaccine contained 9.8 × 1010 to 1.8 × 1011 PCV1 DNA copies/millilitre and between 4.1 × 107 and 5.5 × 108 DNA copies were in the final doses. We found traces of PCV1 and PCV2 DNA in the rotavirus vaccine from manufacturer B. This highlights the issue of vaccine contamination and may impact on vaccine quality control.

http://www.sciencedirect.com/science/article/pii/S1045105612000267

“We found traces of PCV1 and PCV2 DNA in the rotavirus vaccine from manufacturer B. This highlights the issue of vaccine contamination and may impact on vaccine quality control.”

Voprosy Virusologii • September 2012

Analysis of the cell tissue culture contamination with the bovine viral diarrhea virus and mycoplasmas

Author Information

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Abstract

Different cell tissue cultures and commercial fetal calf sera (FTS) used in biological and virological research were screened for the bovine viral diarrhea virus (BVDV, Pestivirus genus, Flaviviridae family) and mycoplasma contamination. BVDV was detected using RT-PCR and Indirect immunofluorescence (with monoclonal antibodies) methods in 33% cases of the studied cell lines and in > 60% cases of FCS. BVDV was shown to present and reproduce in high spectra of human cell lines, as well as in monkey, pig, rabbit, goat, dog, and cat cells at high levels (up to 100-1000 genome-equivalent copies per cell) and reached up to 10(3)-10(7) genome-equivalent copies per serum ml. The molecular mechanisms of the long virus persistence without definite signs of destruction should be studied.

http://www.ncbi.nlm.nih.gov/pubmed/?term=23248854

“Bovine Viral Diarrhea Virus was detected using RT-PCR and Indirect immunofluorescence (with monoclonal antibodies) methods in 33% cases of the studied cell lines and in > 60% cases of Fetal Calf Serum.”

PLoS Pathogens • November 2012

A Wolf in Sheep's Clothing: SV40 Co-opts Host Genome Maintenance Proteins to Replicate Viral DNA

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Abstract

Simian virus 40 (SV40) was discovered in 1960 as a contaminant in early polio vaccines. Its discovery coincided with an explosion of knowledge in the new field of molecular biology, and SV40 was quickly adopted as a model to study eukaryotic genome structure, expression, replication, and cell growth regulation in cultured cells [1]. With a genome of only 5.2 kbp, SV40 relies heavily on host cell machinery to propagate, affording investigators a powerful tool to discover key host proteins that the virus manipulates. Indeed, a single multifunctional viral protein, the large tumor (T) antigen (Tag) (Figure 1A), is sufficient to orchestrate the replication of the viral mini-chromosome in infected monkey cells [2], [3]. The origin DNA binding domain of Tag binds specifically to the viral origin of DNA replication, and the C-terminal helicase domain of Tag unwinds parental DNA at SV40 replication forks. The development of a cell-free reaction containing purified Tag and primate cell extract enabled the identification of ten evolutionarily conserved host proteins that are necessary and sufficient, together with Tag, to replicate SV40 DNA in vitro [3], [4]. Thus, much remains to be learned about how SV40 infection activates DNA damage signaling and uses it to facilitate viral propagation.

Full Report: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3493471/

"Simian virus 40 (SV40) was discovered in 1960 as a contaminant in early polio vaccines ... much remains to be learned about how SV40 infection activates DNA damage signaling and uses it to facilitate viral propagation."

Journal Of Inorganic Biochemistry • December 2012

Detection of human papillomavirus (HPV) L1 gene DNA possibly bound to particulate aluminum adjuvant in the HPV vaccine Gardasil

Author information

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Abstract

Medical practitioners in nine countries submitted samples of Gardasil (Merck & Co.) to be tested for the presence of human papillomavirus (HPV) DNA because they suspected that residual recombinant HPV DNA left in the vaccine might have been a contributing factor leading to some of the unexplained post-vaccination side effects. A total of 16 packages of Gardasil were received from Australia, Bulgaria, France, India, New Zealand, Poland, Russia, Spain and the United States. A nested polymerase chain reaction (PCR) method using the MY09/MY11 degenerate primers for initial amplification and the GP5/GP6-based nested PCR primers for the second amplification were used to prepare the template for direct automated cycle DNA sequencing of a hypervariable segment of the HPV L1 gene which is used for manufacturing of the HPV L1 capsid protein by a DNA recombinant technology in vaccine production. Detection of HPV DNA and HPV genotyping of all positive samples were finally validated by BLAST (Basic Local Alignment Search Tool) analysis of a 45-60 bases sequence of the computer-generated electropherogram. The results showed that all 16 Gardasil samples, each with a different lot number, contained fragments of HPV-11 DNA, or HPV-18 DNA, or a DNA fragment mixture from both genotypes. The detected HPV DNA was found to be firmly bound to the insoluble, proteinase-resistant fraction, presumably of amorphous aluminum hydroxyphosphate sulfate (AAHS) nanoparticles used as adjuvant. The clinical significance of these residual HPV DNA fragments bound to a particulate mineral-based adjuvant is uncertain after intramuscular injection, and requires further investigation for vaccination safety.

http://www.ncbi.nlm.nih.gov/pubmed/23078778

“Medical practitioners in nine countries submitted samples of Gardasil (Merck & Co.) to be tested for the presence of human papillomavirus (HPV) DNA because they suspected that residual recombinant HPV DNA left in the vaccine might have been a contributing factor leading to some of the unexplained post-vaccination side effects.
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“This enables quick, safe, and cost-effective vaccine production that would be required in case of a pandemic.”

Journal of Laboratory Automation • December 2012

Automated production of plant-based vaccines and pharmaceuticals

Author information

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Abstract

A fully automated “factory” was developed that uses tobacco plants to produce large quantities of vaccines and other therapeutic biologics within weeks. This first-of-a-kind factory takes advantage of a plant viral vector technology to produce specific proteins within the leaves of rapidly growing plant biomass. The factory’s custom-designed robotic machines plant seeds, nurture the growing plants, introduce a viral vector that directs the plant to produce a target protein, and harvest the biomass once the target protein has accumulated in the plants-all in compliance with Food and Drug Administration (FDA) guidelines (e.g., current Good Manufacturing Practices). The factory was designed to be time, cost, and space efficient. The plants are grown in custom multiplant trays. Robots ride up and down a track, servicing the plants and delivering the trays from the lighted, irrigated growth modules to each processing station as needed. Using preprogrammed robots and processing equipment eliminates the need for human contact, preventing potential contamination of the process and economizing the operation. To quickly produce large quantities of protein-based medicines, we transformed a laboratory-based biological process and scaled it into an industrial process. This enables quick, safe, and cost-effective vaccine production that would be required in case of a pandemic.

http://www.ncbi.nlm.nih.gov/pubmed/23015521

Archives Of Virology • January 2013

Genetic characterization of bovine viral diarrhoea (BVD) viruses: confirmation of the presence of BVD genotype 2 in Africa

Author information

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Abstract

Bovine viral diarrhoea virus (BVDV) has emerged as one of the economically important pathogens in cattle populations, with a worldwide distribution and causing a complex of disease syndromes. Two genotypes, BVDV 1 and 2, exist and are discriminated on the basis of the sequence of the 5' non-coding region (5' NCR) using real-time PCR. Real-time PCR is more sensitive, specific, and less time-consuming than conventional PCR, and it has less risk of cross-contamination of samples. Limited information exists on BVDV genetic subtypes in South Africa. The aim of this study was to determine the genotypes of BVDV currently circulating in South African feedlots. A total of 279 specimens (219 tissue samples, 59 trans-tracheal aspirates and 1 blood sample) were collected from dead and living cattle with lesions or clinical signs compatible with BVDV infection. Pooled homogenates from the same animals were prepared, and total RNA was extracted. A screening test was performed on the pooled samples, and positive pools were investigated individually. A Cador BVDV Type 1/2 RT-PCR Kit (QIAGEN, Hilden, Germany) was used for the real-time PCR assay on a LightCycler(®) V2.0 real-time PCR machine (Roche Diagnostics, Mannheim, Germany). The results were read at 530 and 640 nm for BVDV 1 and 2, respectively. Bovine viral diarrhoea virus was detected in a total of 103 samples that included 91 tissue samples, 1 blood sample and 11 trans-tracheal aspirates. Eighty-five (82.5 %) of the strains were genotype 1 and 18 (17.5 %) were genotype 2. Comparing the sequencing data, genotypes 1 and 2 from the field strains did not cluster with vaccine strains currently used in feedlots in South Africa. The present study revealed the presence of BVDV genotype 2 in cattle in South Africa based on the high sequence similarity between genotype 2 field strains and strain 890 from North America. The presence of genotype 2 viruses that phylogenetically belong to different clusters and coexist in feedlots is consistent with the possibility of multiple virus introductions. These results represent the first documented evidence for the presence of BVDV genotype 2 in African cattle.

http://www.ncbi.nlm.nih.gov/pubmed/?term=23011308

"These results represent the first documented evidence for the presence of BVDV genotype 2 in African cattle."

Journal Of Veterinary Diagnostic Investigation • January 2013

HoBi-like viruses: an emerging group of pestiviruses

Author information

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Abstract

The genus Pestivirus is composed of 4 important pathogens of livestock: Bovine viral diarrhea virus 1 and 2 (BVDV-1 and BVDV-2), Classical swine fever virus (CSFV), and Border disease virus of sheep (BDV). BVDV are major pathogens of cattle, and infection results in significant economic loss worldwide. A new putative pestivirus species, tentatively called "HoBi-like," "BVDV-3," or "atypical pestiviruses," was first identified in Europe in fetal bovine serum (FBS) imported from Brazil. HoBi-like viruses are related to BVDV at the genetic and antigenic levels. Further, the disease caused by these new viruses resembles clinical presentations historically associated with BVDV infection, including growth retardation, reduced milk production, respiratory disease, reduced reproductive performance, and increased mortality among young stock. Current BVDV diagnostic tests may fail to detect HoBi-like viruses or to differentiate between BVDV and HoBi-like viruses. Further, commercial tests for BVDV exposure, based on serological response, do not reliably detect HoBi-like virus exposure, and cross protection against HoBi-like viruses conferred by current BVDV vaccines is likely limited. As many HoBi-like viruses, characterized to date, were isolated from FBS originating from Brazil, it is assumed that the agent is probably widespread in Brazilian herds. Nevertheless, reports of natural infection in Southeast Asia and Europe demonstrate that these viruses are not restricted to South America. Increased demand for FBS has led to widespread distribution of FBS originating in HoBi-like virus endemic regions. The contamination of such FBS with HoBi-like viruses may lead to spread of this virus to other regions.

http://www.ncbi.nlm.nih.gov/pubmed/?term=23345268

Full Report

http://vdi.sagepub.com/content/25/1/6.long

"Increased demand for fetal bovine serum has led to widespread distribution of fetal bovine serum originating in HoBi-like virus endemic regions. The contamination of such fetal bovine serum with HoBi-like viruses may lead to spread of this virus to other regions."

[fetal bovine serum is an important element of cell research and cell culture applications, especially in vaccine research. Estimated sales of fetal bovine serum in 2008 reached 700,000 liters globally]

ISRN Biochemistry • May 2013

Nanoparticles for Brain Drug Delivery

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Abstract

The central nervous system, one of the most delicate microenvironments of the body, is protected by the blood-brain barrier (BBB) regulating its homeostasis. BBB is a highly complex structure that tightly regulates the movement of ions of a limited number of small molecules and of an even more restricted number of macromolecules from the blood to the brain, protecting it from injuries and diseases. However, the BBB also significantly precludes the delivery of drugs to the brain, thus, preventing the therapy of a number of neurological disorders. As a consequence, several strategies are currently being sought after to enhance the delivery of drugs across the BBB. Within this review, the recently born strategy of brain drug delivery based on the use of nanoparticles, multifunctional drug delivery systems with size in the order of one-billionth of meters, is described. The review also includes a brief description of the structural and physiological features of the barrier and of the most utilized nanoparticles for medical use. Finally, the potential neurotoxicity of nanoparticles is discussed, and future technological approaches are described. The strong efforts to allow the translation from preclinical to concrete clinical applications are worth the economic investments.

Full Report

http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4392984/

“several strategies

are currently being sought after to enhance the

delivery of drugs across the Blood Brain Barrier ...

based on the use of nanoparticles ... the potential

neurotoxicity of nanoparticles is discussed”

Vaccine • July 2013

Transposon leads to contamination of clinical pDNA vaccine

Author information

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Abstract

We report an unexpected contamination during clinical manufacture of a Human Papilomavirus (HPV) 16 E6 encoding plasmid DNA (pDNA) vaccine, with a transposon originating from the Escherichia coli DH5 host cell genome. During processing, presence of this transposable element, insertion sequence 2 (IS2) in the plasmid vector was not noticed until quality control of the bulk pDNA vaccine when results of restriction digestion, sequencing, and CGE analysis were clearly indicative for the presence of a contaminant. Due to the very low level of contamination, only an insert-specific PCR method was capable of tracing back the presence of the transposon in the source pDNA and master cell bank (MCB). Based on the presence of an uncontrolled contamination with unknown clinical relevance, the product was rejected for clinical use. In order to prevent costly rejection of clinical material, both in-process controls and quality control methods must be sensitive enough to detect such a contamination as early as possible, i.e. preferably during plasmid DNA source generation, MCB production and ultimately during upstream processing. However, as we have shown that contamination early in the process development pipeline (source pDNA, MCB) can be present below limits of detection of generally applied analytical methods, the introduction of "engineered" or transposon-free host cells seems the only 100% effective solution to avoid contamination with movable elements and should be considered when searching for a suitable host cell-vector combination.

http://www.ncbi.nlm.nih.gov/pubmed/23707695

"We report an unexpected contamination during clinical manufacture of a Human Papilomavirus (HPV) 16 E6 encoding plasmid DNA (pDNA) vaccine, with a transposon originating from the Escherichia coli DH5 host cell genome. During processing, presence of this transposable element, insertion sequence 2 (IS2) in the plasmid vector was not noticed until quality control of the bulk pDNA vaccine when results of restriction digestion, sequencing, and CGE analysis were clearly indicative for the presence of a contaminant. Due to the very low level of contamination, only an insert-specific PCR method was capable of tracing back the presence of the transposon in the source pDNA and master cell bank (MCB)."

Human Vaccines And Immunotherapy • November 2013

Investigation of a regulatory agency enquiry into potential porcine circovirus type 1 contamination of the human rotavirus vaccine, Rotarix: approach and outcome

Author information

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Abstract

In January 2010, porcine circovirus type 1 (PCV1) DNA was unexpectedly detected in the oral live-attenuated human rotavirus vaccine, Rotarix (GlaxoSmithKline [GSK] Vaccines) by an academic research team investigating a novel, highly sensitive analysis not routinely used for adventitious agent screening. GSK rapidly initiated an investigation to confirm the source, nature and amount of PCV1 in the vaccine manufacturing process and to assess potential clinical implications of this finding. The investigation also considered the manufacturer's inactivated poliovirus (IPV)-containing vaccines, since poliovirus vaccine strains are propagated using the same cell line as the rotavirus vaccine strain. Results confirmed the presence of PCV1 DNA and low levels of PCV1 viral particles at all stages of the Rotarix manufacturing process. PCV type 2 DNA was not detected at any stage. When tested in human cell lines, productive PCV1 infection was not observed. There was no immunological or clinical evidence of PCV1 infection in infants who had received Rotarix in clinical trials. PCV1 DNA was not detected in the IPV-containing vaccine manufacturing process beyond the purification stage. Retrospective testing confirmed the presence of PCV1 DNA in Rotarix since the initial stages of its development and in vaccine lots used in clinical studies conducted pre- and post-licensure. The acceptable safety profile observed in clinical trials of Rotarix therefore reflects exposure to PCV1 DNA. The investigation into the presence of PCV1 in Rotarix could serve as a model for risk assessment in the event of new technologies identifying adventitious agents in the manufacturing of other vaccines and biological products.

http://www.ncbi.nlm.nih.gov/pubmed/24056737

"In January 2010, porcine circovirus type 1 (PCV1) DNA was unexpectedly detected in the oral live-attenuated human rotavirus vaccine, Rotarix (GlaxoSmith-Kline [GSK] Vaccines) by an academic research team investigating a novel, highly sensitive analysis not routinely used for adventitious agent screening."

Biologicals • November 2013

Detection of contaminants in cell cultures, sera and trypsin

Author information

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Abstract

The aim of this study was standardization and application of polymerase chain reaction (PCR) for the detection of contaminants in cell cultures, sera and trypsin. Five PCR protocols were standardized to assess the presence of genetic material from mycoplasma, porcine circovirus 1 (PCV1), bovine leukemia virus (BLV) or bovine viral diarrhea virus (BVDV) in cell culture samples. PCR reactions for the genes GAPDH and beta-actin were used to evaluate the efficiency of nucleic acid extraction. The PCR protocols were applied to 88 cell culture samples from eight laboratories. The tests were also used to assess potential contamination in 10 trypsin samples and 13 fetal calf serum samples from different lots from five of the laboratories. The results showed the occurrence of the following as DNA cell culture contaminants: 34.1% for mycoplasma, 35.2% for PCV1, 23.9% for BVDV RNA and 2.3% for BLV. In fetal calf sera and trypsin samples BVDV RNA and PCV1 DNA was detected. The results demonstrated that cell culture, sera and trypsin used by different laboratories show a high rate of contaminants. The results highlight the need for monitoring cell cultures and controlling for biological contaminants in laboratories and cell banks working with these materials.

http://www.ncbi.nlm.nih.gov/pubmed/?term=24071554

“The results showed the occurrence of the following as DNA cell culture contaminants: 34.1% for mycoplasma, 35.2% for porcine circovirus 1, 23.9% for bovine viral diarrhea virus RNA and 2.3% for bovine leukemia virus. The results demonstrated that cell culture, sera and trypsin used by different laboratories show a high rate of contaminants. ”

Journal Of Pharmaceutical Sciences • March 2014

Mechanism of a decrease in potency for the recombinant influenza A virus hemagglutinin H3 antigen during storage

Author information

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Abstract

The recombinant hemagglutinin (rHA)-based influenza vaccine Flublok® has recently been approved in the United States as an alternative to the traditional egg-derived flu vaccines. Flublok is a purified vaccine with a hemagglutinin content that is threefold higher than standard inactivated influenza vaccines. When rHA derived from an H3N2 influenza virus was expressed, purified, and stored for 1 month, a rapid loss of in vitro potency (□50%) was observed as measured by the single radial immunodiffusion (SRID) assay. A comprehensive characterization of the rHA protein antigen was pursued to identify the potential causes and mechanisms of this potency loss. In addition, the biophysical and chemical stability of the rHA in different formulations and storage conditions was evaluated over time. Results demonstrate that the potency loss over time did not correlate with trends in changes to the higher order structure or hydrodynamic size of the rHA. The most likely mechanism for the early loss of potency was disulfide-mediated cross-linking of rHA, as the formation of non-native disulfide-linked multimers over time correlated well with the observed potency loss. Furthermore, a loss of free thiol content, particularly in specific cysteine residues in the antigen's C-terminus, was correlated with potency loss measured by SRID.

http://www.ncbi.nlm.nih.gov/pubmed/24425059

"When rHA derived from an H3N2 influenza virus was expressed, purified, and stored for 1 month, a rapid loss of in vitro potency (<50%) was observed as measured by the single radial immunodiffusion (SRID) assay."

Currents In Medical Chemistry • March 2014

Melting profiles may affect detection of residual HPV L1 gene DNA fragments in Gardasil

Author information

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Abstract

Gardasil® is a quadrivalent human papillomavirus (HPV) protein-based vaccine containing genotype-specific L1 capsid proteins of HPV-16, HPV-18, HPV-6 and HPV-11 in the form of virus-like-particles (VLPs) as the active ingredient. The VLPs are produced by a DNA recombinant technology. It is uncertain if the residual HPV L1 gene DNA fragments in the vaccine products are considered contaminants or excipients of the Gardasil® vaccine. Because naked viral DNA fragments, if present in the vaccine, may bind to the insoluble amorphous aluminum hydroxyphosphate sulfate (AAHS) adjuvant which may help deliver the foreign DNA into macrophages, causing unintended pathophysiologic effects, experiments were undertaken to develop tests for HPV L1 gene DNA fragments in the final products of Gardasil® by polymerase chain reaction (PCR) and direct DNA sequencing. The results showed that while the HPV-11 and HPV-18 L1 gene DNA fragments in Gardasil® were readily amplified by the common GP6/MY11 degenerate consensus primers, the HPV-16 L1 gene DNA may need specially designed non-degenerate PCR primers for amplification at different regions of the L1 gene and different stringency conditions for detection. These variable melting profiles of HPV DNA in the insoluble fraction of the Gardasil® vaccine suggest that the HPV DNA fragments are firmly bound to the aluminum AAHS adjuvant. All methods developed for detecting residual HPV DNA in the vaccine Gardasil® for quality assurance must take into consideration the variable melting profiles of the DNA to avoid false negative results.

http://www.ncbi.nlm.nih.gov/pubmed/?term=24083601

“All methods developed for detecting residual HPV DNA in the vaccine Gardasil® for quality assurance must take into consideration the variable melting profiles of the DNA to avoid false negative results.”

Journal Of Adolescent Health • March 2014

The role of media and the Internet on vaccine adverse event reporting: a case study of human papillomavirus vaccination

Author information

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Abstract

PURPOSE

This study aimed to determine the temporal association of print media coverage and Internet search activity with adverse events reports associated with the human papillomavirus vaccine Gardasil (HPV4) and the meningitis vaccine Menactra (MNQ) among United States adolescents.

METHODS

We used moderated linear regression to test the relationships between print media reports in top circulating newspapers, Internet search activity, and reports to the Vaccine Adverse Event Reporting System (VAERS) for HPV4 and MNQ during the first 2.5 years after Food and Drug Administration approval.

RESULTS

Compared with MNQ, HPV4 had more coverage in the print media and Internet search activity, which corresponded with the frequency of VAERS reports. In February 2007, we observed a spike in print media for HPV4. Although media coverage waned, Internet search activity remained stable and predicted the rise in HPV4-associated VAERS reports.

CONCLUSIONS

We demonstrate that media coverage and Internet search activity, in particular, may promote increased adverse event reporting. Public health officials who have long recognized the importance of proactive engagement with news media must now consider strategies for meaningful participation in Internet discussions.

Full Report

http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3943880/

“We demonstrate that media coverage and Internet search activity, in particular, may promote increased adverse event reporting. Public health officials who have long recognized the importance of proactive engagement with news media must now consider strategies for meaningful participation in Internet discussions.”

“Porcine circovirus-1 (PCV1) was recently identified as a contaminant in live Rotavirus vaccines ...”

Vaccine • April 2014

Reduction of spiked porcine circovirus during the manufacture of a Vero cell-derived vaccine

Author information

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Biologicals R&D, Baxter BioScience, Vienna, Austria
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Abstract

Porcine circovirus-1 (PCV1) was recently identified as a contaminant in live Rotavirus vaccines, which was likely caused by contaminated porcine trypsin. The event triggered the development of new regulatory guidance on the use of porcine trypsin which shall ensure that cell lines and porcine trypsin in use are free from PCV1. In addition, manufacturing processes of biologicals other than live vaccines include virus clearance steps that may prevent and mitigate any potential virus contamination of product. In this work, artificial spiking of down-scaled models for the manufacturing process of an inactivated pandemic influenza virus vaccine were used to investigate inactivation of PCV1 and the physico-chemically related porcine parvovirus (PPV) by formalin and ultraviolet-C (UV-C) treatment as well as removal by the purification step sucrose gradient ultracentrifugation. A PCV1 infectivity assay, using a real-time PCR infectivity readout was established. The formalin treatment (0.05% for 48h) showed substantial inactivation for both PCV1 and PPV with reduction factors of 3.0log10 and 6.8log10, respectively, whereas UV-C treatment resulted in complete PPV (≥5.9log10) inactivation already at a dose of 13mJ/cm but merely 1.7log10 at 24mJ/cm(2) for PCV1. The UV-C inactivation results with PPV were confirmed using minute virus of mice (MVM), indicating that parvoviruses are far more sensitive to UV-C than PCV1. The sucrose density gradient ultracentrifugation also contributed to PCV1 clearance with a reduction factor of 2log10. The low pH treatment during the production of procine trypsin was investigated and showed effective inactivation for both PCV1 (4.5log10) and PPV (6.4log10). In conclusion, PCV1 in general appears to be more resistant to virus inactivation than PPV. Still, the inactivated pandemic influenza vaccine manufacturing process provides for robust virus reduction, in addition to the already implemented testing for PCV1 to avoid any contaminations.

http://www.ncbi.nlm.nih.gov/pubmed/24560672

Vaccine • May 2014

Systematic evaluation of in vitro and in vivo adventitious virus assays for the detection of viral contamination of cell banks and biological products

Author Information

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Abstract

Viral vaccines and the cell substrates used to manufacture them are subjected to tests for adventitious agents, including viruses, contaminate. Some of the compendial methods (in vivo and in vitro in cell culture) were established in the mid-20th century. These methods have not been subjected to current assay validation, as new methods would need to be. This study was undertaken to provide insight into the breadth (selectivity) and sensitivity (limit of detection) of the routine methods, two such validation parameters. Sixteen viral stocks were prepared and characterized. These stocks were tested in serial dilutions by the routine methods to establish which viruses were detected by which methods and above what limit of detection. Sixteen out of sixteen viruses were detected in vitro, though one (bovine viral diarrhea virus) required special conditions to detect and another (rubella virus) was detected with low sensitivity. Many were detected at levels below 1 TCID50 or PFU (titers were established on the production cell line in most cases). In contrast, in vivo, only 6/11 viruses were detected, and 4 of these were detected only at amounts one or more logs above 1 TCID50 or PFU. Only influenza virus and vesicular stomatitis virus were detected at lower amounts in vivo than in vitro. Given the call to reduce, refine, or replace (3Rs) the use of animals in product safety testing and the emergence of new technologies for the detection of viruses, a re-examination of the current adventitious virus testing strategies seems warranted. Suggested pathways forward are offered.

http://www.sciencedirect.com/science/article/pii/S0264410X14001947

"Given the call to reduce, refine, or replace (3Rs) the use of animals in product safety testing and the emergence of new technologies for the detection of viruses, a re-examination of the current adventitious virus testing strategies seems warranted. Suggested pathways forward are offered."

“The biopharmaceutical industry continues to face enormous pressure to accelerate time to market, improve productivity and efficiency, and reduce costs.”

PDA Journal Of Pharmaceutical Science And Technology • July 2014

Advantages of single-use technology for vaccine fill-finish operations

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Abstract

The biopharmaceutical industry continues to face enormous pressure to accelerate time to market, improve productivity and efficiency, and reduce costs. Vaccine manufacturers face additional challenges, including small batch sizes, varied product portfolios, pandemic outbreaks that require rapid responses and highly potent ingredients that place large demands on cleaning processes. Given these pressures, single-use fill-finish assemblies can represent an attractive option for vaccine manufacturing facilities. This article describes the implementation of a single-use fill-finish system at a large vaccine manufacturer. The new assembly enabled flexibility while reducing set-up time, capital investment, cross-contamination risk, and cleaning requirements.

LAY ABSTRACT

Overall the biopharmaceutical industry is constantly being challenged to bring new products more quickly and efficiently to market while keeping costs as low as possible. One specific segment of this industry is the companies that manufacture vaccines. Vaccines present unique challenges because they tend to be made in smaller amounts for a larger number of individual products. The products can also be very potent, which can require special handling methods. Another challenge is the potential outbreak of a disease that may affect a large area or a large part of the population and would require immediate action. Single-use assemblies for filling the product into its final container are an attractive option for vaccine manufacturing facilities. This article describes the implementation of a single-use filling system at a large vaccine manufacturer. The new assembly was flexible enough to meet the demands of the manufacturer while allowing quick and efficient implementation with low upfront investment.

http://www.ncbi.nlm.nih.gov/pubmed/25035260

Biologicals • September 2014

Adventitious agents in viral vaccines: Lessons learned from 4 case studies

Author Information

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Abstract

Since the earliest days of biological product manufacture, there have been a number of instances where laboratory studies provided evidence for the presence of adventitious agents in a marketed product. Lessons learned from such events can be used to strengthen regulatory preparedness for the future. We have therefore selected four instances where an adventitious agent, or a signal suggesting the presence of an agent, was found in a viral vaccine, and have developed a case study for each. The four cases are: a) SV40 in polio vaccines; b) bacteriophage in measles and polio vaccines; c) reverse transcriptase in measles and mumps vaccines; and d) porcine circovirus and porcine circovirus DNA sequences in rotavirus vaccines. The lessons learned from each event are discussed. Based in part on those experiences, certain scientific principles have been identified by WHO that should be considered in regulatory risk evaluation if an adventitious agent is found in a marketed vaccine in the future.

http://www.sciencedirect.com/science/article/pii/S1045105614000748

“We have therefore selected four instances where an adventitious agent, or a signal suggesting the presence of an agent, was found in a viral vaccine, and have developed a case study for each. The four cases are: a) SV40 in polio vaccines; b) bacteriophage in measles and polio vaccines; c) reverse transcriptase in measles and mumps vaccines; and d) porcine circovirus and porcine circovirus DNA sequences in rotavirus vaccines.”

Bundesgesundheitsblatt Gesundheitsforschung Gesundheitsschutz • October 2014

Viral safety of biological medicinal products

Author information

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Abstract

Viral safety of blood donations, plasma products, viral vaccines and gene therapy medicinal products, biotechnical-derived products and tissue and cell therapy products is a particular challenge. These products are manufactured using a variety of human or animal-derived starting materials and reagents; therefore, extensive testing of donors and of cell banks established for production is required. Furthermore, the viral safety of reagents, such as bovine sera, porcine trypsin and human transferrin or albumin needs to be considered. Whenever possible, manufacturing steps for inactivation or removal of viruses should be introduced; however, sometimes it is not possible to introduce such steps for tissues or cell-based medicinal products as the activity and viability of cells will be compromised. It might be possible to implement steps for inactivation or removal of potential contaminating enveloped viruses only for production of small and stable non-enveloped viral gene vectors.

http://www.ncbi.nlm.nih.gov/pubmed/?term=25123140

“Viral safety of blood donations, plasma products, viral vaccines and gene therapy medicinal products, biotechnical-derived products and tissue and cell therapy products is a particular challenge.”

Journal Of Pharmaceutical Science • November 2014

Historical Data Analyses and Scientific Knowledge Suggest Complete Removal of the Abnormal Toxicity Test as a Quality Control Test

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Abstract

In the early 1900s, the abnormal toxicity test (ATT) was developed as an auxiliary means to ensure safe and consistent antiserum production. Today, the ATT is utilized as a quality control (QC) release test according to pharmacopoeial or other regulatory requirements. The study design has not been changed since around 1940. The evidence of abnormal toxicity testing as a prediction for harmful batches is highly questionable and lacks a scientific rationale. Numerous reviews of historical ATT results have revealed that no reliable conclusions can be drawn from this QC measure. Modern pharmaceutical manufacturers have thorough control of the manufacturing process and comply with good manufacturing practice rules. Contaminants are appropriately controlled by complying with the validated manufacturing processes and strict QC batch release confirming batch-to-batch consistency. Recognizing that product safety, efficacy, and stability can be ensured with strict QC measures, nowadays most regulatory authorities do not require the ATT for most product classes. In line with the replacement, reduction, and refinement (3Rs) initiative, the test requirement has been deleted from approximately 80 monographs of the European Pharmacopoeia and for the majority of product classes in the United States. For these reasons, it is recommended that the ATT should be consistently omitted world-wide and be removed from pharmacopoeias and other regulatory requirements.

http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4278562/

[Here, several divisions of F. Hoffman-La Roche Ltd., AbbVie Ltd., divisions of MSD Europe inc., GlaxoSmithKline, Genzyme, Novartis Pharma AG, Bristol-Myers-Squibb and divisions of Eisai Ltd., write a report justifying the removal of the "Abnormal Toxicity Test" as a quality control element of vaccine production]

Human Vaccines And Immunotherapeutics • 2014

Annual World Vaccine Congress 2014: a re-evaluation of the value proposition for increasing vaccine thermostability

Author information

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Abstract

The 14th Annual World Vaccine Congress was held in Washington DC, March 24-26, 2014 (http://www.terrapinn.com/vaccine2014). More than 400 experts from different regions participated in this scientific event for vaccine professionals from industry, academia, non-profit organizations and government to discuss challenges and successes from all the major vaccine stakeholders. In more than 70 presentations, round tables, and plenary discussions major topics like emerging and re-emerging infectious disease, vaccine production, and innovative technologies were debated. While most contributions focused on specific questions in vaccine research development, some like the one by a representative of the Bill and Melinda Gates Foundation (BMGF) reported about supply chain, logistics topics, and challenges in vaccine implementation.

http://www.ncbi.nlm.nih.gov/pubmed/?term=25483655

“While most contributions focused on specific questions in vaccine research development, some like the one by a representative of the Bill and Melinda Gates Foundation (BMGF) reported about supply chain, logistics topics, and challenges in vaccine implementation.”

Human Vaccines And Immunotherapeutics • 2014

Adjuvants and myeloid-derived suppressor cells: enemies or allies in therapeutic cancer vaccination

Author information

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Abstract

Adjuvants are a critical but largely overlooked and poorly understood component included in vaccine formulations to stimulate and modulate the desired immune responses to an antigen. However, unlike in the protective infectious disease vaccines, adjuvants for cancer vaccines also need to overcome the effect of tumor-induced suppressive immune populations circulating in tumor-bearing individuals. Myeloid-derived suppressor cells (MDSC) are considered to be one of the key immunosuppressive populations that inhibit tumor-specific T cell responses in cancer patients. This review focuses on the different signals for the activation of the immune system induced by adjuvants, and the close relationship to the mechanisms of recruitment and activation of MDSC. This work explores the possibility that a cancer vaccine adjuvant may either strengthen or weaken the effect of tumor-induced MDSC, and the crucial need to address this in present and future cancer vaccines.

http://www.ncbi.nlm.nih.gov/pubmed/?term=25483674

“This work explores the possibility that a cancer vaccine adjuvant may either strengthen or weaken the effect of tumor-induced Myeloid-derived suppressor cells ...”

“This may affect the integrity of the adjuvant, alter its interaction with the drug substance or change the physical characteristics of the drug product.”

Journal Of Pharmaceutical Sciences • February 2015

Shear effects on aluminum phosphate adjuvant particle properties in vaccine drug products

Author information

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Abstract

Adjuvant-containing drug products can be exposed to high levels of interfacial shear during manufacture. This may affect the integrity of the adjuvant, alter its interaction with the drug substance or change the physical characteristics of the drug product. In this study, a solid-liquid interfacial shear device was used to investigate the shear response of aluminum phosphate adjuvant alone and two adjuvant containing vaccine drug products (DP1 and DP2). The relationship between the shear sensitivity of each and its resuspension properties was determined. Changes in the particle dimensions of the bulk adjuvant were minimal at shear strain rates of 10,900 s(-1) . However, at 25,500 s(-1) , the median particle diameter was reduced from 6.2 to 3.5 μm and was marked by the presence of sub-micron fines. A formulation without drug substance and DP2 produced similar shear responses but with less impact on particle diameter. The behavior of DP1 was less predictable. Sheared DP1 was characterized by prolonged sedimentation because of the presence of fine particulates and required in excess of 300 rotations to resuspend after extended storage. The study confirms that the solid-liquid interfacial shear device may be applied to understand product shear sensitivity associated with vaccine manufacturing.

http://www.ncbi.nlm.nih.gov/pubmed/?term=25175154

“The ability to accurately measure and report trace amounts of residual formaldehyde impurity in a vaccine product is not only critical in the product release but also a regulatory requirement.”

Journal Of Pharmaceutical And Biomedical Analysis • March 2015

Determining trace amounts and the origin of formaldehyde impurity in Neisseria meningitidis A/C/Y/W-135-DT conjugate vaccine formulated in isotonic aqueous 1× PBS by improved C18-UPLC method

Author information

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Abstract

The ability to accurately measure and report trace amounts of residual formaldehyde impurity in a vaccine product is not only critical in the product release but also a regulatory requirement. In many bacterial or viral vaccine manufacturing procedures, formaldehyde is used either at a live culture inactivation step or at a protein de-toxification step or at both. Reported here is a validated and improved C18-UPLC method (developed based on previously published C-8 HPLC method) to determine the traces of formaldehyde process impurity in a liquid form Neisseria meningitidis A/C/Y/W-135-DT conjugate vaccine formulated in isotonic aqueous 1× PBS. UPLC C-18 column and the conditions described distinctly resolved the 2,4-DNPH-HCHO adduct from the un-reacted 2,4-DNPH as detected by TUV detector at 360 nm. This method was shown to be compatible with PBS formulation and extremely sensitive (with a quantitation limit of 0.05 ppm) and aided to determine formaldehyde contamination sources by evaluating the in-process materials as a track-down analysis. Final nanogram levels of formaldehyde in the formulated single dose vialed vaccine mainly originated from the diphtheria toxoid carrier protein used in the production of the conjugate vaccine, whereas relative contribution from polysaccharide API was minimal.

http://www.ncbi.nlm.nih.gov/pubmed/25668795

Biologicals • June 2015

Genetic detection and characterization of emerging HoBi-like viruses in archival foetal bovine serum batches

Author Information

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Abstract

Bovine viral diarrhea viruses (BVDV) are members of the Pestivirus genus within the family Flaviviridae. Based on antigenic and nucleotide differences, BVDV are classified into two recognized species, BVDV-1 and BVDV-2. More recently, a new putative pestivirus species, tentatively called "HoBi-like", has been associated with bovine viral diarrhea. HoBi-like viruses were first identified in fetal bovine serum (FBS) imported from Brazil. Subsequently, a number of HoBi-like viruses have been detected as contaminants in FBS or cell culture and in live ruminants. To further investigate the possible pestivirus contamination in commercially available FBS batches, 26 batches of FBS with various countries of origin, were tested in this study for the presence of bovine pestiviruses. All the 26 batches were positive by RT-PCR for at least one species of bovine pestiviruses. HoBi-like viruses were detected in 15 batches. Analysis of the 5'UTR and Npro sequences of 15 newly identified HoBi-like viruses combined with analysis of additional sequences from GenBank, identified 4 genetic groups tentatively named 3a–3d. The current study confirmed the presence of the emerging HoBi-like viruses in FBS products labeled with different geographic origins. This finding has obvious implications for the safety of biological products, such as cell lines and vaccines.

http://www.sciencedirect.com/science/article/pii/S1045105615000536

"... a new putative pestivirus species, tentatively called "HoBi-like", has been associated with bovine viral diarrhea. To further investigate the possible pestivirus contamination in commercially available Fetal Bovine Serum (FBS) batches, 26 batches of FBS with various countries of origin, were tested in this study for the presence of bovine pestiviruses. All the 26 batches were positive by RT-PCR for at least one species of bovine pestiviruses. HoBi-like viruses were detected in 15 batches."

Animal Health Research Reviews • June 2015

Pestivirus control programs: how far have we come and where are we going?

Author information

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Abstract

Classical swine fever (CSF) is endemic in large parts of the world and it is a major threat to the pig industry in general. Vaccination and stamping out have been the most successful tools for the control and elimination of the disease. The systematic use of modified live vaccines (MLV), which are very efficacious and safe, has often preceded the elimination of CSF from regions or countries. Oral vaccination using MLV is a powerful tool for the elimination of CSF from wild boar populations. Bovine virus diarrhea (BVD) is endemic in bovine populations worldwide and programs for its control are only slowly gaining ground. With two genotypes BVD virus (BVDV) is genetically more diverse than CSF virus (CSFV). BVDV crosses the placenta of pregnant cattle resulting in the birth of persistently infected (PI) calves. PI animals shed enormous amounts of virus for the rest of their lives and they are the reservoir for the spread of BVDV in cattle populations. They are the main reason for the failure of conventional control strategies based on vaccination only. In Europe two different approaches for the successful control of BVD are being used: Elimination of PI animals without or with the optional use of vaccines, respectively.

http://www.ncbi.nlm.nih.gov/pubmed/?term=26050577

“They are the main reason for the failure of conventional control strategies based on vaccination only. In Europe two different approaches for the successful control of Bovine virus diarrhea are being used: Elimination of persistently infected animals without or with the optional use of vaccines, respectively.”

International Journal Of Nanomedicine • July 2015

Central nervous system toxicity of metallic nanoparticles

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Abstract

Nanomaterials (NMs) are increasingly used for the therapy, diagnosis, and monitoring of disease- or drug-induced mechanisms in the human biological system. In view of their small size, after certain modifications, NMs have the capacity to bypass or cross the blood–brain barrier. Nanotechnology is particularly advantageous in the field of neurology. Examples may include the utilization of nanoparticle (NP)-based drug carriers to readily cross the blood–brain barrier to treat central nervous system (CNS) diseases, nanoscaffolds for axonal regeneration, nanoelectromechanical systems in neurological operations, and NPs in molecular imaging and CNS imaging. However, NPs can also be potentially hazardous to the CNS in terms of nano-neurotoxicity via several possible mechanisms, such as oxidative stress, autophagy, and lysosome dysfunction, and the activation of certain signaling pathways. In this review, we discuss the dual effect of NMs on the CNS and the mechanisms involved. The limitations of the current research are also discussed.

Summary

There are still many unanswered questions concerning nanoneurotoxicity. For instance, after bypassing the BBB, where do NPs go? How do they leave the brain? The degradation of NP coatings and NP cores inside the cell environment is an important issue that deserves serious consideration when designing safe and functional NMs. No results have been reported on this issue to date.

When NPs enter the body, the surface properties of NPs may change by adsorbing proteins from biological fluids (such as blood, plasma, or interstitial fluid), leading to a distinct new epitope, for example, protein corona exposure in the biological microenvironment. Furthermore, serum protein binding to the NPs can alter the surface charge and accelerate the cellular uptake of NPs through receptor-regulated endocytosis. However, so far, studies addressing the cell surface protein corona interactions with NPs remain limited.

Data regarding the distribution of metal-based NPs in the brain parenchyma are scarce, including data regarding the disruption of the BBB and adverse brain alterations caused by metal-based NPs. The effects of the persistence of poorly soluble metal-based NPs are of particular concern, and few studies have considered the effect of NPs on the CNS.

Full Report: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4498719/

"The effects of the persistence of poorly soluble metal-based nano-particles are of particular concern, and few studies have considered the effect of nano-particles on the Central Nervous System."

“Endotoxin was present in all tested samples and the final product.”

PDA Journal Of Pharmaceutical Science And Technology • July 2015

Quality Control Testing for Tracking Endotoxin-Producing Gram-Negative Bacteria during the Preparation of Polyvalent Snake Antivenom Immunoglobulin

Author information

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Abstract

Snake bites represent a serious public health problem, particularly in rural areas worldwide. Antitoxic sera preparations are antibodies from immunized animals and are considered to be the only treatment option. The purification of antivenom antibodies should aim at obtaining products of consistent quality, safety, efficacy, and adherence to good manufacturing practice principles. Endotoxins are an integral component of the outer cell surface of Gram-negative bacteria. They are common contaminates of the raw materials and processing equipment used in the manufacturing of antivenoms. In this work, and as a part of quality control testing, we establish and examine an environmental monitoring program for identification of potential sources of endotoxin-producing Gram-negative bacteria throughout the whole steps of antivenom preparation. In addition, we follow all the steps of preparation starting from crude plasma till finished product using a validated sterility and endotoxin testing.Samples from air, surface, and personnel were collected and examined through various stages of manufacturing for the potential presence of Gram-negative bacteria. A validated sterility and endotoxin test was carried out in parallel at the different production steps. The results showed that air contributed to the majority of bacterial isolates detected (48.43%), followed by surfaces (37.5%) and then personnel (14%). The most common bacterial isolates detected were Achromobacter xylosoxidans, Ochrobactrum anthropi, and Pseudomonas aeruginosa, which together with Burkholderia cepacia were both also detected in cleaning water and certain equipment parts. A heavy bacterial growth with no fungal contamination was observed in all stages of antivenom manufacturing excluding the formulation stage. All samples were positive for endotoxin including the finished product.Implementation and continued evaluation of quality assurance and quality improvement programs in aseptic preparation is essential in ensuring the safety and quality of these products.

LAY ABSTRACT

Antitoxic sera preparations are the only treatment option for snake bites worldwide. They are prepared by immunizing animals, usually horses, with snake venom and collecting horse plasma, which is then subjected to several purification steps in order to finally prepare the purified immunoglobulins. Components of the bacterial cell wall known as endotoxins can constitute a potential hazardous contamination known as pyrogen in antisera, which can lead to fever and many other adverse reactions to the person subjected to it.In this work, we monitored the environment associated with the different steps of production and purification of snake antivenom prepared from immunized horses. We examined the air quality, surface, and personnel for possible sources of contamination, particularly the presence of Gram-negative bacteria, which is the major source of endotoxin presence. We also monitored all stages of preparation by sterility and endotoxin testing. Our results showed that air contributed to the majority of bacterial isolates. Sterility testing revealed the presence of bacterial contamination in all the intermediate steps, as only the final preparation after filtration was sterile. Endotoxin was present in all tested samples and the final product. Good manufacturing practice procedures are essential in any facility involved in antisera production.

http://www.ncbi.nlm.nih.gov/pubmed/26242786

“A possible disadvantage of using human cell lines

is the potential for human-specific viral contamination ...”

Critical Reviews In Biotechnology • September 2015

Human cell lines for biopharmaceutical manufacturing: history, status, and future perspectives

Author information

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Abstract

Biotherapeutic proteins represent a mainstay of treatment for a multitude of conditions, for example, autoimmune disorders, hematologic disorders, hormonal dysregulation, cancers, infectious diseases and genetic disorders. The technologies behind their production have changed substantially since biotherapeutic proteins were first approved in the 1980s. Although most biotherapeutic proteins developed to date have been produced using the mammalian Chinese hamster ovary and murine myeloma (NS0, Sp2/0) cell lines, there has been a recent shift toward the use of human cell lines. One of the most important advantages of using human cell lines for protein production is the greater likelihood that the resulting recombinant protein will bear post-translational modifications (PTMs) that are consistent with those seen on endogenous human proteins. Although other mammalian cell lines can produce PTMs similar to human cells, they also produce non-human PTMs, such as galactose-a 1,3-galactose and N-glycolylneuraminic acid, which are potentially immunogenic. In addition, human cell lines are grown easily in a serum-free suspension culture, reproduce rapidly and have efficient protein production. A possible disadvantage of using human cell lines is the potential for human-specific viral contamination, although this risk can be mitigated with multiple viral inactivation or clearance steps. In addition, while human cell lines are currently widely used for biopharmaceutical research, vaccine production and production of some licensed protein therapeutics, there is a relative paucity of clinical experience with human cell lines because they have only recently begun to be used for the manufacture of proteins (compared with other types of cell lines). With additional research investment, human cell lines may be further optimized for routine commercial production of a broader range of biotherapeutic proteins.

http://www.ncbi.nlm.nih.gov/pubmed/26383226

Transplant Infectious Disease • November 2015

High rate of vaccine failure after administration of acellular pertussis vaccine pre- and post-liver transplantation in children at a children's hospital in Japan

Author information

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4. Department of Pediatrics, Niigata University Graduate School of Medical and Dental Science, Niigata, Japan
5. Division of Infectious Diseases, Tokyo Metropolitan Tama General Medical Center, Tokyo, Japan

Abstract

We assessed the serological response to pertussis vaccines administered pre- and post-liver transplantation in 58 pediatric patients at a children's hospital in Japan. A high rate of pertussis vaccine failure was observed, 44.8% against the pertussis toxin and 69.0% against filamentous hemagglutinin, with no difference in the seropositivity rate with respect to the timing of the vaccination during the peritransplant period.

http://www.ncbi.nlm.nih.gov/pubmed/26565897

"A high rate of pertussis vaccine failure was observed, 44.8% against the pertussis toxin and 69.0% against filamentous hemagglutinin ..."

Chapter Two
Thimerosal • Ethyl Mercury
1972 - 2015

Environmental Sources Of Mercury

Mercury Concentration	Form	Biological Significance
0.4ppb	MetHg	Median chronic intake of contaminated fish (0.4ug/kg body weight) causes delayed speech and autistic-like symptoms in male children (Corbett & Poor, 2008)
1.6ppb	MetHg	Provisional Tolerable Weekly Intake (PTWI) based on body weight for infants and pregnant women (1.6ug/kg; Food & Agricultural Association/World Health Organization 2006)
2.0ppb	Inorganic Mercury	US EPA limit for drinking water (US EPA, 2011)
200ppb	Various	Level in liquid that the US EPA classifies as hazardous waste based on toxocity characteristics (US EPA, 2010)
600ppb	EtHg	Concentration of mercury in vaccines containing trace amounts of thimerosal (0.3ug/0.5 ml. dose, or 600ug/L;Halsey, 1999)
25,000-50,000ppb	EtHg	Concentration in Thimerosal containing multi-dose influenza, meningococcal pneumococcal polysaccharide and diphtheria-tetanus vaccines (Offit & Jew, 2003)

"The ubiquitous and largely unchecked place of Thimerosal in pharmaceuticals, therefore, represents a medical crisis."

Quoted from:
"A review of Thimerosal (Merthiolate) and its ethyl mercury breakdown product:
specific historical considerations regarding safety and effectiveness"
by DA Geier, LK Sykes and MR Geier

Postgraduate Medical Journal • July 1972

Six cases of poisoning after a parenteral organic mercurial compound (Merthiolate)

J. H. M. Axton

http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2495252/?page=5

Bulletin Of The World Health Organization • May 1976

An outbreak of organomercury poisoning among Iraqi farmers

Al-Tikriti K, Al-Mufti AW.

Abstract

An outbreak of organomercury poisoning due to the consumption of treated grain by farmers and their families occurred in Iraq in 1971-72. A total of 6530 cases were admitted to hospital and of these 459 died. However, there were many more with minor symptoms of poisoning who consulted outpatient departments. This outbreak constituted the largest poisoning epidemic ever recorded. No age was exempt and no pronounced sex difference was apparent. The latent period of up to 60 days between dosage and the onset of symptoms was probably the major factor contributing to the size of the epidemic. Measures taken to limit the outbreak are outlined.

Full Report

http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2366398/

“A total of 6530 cases were admitted to hospital and of these 459 died.”

American Journal Of Obstetrics And Gynecology • October 1976

Mercury toxicity in the pregnant woman, fetus, and newborn infant
A review

Koos BJ, Longo LD.

Abstract

This paper reviews the reported cases of mercury poisoning in pregnancy and the data based on sources of contamination, maternal uptake, and distribution. It analyzes current knowledge of placental transfer of various mercury compounds, fetal uptake, and distribution. It identifies the embryopathic and fetal toxic effects of mercury in general while emphasizing the greater toxicity of methylmercury compounds. Since maternal exposure to methylmercury is primarily through fish consumption, it recommends that women of childbearing age should not consume more than 350 Gm. of fish per week. In addition, they should not be occupationally exposed to air concentrations of mercury vapor greater than 0.01 mg. per cubic meter, of inorganic and phenylmercuric compounds greater than 0.02 mg. per cubic meter, or any detectable concentration of methylmercury.

http://www.ncbi.nlm.nih.gov/pubmed/786026

“This paper reviews the reported cases of mercury poisoning in pregnancy and the data based on sources of contamination, maternal uptake, and distribution. It analyzes current knowledge of placental transfer of various mercury compounds, fetal uptake, and distribution.”

British Journal Of Industrial Medicine • May 1982

Elemental mercury exposure: peripheral neurotoxicity

Levine SP, Cavender GD,
Langolf GD, Albers JW.

Abstract

Nerve conduction tests were performed on the right ulnar nerve of factory workers exposed to elemental mercury vapour. Time integrated urine mercury indices were used to measure the degree of exposure. Workers with prolonged distal latencies had significantly higher urine mercury concentrations when compared with those with normal latencies. Significant correlations between increasing urine mercury concentrations and prolonged motor and sensory distal latencies were established. Elemental mercury can affect both motor and sensory peripheral nerve conduction and the degree of involvement may be related to time-integrated urine mercury concentrations.

http://www.ncbi.nlm.nih.gov/pubmed/6279139

“Significant correlations between increasing urine mercury concentrations and prolonged motor and sensory distal latencies were established. Elemental mercury can affect both motor and sensory peripheral nerve conduction and the degree of involvement may be related to time-integrated urine mercury concentrations.”

Annals Of Neurology • November 1988

Neurological abnormalities associated with remote occupational elemental mercury exposure

Author information

Albers JW1, Kallenbach LR, Fine LJ, Langolf GD,
Wolfe RA, Donofrio PD, Alessi AG, Stolp-Smith KA, Bromberg MB.

Department of Neurology
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Abstract

We examined 502 subjects, 247 of whom had occupational elemental mercury exposures 20 to 35 years previously, to identify potential exposure-related neurological abnormalities. Few significant (p less than 0.05) differences existed between exposed and unexposed subjects. However, multiple linear regression analysis demonstrated several significant correlations between declining neurological function and increasing exposure as determined by urine mercury measurements from the exposure interval. Subjects with urine mercury peak levels above 0.6 mg/L demonstrated significantly decreased strength, decreased coordination, increased tremor, decreased sensation, and increased prevalence of Babinski and snout reflexes when compared with the remaining subjects. Furthermore, subjects with clinical polyneuropathy had significantly higher peak levels than normal subjects (0.85 vs 0.61 mg/L; p = 0.04), but not increased exposure duration (20.1 vs 20.8 quarters; p = 0.34), and 28% of subjects with peak levels above 0.85 mg/L had clinical evidence of polyneuropathy, compared with 10% of remaining subjects (p = 0.005). Although exposure was not age dependent, several neurological measures showed significant age-mercury interaction, suggesting that natural neuronal attrition may unmask prior exposure-related subclinical abnormalities.

http://www.ncbi.nlm.nih.gov/pubmed/2849369

“... multiple linear regression analysis demonstrated several significant correlations between declining neurological function and increasing exposure as determined by urine mercury measurements from the exposure interval. Subjects with urine mercury peak levels above 0.6 mg/L demonstrated significantly decreased strength, decreased coordination, increased tremor, decreased sensation, and increased prevalence of Babinski and snout reflexes when compared with the remaining subjects.”

Journal Of Toxicology And Environmental Health. • 1989

Brain and tissue levels of mercury after chronic methylmercury exposure in the monkey

Author information

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Ottawa, Ontario, Canada

Abstract

Estimated half-lives of mercury following methylmercury exposure in humans are 52-93 d for whole body and 49-164 d for blood. In its most recent 1980 review, the World Health Organization concluded that there was no evidence to suggest that brain half-life differed from whole-body half-life. In the present study, female monkeys (Macaca fascicularis) were dosed for at least 1.7 yr with 10, 25, or 50 micrograms/kg.d of mercury as methylmercuric chloride. Dosing was discontinued, and blood half-life was determined to be about 14 d. Approximately 230 d after cessation of dosing, monkeys were sacrificed and organ and regional brain total mercury levels determined. One monkey that died while still being dosed had brain mercury levels three times higher than levels in blood. Theoretical calculations were performed assuming steady-state brain:blood ratios of 3, 5, or 10. Brain mercury levels were at least three orders of magnitude higher than those predicted by assuming the half-life in brain to be the same as that in blood. Estimated half-lives in brain were between 56 (brain:blood ratio of 3) and 38 (brain:blood ratio of 10) d. In addition, there was a dose-dependent difference in half-lives for some brain regions. These data clearly indicate that brain half-life is considerably longer than blood half-life in the monkey under conditions of chronic dosing.

http://www.ncbi.nlm.nih.gov/pubmed/2499694

“These data clearly indicate that brain half-life is considerably longer than blood half-life in the monkey under conditions of chronic dosing.”

“This review gives an up-to-date account of mercury’s physical and chemical properties and its interaction with biologically active sites pertinent to transport across the blood-brain barrier ...”

Neuroscience & Biobehavioral Reviews • Summer 1990

Mercury neurotoxicity: Mechanisms of blood-brain barrier transport

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†Department of Pediatrics, Division of Neonatal Medicine Albany Medical College
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Abstract

Mercury exists in a wide variety of physical and chemical states, each of which has unique characteristics of target organ toxicity. The classic symptoms associated with exposure to elemental mercury vapor (Hg0) and methyl-mercury (Ch3Hg+; MeHg) involve the central nervous system (CNS), while the kidney is the target organ for the mono- and divalent salts of mercury (Hg+ and Hg++, respectively). Physical properties and redox potentials determine the qualitative and quantitative differences in toxicity among inorganic mercury compounds, while the ability of MeHg to cross the blood-brain barrier accounts for its accumulation in the CNS and a clinical picture that is dominated by neurological disturbances. This review gives an up-to-date account of mercury’s physical and chemical properties and its interaction with biologically active sites pertinent to transport across the blood-brain barrier, a major regulator of the CNS millieu.

http://www.sciencedirect.com/science/article/pii/S0149763405802179

Contact Dermatitis • March 1991

A probable role for vaccines containing thimerosal in thimerosal hypersensitivity

Author information

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Department of Dermatology
Yokohama City University School of Medicine
Kanagawa, Japan

Abstract

We patch tested 141 patients with 0.05% aq. thimerosal and 222 patients with 0.05% aq. mercuric chloride, including 63 children. The frequency of positive patch test reactions to thimerosal was 16.3%. There was a marked preponderance in the young age groups after vaccination, while none of 36 infants (aged 3-48 months) reacted to thimerosal. Positive reactions to mercuric chloride were found in 23 (10.4%) of 222 patients. We also sensitized guinea pigs with diphtheria-pertussis-tetanus (DPT) vaccine containing 0.01% thimerosal and succeeded in inducing hypersensitivity to thimerosal. From patch testing in humans and animal experiments, it is suggested that 0.01% thimerosal in vaccines can sensitize children, and that hypersensitivity to thimerosal is due to the thiosalicylic part of the molecule and correlates with photosensitivity to piroxicam.

http://www.ncbi.nlm.nih.gov/pubmed/1868700?dopt=Abstract

“... it is suggested that 0.01% thimerosal in vaccines can sensitize children ...”

Environmental Research • February 1993

Psychological effects of low exposure to mercury vapor: application of a computer-administered neurobehavioral evaluation system

Author information

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Abstract

A computer-administered neurobehavioral evaluation system in a Chinese language version (NES-C) and a mood inventory of the profile of mood states (POMS) were applied to assess the psychological effects of low-level exposure to mercury vapor in a group of 88 workers (19 males and 69 females, with mean age of 34.2 years) exposed to mercury vapor (average duration of exposure 10.4 years). The well-matched group of 97 nonexposed workers was treated as the control. The intensity of current mercury vapor was relatively mild as reflected by the average level of mercury in the air of the workplace (0.033 mg/m3) and in urine (0.025 mg/liter). The results indicated that the profile of mood states posed was moving to the negative side in Hg-exposed group and most of the NES-C performances, in particular, the mental arithmetic, two-digit search, switching attention, visual choice reaction time, and finger tapping, were also significantly affected compared with those obtained from controls ($P < 0.05$-0.01). The present study and the previous study on the validation of the system suggest that the NES-C we developed is valid for the neurotoxicity screening among the working population exposed to neurotoxic agents.

http://www.ncbi.nlm.nih.gov/pubmed/8472661

"The results indicated that the profile of mood states posed was moving to the negative side in mercury-exposed group and most of the NES-C performances, in particular, the mental arithmetic, two-digit search, switching attention, visual choice reaction time, and finger tapping, were also significantly affected compared with those obtained from controls ..."

“... neurotoxic effects of inorganic mercury could be partially due to the irreversible blockade of voltage-activated calcium channels.”

Brain Research • December 1993

Mercury (Hg2+) decreases voltage-gated calcium channel currents in rat DRG and Aplysia neurons

M. Pekel, B. Platt, D. Büsselberg

Abstract

Inorganic mercury (Hg2+) reduced voltage-gated calcium channel currents irreversibility in two different preparations. In cultured rat dorsal root ganglion (DRG) neurons, studied with the whole cell patch clamp technique, a rapid concentration-dependent decrease in the L/N-type currents to a steady state was observed with an IC50 of 1.1 μM and a Hill coefficient of 1.3 T-currents were blocked with Hg2+ in the same concentration range (0.5–2 μM). With increasing Hg2+ concentrations a slow membrane current was additionally activated most obviously at concentrations over 2 μM Hg2+. This current was irreversible and might be due to the opening of other (non-specific) ion channels by Hg2+. The current-voltage (I–V) relation of DRG neurons shifted to more positive values, suggesting a binding of Hg2+ to the channel protein and/or modifying its gating properties. In neurons of the abdominal ganglion of Aplysia californica, studied with the two electrode voltage clamp technique, a continous decrease of calcium channel currents was seen even with the lowest used concentration of Hg2+ (5 μM). A steady state was not reached and the effect was irreversible without any change on resting membrane currents, even with high concentrations (up to 50 μM). No shift of the I–V relation of the calcium channel currents was observed. Effects on voltage-activated calcium channel currents with Hg2+ concentrations such low have not been reported before. We conclude that neurotoxic effects of inorganic mercury could be partially due to the irreversible blockade of voltage-activated calcium channels.

http://www.sciencedirect.com/science/article/pii/000689939391146J

European Journal Of Pediatrics • August 1994

Mercury burden of human fetal and infant tissues

Author information

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Abstract

The total mercury concentrations in the liver (Hg-L), the kidney cortex (Hg-K) and the cerebral cortex (Hg-C) of 108 children aged 1 day-5 years, and the Hg-K and Hg-L of 46 fetuses were determined. As far as possible, the mothers were interviewed and their dental status was recorded. The results were compared to mercury concentrations in the tissues of adults from the same geographical area. The Hg-K (n = 38) and Hg-L (n = 40) of fetuses and Hg-K (n = 35) and Hg-C (n = 35) of older infants (11-50 weeks of life) correlated significantly with the number of dental amalgam fillings of the mother. The toxicological relevance of the unexpected high Hg-K of older infants from mothers with higher numbers of dental amalgam fillings is discussed.

CONCLUSION

Future discussion on the pros and cons of dental amalgam should not be limited to adults or children with their own amalgam fillings, but also include fetal exposure. The unrestricted application of amalgam for dental restorations in women before and during the child-bearing age should be reconsidered.

http://www.ncbi.nlm.nih.gov/pubmed/7957411

“The mercury of fetuses and mercury of older infants (11-50 weeks of life) correlated significantly with the number of dental amalgam fillings of the mother. The toxicological relevance of the unexpected high kidney cortex of older infants from mothers with higher numbers of dental amalgam fillings is discussed.”

Developmental Brain Research • March 1995

The effect of mercury vapour on cholinergic neurons in the fetal brain: studies on the expression of nerve growth factor and its low- and high-affinity receptors

Author information

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Abstract

The effects of mercury vapour on the production of nerve growth factor during development have been examined. Pregnant rats were exposed to two different concentrations of mercury vapour during either embryonic days E6-E11 (early) or E13-E18 (late) in pregnancy, increasing the postnatal concentration of mercury in the brain from 1 ng/g tissue to 4 ng/g tissue (low-dose group) or 11 ng/g (high-dose group). The effect of this exposure in offspring was determined by looking at the NGF concentration at postnatal days 21 and 60 and comparing these levels to age-matched controls from sham-treated mothers. Changes in the expression of mRNA encoding NGF, the low- and high-affinity receptors for NGF (p75 and p140 trk, respectively) and choline acetyltransferase (ChAT) were also determined. When rats were exposed to high levels of mercury vapour during early embryonic development there was a significant (62%) increase in hippocampal NGF levels at P21 accompanied by a 50% decrease of NGF in the basal forebrain. The expression of NGF mRNA was found to be unaltered in the dentate gyrus. The expression of p75 mRNA was significantly decreased to 39% of control levels in the diagonal band of Broca (DB) and to approximately 50% in the medial septal nucleus (MS) whereas no alterations in the level of trk mRNA expression were detectable in the basal forebrain. ChAT mRNA was slightly decreased in the DB and MS, significantly in the striatum. These findings suggest that low levels of prenatal mercury vapour exposure can alter the levels of the NGF and its receptors, indicating neuronal damage and disturbed trophic regulations during development.

http://www.ncbi.nlm.nih.gov/pubmed/7781173

“These findings suggest that low levels of prenatal mercury vapour exposure can alter the levels of the NGF and its receptors, indicating neuronal damage and disturbed trophic regulations during development.”

Canadian Journal Of Physiology • February 1996

Altered porphyrin metabolism as a biomarker of mercury exposure and toxicity

Author information

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Abstract

Changes in urinary porphyrin excretion patterns (porphyrin profiles) have been described in response to a variety of drugs and chemicals. The present studies were conducted to define the specific changes in the urinary porphyrin profile associated with prolonged exposure to mercury and mercury compounds. In rats, exposure for a prolonged period to mercury as methyl mercury hydroxide was associated with urinary porphyrin changes, which were uniquely characterized by highly elevated levels of 4- and 5-carboxyl porphyrins and by the expression of an atypical porphyrin ("precoproporphyrin") not found in urine of unexposed animals. These distinct changes in urinary porphyrin concentrations were observed as early as 1-2 weeks after initiation of mercury exposure, and increased in a dose- and time-related fashion with the concentration of mercury in the kidney, a principal target organ of mercury compounds. Following cessation of mercury exposure, urinary porphyrin concentrations reverted to normal levels, consistent with renal mercury clearance. In human studies, a comparable change in the urinary porphyrin profile was observed among subjects with occupational exposure to mercury as mercury vapor sufficient to elicit urinary mercury levels greater than 20 micrograms/L. Urinary porphyrin profiles were also shown to correlate significantly with mercury body burden and with specific neurobehavioral deficits associated with low level mercury exposure. These findings support the utility of urinary porphyrin profiles as a useful biomarker of mercury exposure and potential health effects in human subjects.

http://www.ncbi.nlm.nih.gov/pubmed/?term=8723034

"These findings support the utility of urinary porphyrin profiles as a useful biomarker of mercury exposure and potential health effects in human subjects."

Clinical Neuropathology • May 1996

Demonstration of mercury in the human brain and other organs 17 years after metallic mercury exposure

Author information

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Wendt-Gallitelli MF, Meyermann R.

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Abstract

A male subject became exposed to metallic mercury vapor at work in 1973. He excreted 1,850 mg Hg/l urine initially. Controls of urine mercury excretion after D-penicillamine administration led to the assumption of a total body clearance of mercury latest since 1976. Subsequently he developed an organic psychosyndrome without detectable signs of classical mercurialism. He never returned to work again and died of lung cancer in 1990. In different organs (brain, kidney, and lung) which were sampled at autopsy elevated levels of mercury were documented by atomic absorption analysis. Histological examination of the tissue by the Danscher and Schroder method, which is specific for mercury, showed a highly positive staining in the majority of nerve cells and cells of other organs. Ultrastructurally mercury could be demonstrated by elemental x-ray analysis within lipofuscin deposits. The lipofuscin content was increased in the mercury positive nerve cells as demonstrated by a strong positive autofluorescence.

http://www.ncbi.nlm.nih.gov/pubmed/?term=8793247

“He never returned to work again and died of lung cancer in 1990. In different organs (brain, kidney, and lung) which were sampled at autopsy elevated levels of mercury were documented by atomic absorption analysis.”

Neurotoxicology • Fall 1996

Effect of subchronic mercury exposure on electrocorticogram of rats

Author information

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Department of Public Health
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Abstract

Mercury is a neurotoxic compound causing irreversible disorders of the central and peripheral nervous system. In some of the previous human and experimental studies mercury also affected some functional neurological parameters such as EEG, and cortical evoked potentials. In the present study, the effect of subchronic (4, 8, and 12 weeks) relatively low-level (0.4, 0.8, and 1.6 mg/kg mercury in form of HgCl2, per os by gavage) treatment on the basic cortical activity was investigated. Certain parameters of electrocorticogram (ECoG) recorded simultaneously from the primary somatosensory, visual and auditory centres were analyzed. The results showed that mercury had a dose- and time-dependent effect on the examined ECoG parameters, and the changes became significant by the end of the experiment of week 12.

http://www.ncbi.nlm.nih.gov/pubmed/9086494

“Mercury is a neurotoxic compound causing irreversible disorders of the central and peripheral nervous system.”

Neurotoxicology And Teratology • November 1997

Cognitive deficit in 7-year-old children with prenatal exposure to methylmercury

Author information

Grandjean P1, Weihe P, White RF, Debes F, Araki S, Yokoyama K, Murata K, Sørensen N, Dahl R, Jørgensen PJ.

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Abstract

A cohort of 1022 consecutive singleton births was generated during 1986-1987 in the Faroe Islands. Increased methylmercury exposure from maternal consumption of pilot whale meat was indicated by mercury concentrations in cord blood and maternal hair. At approximately 7 years of age, 917 of the children underwent detailed neurobehavioral examination. Neuropsychological tests included Finger Tapping; Hand-Eye Coordination; reaction time on a Continuous Performance Test; Wechsler Intelligence Scale for Children-Revised Digit Spans, Similarities, and Block Designs; Bender Visual Motor Gestalt Test; Boston Naming Test; and California Verbal Learning Test (Children). Clinical examination and neurophysiological testing did not reveal any clear-cut mercury-related abnormalities. However, mercury-related neuropsychological dysfunctions were most pronounced in the domains of language, attention, and memory, and to a lesser extent in visuospatial and motor functions. These associations remained after adjustment for covariates and after exclusion of children with maternal hair mercury concentrations above 10 microgram(s) (50 nmol/g). The effects on brain function associated with prenatal methylmercury exposure therefore appear widespread, and early dysfunction is detectable at exposure levels currently considered safe.

http://www.ncbi.nlm.nih.gov/pubmed/9392777

“The effects on brain function associated with prenatal methylmercury exposure therefore appear widespread, and early dysfunction is detectable at exposure levels currently considered safe.”

General Pharmacology • July 1999

Thimerosal: a versatile sulfhydryl reagent, calcium mobilizer, and cell function-modulating agent

Author information

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Abstract

An overview of the literature concerning the effects of thimerosal is presented. Because of its antibacterial effect, thimerosal is used for a variety of practical purposes such as antiseptic and preservative. In biomedical studies, thimerosal is used as a sulfhydryl reagent, and as a calcium-mobilizing agent. The ability of thimerosal to act as a sulfhydryl group is related to the presence of mercury. Relatively little study has been devoted to the mechanism of the reaction of thimerosal with the sulfhydryl group; the sulfhydryl reactive capacity is mostly concluded on the basis of inactivation of the effect by dithiothreitol (DTT). Thimersal causes a release of calcium from intracellular stores in many cells types; this is followed by an influx of extracellular calcium. Both InsP3- and ryanodine-sensitive calcium stores may be affected. Studies with permeabilized cells or organelles show that the effect of thimerosal on calcium is dependent on the concentration: low concentrations of thimerosal stimulate calcium release, high concentrations are inhibitory. This dependence is not found in intact cells. Thimerosal may activate or inhibit a number of cell functions. These are often related to the ability to release calcium or with the sulfhydryl reactivity. In platelets, thimerosal causes aggregation, increase of arachidonic acid metabolism, and exocytotic release of serotonin. In neutrophils, thimerosal causes, besides an increase of cytosolic free calcium, an increase of formyl-methionyl-leucyl-phenylalanine (fMLP)-activated leukotriene release, and a modulation of chemotactic migration and exocytosis. At low concentrations, thimerosal induces chemotactic migration of neutrophils, in the absence of other chemoattractants. The effect is also observed with thiosalicylic acid, indicating that the stimulation of migration was due to the thiosalicylic acid moiety of the thimerosal molecule. At higher concentrations, thimerosal causes inhibition of fMLP-activated migration. Low concentrations of thimerosal, but not of thiosalicylic acid, induced exocytotic enzyme release from neutrophils. High concentrations of thimerosal inhibited fMLP-activated exocytosis. The results point to an involvement of calcium mobilization and calcium influx of activation, and reaction with sulfhydryl groups for inhibition.

http://www.ncbi.nlm.nih.gov/pubmed/?term=10428009

“Thimerosal may activate or inhibit a number of cell functions.”

Journal Of Neurochemistry • January 2000

Mercury induces cell cytotoxicity and oxidative stress and increases beta-amyloid secretion and tau phosphorylation in SHSY5Y neuroblastoma cells

Author information

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Abstract

Concentrations of heavy metals, including mercury, have been shown to be altered in the brain and body fluids of Alzheimer's disease (AD) patients. To explore potential pathophysiological mechanisms we used an in vitro model system (SHSY5Y neuroblastoma cells) and investigated the effects of inorganic mercury (HgCl2) on oxidative stress, cell cytotoxicity, beta-amyloid production, and tau phosphorylation. We demonstrated that exposure of cells to 50 microg/L (180 nM) HgCl2 for 30 min induces a 30% reduction in cellular glutathione (GSH) levels (n = 13, $p<0.001$). Preincubation of cells for 30 min with 1 microM melatonin or premixing melatonin and HgCl2 appeared to protect cells from the mercury-induced GSH loss. Similarly, 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT) cytotoxicity assays revealed that 50 microg/L HgCl2 for 24 h produced a 50% inhibition of MTT reduction (n = 9, $p<0.001$). Again, melatonin preincubation protected cells from the deleterious effects of mercury, resulting in MTT reduction equaling control levels. The release of beta-amyloid peptide (Abeta) 1-40 and 1-42 into cell culture supernatants after exposure to HgCl2 was shown to be different: Abeta 1-40 showed maximal (15.3 ng/ml) release after 4 h, whereas Abeta 1-42 showed maximal (9.3 ng/ml) release after 6 h of exposure to mercury compared with untreated controls (n = 9, $p<0.001$). Preincubation of cells with melatonin resulted in an attenuation of Abeta 1-40 and Abeta 1-42 release. Tau phosphorylation was significantly increased in the presence of mercury (n = 9, $p<0.001$), whereas melatonin preincubation reduced the phosphorylation to control values. These results indicate that mercury may play a role in pathophysiological mechanisms of AD.

http://www.ncbi.nlm.nih.gov/pubmed/10617124

"These results indicate that mercury may play a role in pathophysiological mechanisms of Alzheimer's disease."

Journal Of Pediatrics • May 2000

Iatrogenic exposure to mercury after hepatitis B vaccination in preterm infants

Author information

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Abstract

Thimerosal, a derivative of mercury, is used as a preservative in hepatitis B vaccines. We measured total mercury levels before and after the administration of this vaccine in 15 preterm and 5 term infants. Comparison of pre- and post-vaccination mercury levels showed a significant increase in both preterm and term infants after vaccination. Additionally, post-vaccination mercury levels were significantly higher in preterm infants as compared with term infants. Because mercury is known to be a potential neurotoxin to infants, further study of its pharmacodynamics is warranted.

http://www.ncbi.nlm.nih.gov/pubmed/10802503

“Comparison of pre- and post-vaccination mercury levels showed a significant increase in both preterm and term infants after vaccination.”

MMWR Morbidity And Mortality Weekly Report • July 14, 2000

Summary of the joint statement on thimerosal in vaccines American Academy of Family Physicians American Academy of Pediatrics Advisory Committee on Immunization Practices Public Health Service

Centers for Disease Control and Prevention (CDC)

Abstract

In June 2000, a joint statement on thimerosal in vaccines was prepared by the American Academy of Family Physicians (AAFP), the American Academy of Pediatrics (AAP), the Advisory Committee on Immunization Practices (ACIP), and the Public Health Service (PHS) in response to 1) the progress in achieving the national goal declared in July 1999 to remove thimerosal from vaccines in the recommended childhood vaccination schedule, and 2) results of recent studies that examined potential associations between exposure to mercury in thimerosal-containing vaccines and health effects. In this statement, AAFP, AAP, ACIP, and PHS recommend continuation of the current policy of moving rapidly to vaccines that are free of thimerosal as a preservative. Until adequate supplies are available, use of vaccines that contain thimerosal as a preservative is acceptable.

http://www.ncbi.nlm.nih.gov/pubmed/?term=10914930

“AAFP, AAP, ACIP, and PHS recommend continuation of the current policy of moving rapidly to vaccines that are free of thimerosal as a preservative. Until adequate supplies are available, use of vaccines that contain thimerosal as a preservative is acceptable.”

Drugs • 2001

Vaccines without thiomersal: why so necessary, why so long coming?

Author information

van't Veen AJ.

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Abstract

The inorganic mercurial thiomersal (merthiolate) has been used as an effective preservative in numerous medical and non-medical products since the early 1930s. Both the potential toxicity of thiomersal and sensitisation to thiomersal in relation to the application of thiomersal-containing vaccines and immunoglobulins, especially in children, have been debated in the literature. The very low thiomersal concentrations in pharmacological and biological products are relatively non-toxic, but probably not in utero and during the first 6 months of life. The developing brain of the fetus is most susceptible to thiomersal and, therefore, women of childbearing age, in particular, should not receive thiomersal-containing products. Definitive data of doses at which developmental effects occur are not available. Moreover, revelation of subtle effects of toxicity needs long term observation of children. The ethylmercury radical of the thiomersal molecule appears to be the prominent sensitiser. The prevalence of thiomersal hypersensitivity in mostly selected populations varies up to 18%, but higher figures have been reported. The overall exposure to thiomersal differs considerably between countries. In many cases a positive routine patch test to thiomersal should be considered an accidental finding without or, probably more accurately, with low clinical relevance. In practice, some preventive measures can be taken with respect to thiomersal hypersensitivity. However, with regard to the debate on primary sensitisation during childhood and renewed attention for a reduction of children's exposure to mercury from all sources, the use of thiomersal should preferably be eliminated or at least be reduced. In 1999 the manufacturers of vaccines and immunoglobulins in the US and Europe were approached with this in mind. The potential toxicity in children seems to be of much more concern to them than the hidden sensitising properties of thiomersal. In The Netherlands, unlike many other countries, the exposure to thiomersal from pharmaceutical sources has already been reduced. Replacement of thiomersal in all products should have a high priority in all countries.

http://www.ncbi.nlm.nih.gov/pubmed/?term=11368282

"The potential toxicity in children seems to be of much more concern to them [the vaccine manufacturers] than the hidden sensitising properties of thiomersal. Replacement of thiomersal in all products should have a high priority in all countries. In 1999 the manufacturers of vaccines and immunoglobulins in the US and Europe were approached with this in mind."

Medical Hypotheses • April 2001

Autism:
a novel form of mercury poisoning

Author information

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Abstract

Autism is a syndrome characterized by impairments in social relatedness and communication, repetitive behaviors, abnormal movements, and sensory dysfunction. Recent epidemiological studies suggest that autism may affect 1 in 150 US children. Exposure to mercury can cause immune, sensory, neurological, motor, and behavioral dysfunctions similar to traits defining or associated with autism, and the similarities extend to neuroanatomy, neurotransmitters, and biochemistry. Thimerosal, a preservative added to many vaccines, has become a major source of mercury in children who, within their first two years, may have received a quantity of mercury that exceeds safety guidelines. A review of medical literature and US government data suggests that: (i) many cases of idiopathic autism are induced by early mercury exposure from thimerosal; (ii) this type of autism represents an unrecognized mercurial syndrome; and (iii) genetic and non-genetic factors establish a predisposition whereby thimerosal's adverse effects occur only in some children.

http://www.ncbi.nlm.nih.gov/pubmed/11339848

"A review of medical literature and US government data suggests that many cases of idiopathic autism are induced by early mercury exposure from thimerosal."

Neuroreport • May 2001

Retrograde degeneration of neurite membrane structural integrity of nerve growth cones following in vitro exposure to mercury

Author information

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Abstract

Inhalation of mercury vapor (Hg0) inhibits binding of GTP to rat brain tubulin, thereby inhibiting tubulin polymerization into microtubules. A similar molecular lesion has also been observed in 80% of brains from patients with Alzheimer disease (AD) compared to age-matched controls. However the precise site and mode of action of Hg ions remain illusive. Therefore, the present study examined whether Hg ions could affect membrane dynamics of neurite growth cone morphology and behavior. Since tubulin is a highly conserved cytoskeletal protein in both vertebrates and invertebrates, we hypothesized that growth cones from animal species could be highly susceptible to Hg ions. To test this possibility, the identified, large Pedal A (PeA) neurons from the central ring ganglia of the snail Lymnoea stagnalis were cultured for 48 h in 2 ml brain conditioned medium (CM). Following neurite outgrowth, metal chloride solution (2 microl) of Hg, Al, Pb, Cd, or Mn (10(-7) M) was pressure applied directly onto individual growth cones. Time-lapse images with inverted microscopy were acquired prior to, during, and after the metal ion exposure. We demonstrate that Hg ions markedly disrupted membrane structure and linear growth rates of imaged neurites in 77% of all nerve growth cones. When growth cones were stained with antibodies specific for both tubulin and actin, it was the tubulin/microtubule structure that disintegrated following Hg exposure. Moreover, some denuded neurites were also observed to form neurofibrillary aggregates. In contrast, growth cone exposure to other metal ions did not effect growth cone morphology, nor was their motility rate compromised. To determine the growth suppressive effects of Hg ions on neuronal sprouting, cells were cultured either in the presence or absence of Hg ions. We found that in the presence of Hg ions, neuronal somata failed to sprout, whereas other metalic ions did not effect growth patterns of cultured PeA cells. We conclude that this visual evidence and previous biochemical data strongly implicate Hg as a potential etiological factor in neurodegeneration.

http://www.ncbi.nlm.nih.gov/pubmed/?term=11277574

“We found that in the presence of mercury ions, neuronal somata failed to sprout, whereas other metalic ions did not effect growth patterns of cultured PeA cells. We conclude that this visual evidence and previous biochemical data strongly implicate mercury as a potential etiological factor in neurodegeneration.”

Neurotoxicology • October 2001

Predicted mercury concentrations in hair from infant immunizations: cause for concern

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Abstract

Mercury (Hg) is considered one of the worlds most toxic metals. Current thinking suggests that exposure to mercury occurs primarily from seafood contamination and rare catastrophic events. Recently, another common source of exposure has been identified. Thimerosal (TMS), a preservative found in many infant vaccines, contains 49.6% ethyl mercury (EtHg) by weight and typically contributes 25 microg of EtHg per dose of infant vaccine. As part of an ongoing review, the Food and Drug Administration (FDA) announced in 1999 that infants who received multiple TMS-preserved vaccines may have been exposed to cumulative Hg in excess of Federal safety guidelines. According to the centers for disease control (CDC) recommended immunization schedule, infants may have been exposed to 12.5 microg Hg at birth, 62.5 microg EtHg at 2 months, 50 microg EtHg at 4 months, 62.5 microg EtHg at 6 months, and 50 microg EtHg at approximately 18 months, for a total of 237.5 microg EtHg during the first 18 months of life, if all TMS-containing vaccines were administered. Neurobehavioral alterations, especially to the more susceptible fetus and infant, are known to occur after relatively low dose exposures to organic mercury compounds. In effort, to further elucidate the levels of ethyl mercury resulting from exposure to vaccinal TMS, we estimated hair Hg concentrations expected to result from the recommended CDC schedule utilizing a one compartment pharmacokinetic model. This model was developed to predict hair concentrations from acute exposure to methymercury (MeHg) in fish. Modeled hair Hg concentrations in infants exposed to vaccinal TMS are in excess of the Environmental Protection Agency (EPA) safety guidelines of 1 ppm for up to 365 days, with several peak concentrations within this period. More sensitive individuals and those with additional sources of exposure would have higher Hg concentrations. Given that exposure to low levels of mercury during critical stages of development has been associated with neurological disorders in children, including ADD, learning difficulties, and speech delays, the predicted hair Hg concentration resulting from childhood immunizations is cause for concern. Based on these findings, the impact which vaccinal mercury has had on the health of American children warrants further investigation.

http://www.ncbi.nlm.nih.gov/pubmed/?term=11770890

“Given that exposure to low levels of mercury during critical stages of development has been associated with neurological disorders in children, including ADD, learning difficulties, and speech delays, the predicted hair ethyl mercury concentration resulting from childhood immunizations is cause for concern.”

Molecular Psychiatry • 2002

The role of mercury in the pathogenesis of autism

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Autism Spectrum Disorder (ASD) is a neurodevelopmental disorder of unknown etiology in most cases. Studies of monozygotic twins report an average 60% concordance rate, indicating a role for both genetic and environmental factors in disease expression.1 Recent reviews in environmental health have suggested that early exposure to hazardous substances may underlie some cases of neurodevelopmental disorders, including ADHD, learning disabilities, and speech/language difficulties.2 In 1999, thimerosal used as a vaccine preservative was identified as a widespread source of organic mercury exposure in infants.3 Mercury (Hg), a heavy metal, is considered highly neurotoxic.4 The amount of mercury in vaccines, while small, exceeded USEPA safety guidelines on a cumulative basis.3 Certain individuals may exhibit severe adverse reactions to low doses of Hg which are otherwise largely benign to the majority of those exposed.5 Some individuals with idiopathic autism spectrum disorder may represent such a sensitive population. As summarized in this paper, disease characteristics suggest this possibility: (a) ASD traits are known to arise from mercury exposure; (b) onset of ASD symptoms is temporally associated with administration of immunizations; (c) the reported increase in the prevalence of autism in the 1990s closely follows the introduction of two mercury-containing vaccines; and (d) elevated mercury has been detected in biological samples of autistic patients. Since ASD may now affect as many as one in 150 US children,6 and since thimerosal is still used in many products worldwide, confirmation of thimerosal as an environmental agent in autism pathogenesis has important societal and patient implications.

Full Report

http://www.nature.com/mp/journal/v7/n2s/pdf/4001177a.pdf

"... onset of ASD symptoms is temporally associated with administration of immunizations; the reported increase in the prevalence of autism in the 1990s closely follows the introduction of two mercury-containing vaccines; and elevated mercury has been detected in biological samples of autistic patients."

Genes And Immunity • August 2002

Biochemical and molecular basis of thimerosal-induced apoptosis in T cells: a major role of mitochondrial pathway

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Abstract

The major source of thimerosal (ethyl mercury thiosalicylate) exposure is childhood vaccines. It is believed that the children are exposed to significant accumulative dosage of thimerosal during the first 2 years of life via immunization. Because of health-related concerns for exposure to mercury, we examined the effects of thimerosal on the biochemical and molecular steps of mitochondrial pathway of apoptosis in Jurkat T cells. Thimerosal and not thiosalcylic acid (non-mercury component of thimerosal), in a concentration-dependent manner, induced apoptosis in T cells as determined by TUNEL and propidium iodide assays, suggesting a role of mercury in T cell apoptosis. Apoptosis was associated with depolarization of mitochondrial membrane, release of cytochrome c and apoptosis inducing factor (AIF) from the mitochondria, and activation of caspase-9 and caspase-3, but not of caspase-8. In addition, thimerosal in a concentration-dependent manner inhibited the expression of XIAP, cIAP-1 but did not influence cIAP-2 expression. Furthermore, thimerosal enhanced intracellular reactive oxygen species and reduced intracellular glutathione (GSH). Finally, exogenous glutathione protected T cells from thimerosal-induced apoptosis by upregulation of XIAP and cIAP1 and by inhibiting activation of both caspase-9 and caspase-3. These data suggest that thimerosal induces apoptosis in T cells via mitochondrial pathway by inducing oxidative stress and depletion of GSH.

http://www.ncbi.nlm.nih.gov/pubmed/?term=12140745

“The major source of thimerosal (ethyl mercury thiosalicylate) exposure is childhood vaccines. It is believed that the children are exposed to significant accumulative dosage of thimerosal during the first 2 years of life via immunization. These data suggest that thimerosal induces apoptosis in T cells via mitochondrial pathway by inducing oxidative stress and depletion of intracellular glutathione.”

Society for Experimental Biology and Medicine • 2003

Neurodevelopmental Disorders after Thimerosal-Containing Vaccines: A Brief Communication

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Abstract

We were initially highly skeptical that differences in the concentrations of thimerosal in vaccines would have any effect on the incidence rate of neurodevelopmental disorders after childhood immunization. This study presents the first epidemiologic evidence, based upon tens of millions of doses of vaccine administered in the United States, that associates increasing thimerosal from vaccines with neurodevelopmental disorders. Specifically, an analysis of the Vaccine Adverse Events Reporting System (VAERS) database showed statistical increases in the incidence rate of autism (relative risk [RR] = 6.0), mental retardation (RR = 6.1), and speech disorders (RR = 2.2) after thimerosal-containing diphtheria, tetanus, and acellular pertussis (DTaP) vaccines in comparison with thimerosal-free DTaP vaccines. The male/female ratio indicated that autism (17) and speech disorders (2.3) were reported more in males than females after thimerosal-containing DTaP vaccines, whereas mental retardation (1.2) was more evenly reported among male and female vaccine recipients. Controls were employed to determine if biases were present in the data, but none were found. It was determined that overall adverse reactions were reported in similar-aged populations after thimerosal-containing DTaP (2.4 ± 3.2 years old) and thimerosal-free DTaP (2.1 ± 2.8 years old) vaccinations. Acute control adverse reactions such as deaths (RR = 1.0), vasculitis (RR = 1.2), seizures (RR = 1.6), ED visits (RR = 1.4), total adverse reactions (RR = 1.4), and gastroenteritis (RR = 1.1) were reported similarly after thimerosal- containing and thimerosal-free DTaP vaccines. An association between neurodevelopmental disorders and thimerosal-containing DTaP vaccines was found, but additional studies should be conducted to confirm and extend this study.

In recent years, thimerosal, an organic mercury compound that is metabolized to ethylmercury and thiosalicylate and has been present since the 1930s as a preservative in some vaccines and pharmaceutical products to prevent bacterial and fungal contamination, has come under scrutiny. It was determined by the U.S. Food and Drug Administration (FDA) in 1999 under the recommended childhood immunization schedule that infants might be exposed to cumulative doses of ethylmercury that exceed some federal safety guidelines established for exposure to methylmercury, another form of organic mercury (1).

The hypothesis that exposure to thimerosal-containing vaccines could be associated with neurodevelopmental disorders is not established and rests on indirect and incomplete information, primarily from analogies with methylmercury and levels of maximum mercury exposure from vaccines given in children. The hypothesis is biologically possible, but the possible relationship between thimerosal from vaccines and neurodevelopmental disorders of autism, attention deficit/hyperactivity disorder (ADHD), and speech or language delay remains seriously suspect. As of the present, there are no peer-reviewed epidemiological studies in the scientific literature examining the potential association between thimerosal-containing vaccines and neurodevelopmental disorders. Here, we show the first epidemiologic evidence, based upon tens of millions of doses of vaccine administered in the United States, that associates increasing thimerosal from vaccines with neurodevelopmental disorders.

Full Report: http://www.autismhelpforyou.com/EXPERT%20PAPER%20-%20Geier%20-%20Internet%20File.pdf

“... we show the first epidemiologic evidence, based upon tens of millions of doses of vaccine administered in the United States, that associates increasing thimerosal from vaccines with neurodevelopmental disorders.”

Neurotoxic Research • February 2003

Neurotoxicity of organomercurial compounds

Author information

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Abstract

Mercury is a ubiquitous contaminant, and a range of chemical species is generated by human activity and natural environmental change. Elemental mercury and its inorganic and organic compounds have different toxic properties, but all them are considered hazardous in human exposure. In an equimolecular exposure basis, organomercurials with a short aliphatic chain are the most harmful compounds and they may cause irreversible damage to the nervous system. Methylmercury (CH(3)Hg(+)) is the most studied following the neurotoxic outbreaks identified as Minamata disease and the Iraq poisoning. The first description of the CNS pathology dates from 1954. Since then, the clinical neurology, the neuropathology and the mechanisms of neurotoxicity of organomercurials have been widely studied. The high thiol reactivity of CH(3)Hg(+), as well as all mercury compounds, has been suggested to be the basis of their harmful biological effects. However, there is clear selectivity of CH(3)Hg(+) for specific cell types and brain structures, which is not yet fully understood. The main mechanisms involved are inhibition of protein synthesis, microtubule disruption, increase of intracellular Ca(2+) with disturbance of neurotransmitter function, oxidative stress and triggering of excitotoxicity mechanisms. The effects are more damaging during CNS development, leading to alterations of the structure and functionality of the nervous system. The major source of CH(3)Hg(+) exposure is the consumption of fish and, therefore, its intake is practically unavoidable. The present concern is on the study of the effects of low level exposure to CH(3)Hg(+) on human neurodevelopment, with a view to establishing a safe daily intake. Recommendations are 0.4 micro g/kg body weight/day by the WHO and US FDA and, recently, 0.1 micro g/kg body weight/day by the US EPA. Unfortunately, these levels are easily attained with few meals of fish per week, depending on the source of the fish and its position in the food chain.

http://www.ncbi.nlm.nih.gov/pubmed/12835120

"Elemental mercury and its inorganic and organic compounds have different toxic properties, but all them are considered hazardous in human exposure. Recommendations are 0.4 micro g/kg body weight/day by the WHO and US FDA and, recently, 0.1 micro g/kg body weight/day by the US EPA. Unfortunately, these levels are easily attained with few meals of fish per week, depending on the source of the fish and its position in the food chain."

“The evidence presented here shows that the occurrence of neurodevelopmental disorders following thimerosal-containing childhood vaccines does not appear to be coincidental.”

Pediatric Rehabilitation • April 2003

An assessment of the impact of thimerosal on childhood neurodevelopmental disorders

Author information

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Abstract

The prevalence of autism in the US has risen from 1 in approximately 2500 in the mid-1980s to 1 in approximately 300 children in the mid-1990s. The purpose of this study was to evaluate whether mercury from thimerosal in childhood vaccines contributed to neurodevelopmental disorders. Neurodevelopmental disorder dose-response curves for increasing mercury doses of thimerosal in childhood vaccines were determined based upon examination of the Vaccine Adverse Events Reporting System (VAERS) database and the 2001 US’ Department of Education Report. The instantaneous dosage of mercury children received in comparison to the Food and Drug Administration (FDA)’s maximum permissible dose for the oral ingestion of methylmercury was also determined. The dose-response curves showed increases in odds ratios of neurodevelopmental disorders from both the VAERS and US Department of Education data closely linearly correlated with increasing doses of mercury from thimerosal-containing childhood vaccines and that for overall odds ratios statistical significance was achieved. Similar slopes and linear regression coefficients for autism odds ratios in VAERS and the US Department of Education data help to mutually validate each other. Controls employed in the VAERS and US Department of Education data showed minimal biases. The evidence presented here shows that the occurrence of neurodevelopmental disorders following thimerosal-containing childhood vaccines does not appear to be coincidental.

http://www.ncbi.nlm.nih.gov/pubmed/14534046

“An association between neurodevelopmental disorders and thimerosal-containing DTaP vaccines was found ...”

Experiments In Biological Medicine • June 2003

Neurodevelopmental disorders after thimerosal-containing vaccines: a brief communication

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Abstract

We were initially highly skeptical that differences in the concentrations of thimerosal in vaccines would have any effect on the incidence rate of neurodevelopmental disorders after childhood immunization. This study presents the first epidemiologic evidence, based upon tens of millions of doses of vaccine administered in the United States, that associates increasing thimerosal from vaccines with neurodevelopmental disorders. Specifically, an analysis of the Vaccine Adverse Events Reporting System (VAERS) database showed statistical increases in the incidence rate of autism (relative risk [RR] = 6.0), mental retardation (RR = 6.1), and speech disorders (RR = 2.2) after thimerosal-containing diphtheria, tetanus, and acellular pertussis (DTaP) vaccines in comparison with thimerosal-free DTaP vaccines. The male/female ratio indicated that autism (17) and speech disorders (2.3) were reported more in males than females after thimerosal-containing DTaP vaccines, whereas mental retardation (1.2) was more evenly reported among male and female vaccine recipients. Controls were employed to determine if biases were present in the data, but none were found. It was determined that overall adverse reactions were reported in similar-aged populations after thimerosal-containing DTaP (2.4 +/- 3.2 years old) and thimerosal-free DTaP (2.1 +/- 2.8 years old) vaccinations. Acute control adverse reactions such as deaths (RR = 1.0), vasculitis (RR = 1.2), seizures (RR = 1.6), ED visits (RR = 1.4), total adverse reactions (RR = 1.4), and gastroenteritis (RR = 1.1) were reported similarly after thimerosal-containing and thimerosal-free DTaP vaccines. An association between neurodevelopmental disorders and thimerosal-containing DTaP vaccines was found, but additional studies should be conducted to confirm and extend this study.

http://www.ncbi.nlm.nih.gov/pubmed/12773696

Environmental Toxicology • June 2003

Environmental exposure to mercury and its toxicopathologic implications for public health

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Abstract

Mercury is a toxic and hazardous metal that occurs naturally in the earth's crust. Natural phenomena such as erosion and volcanic eruptions, and anthropogenic activities like metal smelting and industrial production and use may lead to substantial contamination of the environment with mercury. Through consumption of mercury in food, the populations of many areas, particularly in the developing world, have been confronted with catastrophic outbreaks of mercury-induced diseases and mortality. Countries such as Japan, Iraq, Ghana, the Seychelles, and the Faroe Islands have faced such epidemics, which have unraveled the insidious and debilitating nature of mercury poisoning. Its creeping neurotoxicity is highly devastating, particularly in the central and peripheral nervous systems of children. Central nervous system defects and erethism as well as arrythmias, cardiomyopathies, and kidney damage have been associated with mercury exposure. Necrotizing bronchitis and pneumonitis arising from inhalation of mercury vapor can result in respiratory failure. Mercury is also considered a potent immunostimulant and -suppressant, depending on exposure dose and individual susceptibility, producing a number of pathologic sequelae including lymphoproliferation, hypergammaglobulinemia, and total systemic hyper- and hyporeactivities. In this review we discuss the sources of mercury and the potential for human exposure; its biogeochemical cycling in the environment; its systemic, immunotoxic, genotoxic/carcinogenic, and teratogenic health effects; and the dietary influences on its toxicity; as well as the important considerations in risk assessment and management of mercury poisoning.

http://www.ncbi.nlm.nih.gov/pubmed/12740802

"Its creeping neurotoxicity is highly devastating, particularly in the central and peripheral nervous systems of children."

"... the present study provides further insight into one possible mechanism by which early mercury exposures could increase the risk of autism."

International Journal Of Toxicology • July 2003

Reduced levels of mercury in first baby haircuts of autistic children

Author information

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Abstract

Reported rates of autism have increased sharply in the United States and the United Kingdom. One possible factor underlying these increases is increased exposure to mercury through thimerosal-containing vaccines, but vaccine exposures need to be evaluated in the context of cumulative exposures during gestation and early infancy. Differential rates of postnatal mercury elimination may explain why similar gestational and infant exposures produce variable neurological effects. First baby haircut samples were obtained from 94 children diagnosed with autism using Diagnostic and Statistical Manual of Mental Disorders, 4th edition (DSM IV) criteria and 45 age- and gender-matched controls. Information on diet, dental amalgam fillings, vaccine history, Rho D immunoglobulin administration, and autism symptom severity was collected through a maternal survey questionnaire and clinical observation. Hair mercury levels in the autistic group were 0.47 ppm versus 3.63 ppm in controls, a significant difference. The mothers in the autistic group had significantly higher levels of mercury exposure through Rho D immunoglobulin injections and amalgam fillings than control mothers. Within the autistic group, hair mercury levels varied significantly across mildly, moderately, and severely autistic children, with mean group levels of 0.79, 0.46, and 0.21 ppm, respectively. Hair mercury levels among controls were significantly correlated with the number of the mothers' amalgam fillings and their fish consumption as well as exposure to mercury through childhood vaccines, correlations that were absent in the autistic group. Hair excretion patterns among autistic infants were significantly reduced relative to control. These data cast doubt on the efficacy of traditional hair analysis as a measure of total mercury exposure in a subset of the population. In light of the biological plausibility of mercury's role in neurodevelopmental disorders, the present study provides further insight into one possible mechanism by which early mercury exposures could increase the risk of autism.

http://www.ncbi.nlm.nih.gov/pubmed/12933322

Toxicological Science • August 2003

Thimerosal induces DNA breaks, caspase-3 activation, membrane damage, and cell death in cultured human neurons and fibroblasts

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Abstract

Thimerosal is an organic mercurial compound used as a preservative in biomedical preparations. Little is known about the reactions of human neuronal and skin cells to its micro- and nanomolar concentrations, which can occur after using thimerosal-containing products. A useful combination of fluorescent techniques for the assessment of thimerosal toxicity is introduced. Short-term thimerosal toxicity was investigated in cultured human cerebral cortical neurons and in normal human fibroblasts. Cells were incubated with 125-nM to 250-microM concentrations of thimerosal for 45 min to 24 h. A 4', 6-diamidino-2-phenylindole dihydrochloride (DAPI) dye exclusion test was used to identify nonviable cells and terminal transferase-based nick-end labeling (TUNEL) to label DNA damage. Detection of active caspase-3 was performed in live cell cultures using a cell-permeable fluorescent caspase inhibitor. The morphology of fluorescently labeled nuclei was analyzed. After 6 h of incubation, the thimerosal toxicity was observed at 2 microM based on the manual detection of the fluorescent attached cells and at a 1-microM level with the more sensitive GENios Plus Multi-Detection Microplate Reader with Enhanced Fluorescence. The lower limit did not change after 24 h of incubation. Cortical neurons demonstrated higher sensitivity to thimerosal compared to fibroblasts. The first sign of toxicity was an increase in membrane permeability to DAPI after 2 h of incubation with 250 microM thimerosal. A 6-h incubation resulted in failure to exclude DAPI, generation of DNA breaks, caspase-3 activation, and development of morphological signs of apoptosis. We demonstrate that thimerosal in micromolar concentrations rapidly induce membrane and DNA damage and initiate caspase-3-dependent apoptosis in human neurons and fibroblasts. We conclude that a proposed combination of fluorescent techniques can be useful in analyzing the toxicity of thimerosal.

http://www.ncbi.nlm.nih.gov/pubmed/12773768

"We demonstrate that thimerosal in micromolar concentrations rapidly induce membrane and DNA damage and initiate caspase-3-dependent apoptosis in human neurons and fibroblasts."

"This study provides strong epidemiological evidence for a link between increasing mercury from thimerosal-containing childhood vaccines and neurodevelopment disorders and heart disease."

Journal of American Physicians and Surgeons • Volume 8, Number 1 • Spring 2003

Thimerosal in Childhood Vaccines, Neurodevelopment Disorders, and Heart Disease in the United States

Mark R. Geier, M.D., Ph.D. David A. Geier

Abstract

In this study, we evaluated doses of mercury from thimerosal-containing childhood immunizations in compari- son to US Federal Safety Guidelines and the effects of increasing doses of mercury on the incidence of neurodevelopment disorders and heart disease. This study showed that children received mercury from this source in excess of the Federal Safety Guidelines for the oral ingestion of methylmercury. Our analyses showed increasing relative risks for neurodevelopment disorders and heart disease with increasing doses of mercury. This study provides strong epidemiological evidence for a link between mercury exposure from thimerosal-containing childhood vaccines and neurodevelopment disorders.

Conclusion

This study provides strong epidemiological evidence for a link between increasing mercury from thimerosal-containing childhood vaccines and neurodevelopment disorders and heart disease. In light of voluminous literature supporting the biologic mechanisms for mercury-induced adverse reactions, the presence of amounts of mercury in thimerosal-containing childhood vaccines exceeding Federal Safety Guidelines for the oral ingestion of mercury, and previous epidemiological studies showing adverse reactions from such vaccines, a causal relationship between thimerosal- containing childhood vaccines and neurodevelopment disorders and heart disease appears to be confirmed. It is to be hoped that complete removal of thimerosal from all childhood vaccines will help to stem the tragic, apparently iatrogenic epidemic of autism and speech disorders that the United States is now facing.

Full Report

http://www.jpands.org/vol8no1/geier.pdf

Toxicology And Applied Pharmacology • October 2003

Brain barrier systems: a new frontier in metal neurotoxicological research

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Abstract

The concept of brain barriers or a brain barrier system embraces the blood-brain interface, referred to as the blood-brain barrier, and the blood-cerebrospinal fluid (CSF) interface, referred to as the blood-CSF barrier. These brain barriers protect the CNS against chemical insults, by different complementary mechanisms. Toxic metal molecules can either bypass these mechanisms or be sequestered in and therefore potentially deleterious to brain barriers. Supportive evidence suggests that damage to blood-brain interfaces can lead to chemical-induced neurotoxicities. This review article examines the unique structure, specialization, and function of the brain barrier system, with particular emphasis on its toxicological implications. Typical examples of metal transport and toxicity at the barriers, such as lead (Pb), mercury (Hg), iron (Fe), and manganese (Mn), are discussed in detail with a special focus on the relevance to their toxic neurological consequences. Based on these discussions, the emerging research needs, such as construction of the new concept of blood-brain regional barriers, understanding of chemical effect on aged or immature barriers, and elucidation of the susceptibility of tight junctions to toxicants, are identified and addressed in this newly evolving field of neurotoxicology. They represent both clear challenges and fruitful research domains not only in neurotoxicology, but also in neurophysiology and pharmacology.

http://www.ncbi.nlm.nih.gov/pubmed/14554098

“This review article examines the unique structure, specialization, and function of the brain barrier system, with particular emphasis on its toxicological implications. Typical examples of metal transport and toxicity at the barriers, such as ... mercury ... are discussed in detail with a special focus on the relevance to their toxic neurological consequences.”

Toxicology And Applied Pharmacology • January 2004

Dose-response study of thimerosal-induced murine systemic autoimmunity

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Abstract

The organic compound ethylmercurithiosalicylate (thimerosal), which is primarily present in the tissues as ethylmercury, has caused illness and several deaths due to erroneous handling when used as a disinfectant or as a preservative in medical preparations. Lately, possible health effects of thimerosal in childhood vaccines have been much discussed. Thimerosal is a well-known sensitizing agent, although usually of no clinical relevance. In rare cases, thimerosal has caused systemic immune reactions including acrodynia. We have studied if thimerosal might induce the systemic autoimmune condition observed in genetically susceptible mice after exposure to inorganic mercury. A.SW mice were exposed to 1.25-40 mg thimerosal/l drinking water for 70 days. Antinucleolar antibodies, targeting the 34-kDa protein fibrillarin, developed in a dose-related pattern and first appeared after 10 days in the two highest dose groups. The lowest observed adverse effect level (LOAEL) for antifibrillarin antibodies was 2.5 mg thimerosal/l, corresponding to an absorbed dose of 147 microg Hg/kg bw and a concentration of 21 and 1.9 microg Hg/g in the kidney and lymph nodes, respectively. The same LOAEL was found for tissue immune-complex deposits. The total serum concentration of IgE, IgG1, and IgG2a showed a significant dose-related increase in thimerosal-treated mice, with a LOAEL of 5 mg thimerosal/l for IgG1 and IgE, and 20 mg thimerosal/l for IgG2a. The polyclonal B-cell activation showed a significant dose-response relationship with a LOAEL of 10 mg thimerosal/l. Therefore, thimerosal induces in genetically susceptible mice a systemic autoimmune syndrome very similar to that seen after treatment with inorganic mercury, although a higher absorbed dose of Hg is needed using thimerosal. The autoimmune syndrome induced by thimerosal is different from the weaker and more restricted autoimmune reaction observed after treatment with an equipotent dose of methylmercury.

http://www.ncbi.nlm.nih.gov/pubmed/14736497

“... thimerosal induces in genetically susceptible mice a systemic autoimmune syndrome ...”

Toxicology • January 2004

Effect of thimerosal, a preservative in vaccines, on intracellular Ca2+ concentration of rat cerebellar neurons

Author information

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Abstract

The effect of thimerosal, an organomercurial preservative in vaccines, on cerebellar neurons dissociated from 2-week-old rats was compared with those of methylmercury using a flow cytometer with appropriate fluorescent dyes. Thimerosal and methylmercury at concentrations ranging from 0.3 to 10 microM increased the intracellular concentration of Ca2+ ([Ca2+]i) in a concentration-dependent manner. The potency of 10 microM thimerosal to increase the [Ca2+]i was less than that of 10 microM methylmercury. Their effects on the [Ca2+]i were greatly attenuated, but not completely suppressed, under external Ca(2+)-free condition, suggesting a possibility that both agents increase membrane Ca2+ permeability and release Ca2+ from intracellular calcium stores. The effect of 10 microM thimerosal was not affected by simultaneous application of 30 microM L-cysteine whereas that of 10 microM methylmercury was significantly suppressed. The potency of thimerosal was similar to that of methylmercury in the presence of L-cysteine. Both agents at 1 microM or more similarly decreased the cellular content of glutathione in a concentration-dependent manner, suggesting an increase in oxidative stress. Results indicate that thimerosal exerts some cytotoxic actions on cerebellar granule neurons dissociated from 2-week-old rats and its potency is almost similar to that of methylmercury.

http://www.ncbi.nlm.nih.gov/pubmed/14698570

“Results indicate that thimerosal exerts some cytotoxic actions on cerebellar granule neurons ... its potency is almost similar to that of methylmercury.”

Medical Science Monitor • March 2004

A comparative evaluation of the effects of MMR immunization and mercury doses from thimerosal-containing childhood vaccines on the population prevalence of autism

Author information

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Abstract

BACKGROUND

The purpose of the study was to evaluate the effects of MMR immunization and mercury from thimerosal-containing childhood vaccines on the prevalence of autism.

MATERIAL/METHODS

Evaluations of the Biological Surveillance Summaries of the Centers for Disease Control and Prevention (CDC), the U.S. Department of Education datasets, and the CDC's yearly live birth estimates were undertaken.

RESULTS

It was determined that there was a close correlation between mercury doses from thimerosal--containing childhood vaccines and the prevalence of autism from the late 1980s through the mid-1990s. In contrast, there was a potential correlation between the number of primary pediatric measles-containing vaccines administered and the prevalence of autism during the 1980s. In addition, it was found that there were statistically significant odds ratios for the development of autism following increasing doses of mercury from thimerosal-containing vaccines (birth cohorts: 1985 and 1990-1995) in comparison to a baseline measurement (birth cohort: 1984). The contribution of thimerosal from childhood vaccines (>50% effect) was greater than MMR vaccine on the prevalence of autism observed in this study.

CONCLUSIONS

The results of this study agree with a number of previously published studies. These studies have shown that there is biological plausibility and epidemiological evidence showing a direct relationship between increasing doses of mercury from thimerosal-containing vaccines and neurodevelopmental disorders, and measles-containing vaccines and serious neurological disorders. It is recommended that thimerosal be removed from all vaccines, and additional research be undertaken to produce a MMR vaccine with an improved safety profile.

http://www.ncbi.nlm.nih.gov/pubmed/14976450

"The results of this study agree with a number of previously published studies. These studies have shown that there is biological plausibility and epidemiological evidence showing a direct relationship between increasing doses of mercury from thimerosal-containing vaccines and neurodevelopmental disorders, and measles-containing vaccines and serious neurological disorders."

Medical Hypotheses • March 2004

Thimerosal and autism?
A plausible hypothesis that should not be dismissed

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Abstract

The autism-mercury hypothesis first described by Bernard et al. has generated much interest and controversy. The Institute of Medicine (IOM) reviewed the connection between mercury-containing vaccines and neurodevelopmental disorders, including autism. They concluded that the hypothesis was biologically plausible but that there was insufficient evidence to accept or reject a causal connection and recommended a comprehensive research program. Without citing new experimental evidence, a number of observers have offered opinions on the subject, some of which reject the IOM's conclusions. In a recent review, Nelson and Bauman argue that a link between the preservative thimerosal, the source of the mercury in childhood vaccines, is improbable. In their defense of thimerosal, these authors take a narrow view of the original hypothesis, provide no new evidence, and rely on selective citations and flawed reasoning. We provide evidence here to refute the Nelson and Bauman critique and to defend the autism-mercury hypothesis.

http://www.ncbi.nlm.nih.gov/pubmed/?term=15082108

"We provide evidence here to refute the Nelson and Bauman critique and to defend the autism-mercury hypothesis."

Molecular Psychiatry • April 2004

Activation of methionine synthase by insulin-like growth factor-1 and dopamine: a target for neurodevelopmental toxins and thimerosal

Author information

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Abstract

Methylation events play a critical role in the ability of growth factors to promote normal development. Neurodevelopmental toxins, such as ethanol and heavy metals, interrupt growth factor signaling, raising the possibility that they might exert adverse effects on methylation. We found that insulin-like growth factor-1 (IGF-1)- and dopamine-stimulated methionine synthase (MS) activity and folate-dependent methylation of phospholipids in SH-SY5Y human neuroblastoma cells, via a PI3-kinase- and MAP-kinase-dependent mechanism. The stimulation of this pathway increased DNA methylation, while its inhibition increased methylation-sensitive gene expression. Ethanol potently interfered with IGF-1 activation of MS and blocked its effect on DNA methylation, whereas it did not inhibit the effects of dopamine. Metal ions potently affected IGF-1 and dopamine-stimulated MS activity, as well as folate-dependent phospholipid methylation: Cu(2+) promoted enzyme activity and methylation, while Cu(+), Pb(2+), Hg(2+) and Al(3+) were inhibitory. The ethylmercury-containing preservative thimerosal inhibited both IGF-1- and dopamine-stimulated methylation with an IC(50) of 1 nM and eliminated MS activity. Our findings outline a novel growth factor signaling pathway that regulates MS activity and thereby modulates methylation reactions, including DNA methylation. The potent inhibition of this pathway by ethanol, lead, mercury, aluminum and thimerosal suggests that it may be an important target of neurodevelopmental toxins.

http://www.ncbi.nlm.nih.gov/pubmed/14745455

“The potent inhibition of this pathway by ethanol, lead, mercury, aluminum and thimerosal suggests that it may be an important target of neurodevelopmental toxins.”

International Journal Of Hygiene And Environmental Health • September 2004

Amalgam studies: disregarding basic principles of mercury toxicity

Author information

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Abstract

Dental amalgam, which has been used for over 150 years in dental practice, consists of about 50% metallic mercury. Studies on animal and humans show that mercury is continuously released from dental amalgam and absorbed by several body tissues. It is widely accepted that the main source of mercury vapor is dental amalgam and it contributes substantially to mercury load in human body tissues. There is still a controversy about the consequences of this additional mercury exposure from amalgam to human health. Many studies were performed to evaluate possible adverse effects. In this comment, these studies were analyzed with regard to their methodical quality by considering the newest findings on mercury toxicity and metabolism. In sum, a number of studies are methodically flawed drawing inaccurate conclusions as to the safety of dental amalgam.

http://www.ncbi.nlm.nih.gov/pubmed/?term=15471104

“Studies on animal and humans show that mercury is continuously released from dental amalgam and absorbed by several body tissues. It is widely accepted that the main source of mercury vapor is dental amalgam and it contributes substantially to mercury load in human body tissues. In sum, a number of studies are methodically flawed drawing inaccurate conclusions as to the safety of dental amalgam.”

Molecular Psychiatry • September 2004

Neurotoxic effects of postnatal thimerosal are mouse strain dependent

Author information

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Abstract

The developing brain is uniquely susceptible to the neurotoxic hazard posed by mercurials. Host differences in maturation, metabolism, nutrition, sex, and autoimmunity influence outcomes. How population-based variability affects the safety of the ethylmercury-containing vaccine preservative, thimerosal, is unknown. Reported increases in the prevalence of autism, a highly heritable neuropsychiatric condition, are intensifying public focus on environmental exposures such as thimerosal. Immune profiles and family history in autism are frequently consistent with autoimmunity. We hypothesized that autoimmune propensity influences outcomes in mice following thimerosal challenges that mimic routine childhood immunizations. Autoimmune disease-sensitive SJL/J mice showed growth delay; reduced locomotion; exaggerated response to novelty; and densely packed, hyperchromic hippocampal neurons with altered glutamate receptors and transporters. Strains resistant to autoimmunity, C57BL/6J and BALB/cJ, were not susceptible. These findings implicate genetic influences and provide a model for investigating thimerosal-related neurotoxicity.

http://www.ncbi.nlm.nih.gov/pubmed/?term=15184908

“These findings implicate genetic influences and provide a model for investigating thimerosal-related neurotoxicity.”

Toxicology In Vitro • October 2004

Property of thimerosal-induced decrease in cellular content of glutathione in rat thymocytes: a flow cytometric study with 5-chloromethylfluorescein diacetate

Author information

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Abstract

There is a concern on the part of public health community that adverse health consequences by thimerosal, a preservative in vaccines for infants, may occur among infants during immunization schedule. Therefore, the effect of thimerosal on cellular content of glutathione was examined on thymocytes obtained from 4-week-old rats using a flow cytometer and 5-chloromethylfluorescein diacetate. Thimerosal at concentrations ranging from 1 to 10 microM reduced the cellular content of glutathione in a concentration-dependent manner, and the complete depletion of cellular glutathione was observed when the cells were treated with 30 microM thimerosal. L-Cysteine significantly attenuated the actions of thimerosal to reduce the glutathione content and to increase the intracellular Ca2+ concentration. Prolonged incubation (24 h) with 1-3 microM thimerosal induced the apoptosis. The cytotoxic action of thimerosal was greatly augmented when the cells suffered oxidative stress induced by H2O2. It may be unlikely that thimerosal exerts potent cytotoxic action under the in vivo condition because the blood concentration of thimerosal after receiving vaccines does not seem to reach micromolar range and nonprotein thiols at micromolar concentrations are present in the blood.

http://www.ncbi.nlm.nih.gov/pubmed/?term=15251173

“Thimerosal at concentrations ranging from 1 to 10 microM reduced the cellular content of glutathione in a concentration-dependent manner, and the complete depletion of cellular glutathione was observed when the cells were treated with 30 microM thimerosal.”

"The present study provides additional epidemiological evidence supporting previous epidemiological, clinical and experimental evidence that administration of thimerosal-containing vaccines in the United States resulted in a significant number of children developing Neurological Disorders."

International Journal Of Toxicology • November 2004

Neurodevelopmental disorders following thimerosal-containing childhood immunizations: a follow-up analysis

Author information

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Abstract

The authors previously published the first epidemiological study from the United States associating thimerosal from childhood vaccines with neurodevelopmental disorders (NDs) based upon assessment of the Vaccine Adverse Event Reporting System (VAERS). A number of years have gone by since their previous analysis of the VAERS. The present study was undertaken to determine whether the previously observed effect between thimerosal-containing childhood vaccines and NDs are still apparent in the VAERS as children have had a chance to further mature and potentially be diagnosed with additional NDs. In the present study, a cohort of children receiving thimerosal-containing diphtheria-tetanus-acellular pertussis (DTaP) vaccines in comparison to a cohort of children receiving thimerosal-free DTaP vaccines administered from 1997 through 2000 based upon an assessment of adverse events reported to the VAERS were evaluated. It was determined that there were significantly increased odds ratios (ORs) for autism (OR = 1.8, $p < .05$), mental retardation (OR = 2.6, $p < .002$), speech disorder (OR = 2.1, $p < .02$), personality disorders (OR = 2.6, $p < .01$), and thinking abnormality (OR = 8.2, $p < .01$) adverse events reported to the VAERS following thimerosal-containing DTaP vaccines in comparison to thimerosal-free DTaP vaccines. Potential confounders and reporting biases were found to be minimal in this assessment of the VAERS. It was observed, even though the media has reported a potential association between autism and thimerosal exposure, that the other NDs analyzed in this assessment of the VAERS had significantly higher ORs than autism following thimerosal-containing DTaP vaccines in comparison to thimerosal-free DTaP vaccines. The present study provides additional epidemiological evidence supporting previous epidemiological, clinical and experimental evidence that administration of thimerosal-containing vaccines in the United States resulted in a significant number of children developing NDs.

http://www.ncbi.nlm.nih.gov/pubmed/15764492

Washington, D.C. • 2004

Vaccines And Autism

Immunization Safety Review Committee
Board on Health Promotion and Disease Prevention
Institute Of Medicine Of The National Academies
The National Academies Press

http://www.nap.edu/read/10997/chapter/1

"It has been estimated that about 15% of the population may show enhanced susceptibility to mercury exposure."

“We provide evidence here to refute the Nelson and Bauman critique and to defend the autism-mercury hypothesis.”

Medical Hypotheses • 2004

Thimerosal and autism? A plausible hypothesis that should not be dismissed

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Abstract

The autism-mercury hypothesis first described by Bernard et al. has generated much interest and controversy. The Institute of Medicine (IOM) reviewed the connection between mercury-containing vaccines and neurodevelopmental disorders, including autism. They concluded that the hypothesis was biologically plausible but that there was insufficient evidence to accept or reject a causal connection and recommended a comprehensive research program. Without citing new experimental evidence, a number of observers have offered opinions on the subject, some of which reject the IOM’s conclusions. In a recent review, Nelson and Bauman argue that a link between the preservative thimerosal, the source of the mercury in childhood vaccines, is improbable. In their defense of thimerosal, these authors take a narrow view of the original hypothesis, provide no new evidence, and rely on selective citations and flawed reasoning. We provide evidence here to refute the Nelson and Bauman critique and to defend the autism-mercury hypothesis.

http://www.ncbi.nlm.nih.gov/pubmed/15082108

Neurotoxicology • January 2005

Thimerosal neurotoxicity is associated with glutathione depletion: protection with glutathione precursors

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Abstract

Thimerosol is an antiseptic containing 49.5% ethyl mercury that has been used for years as a preservative in many infant vaccines and in flu vaccines. Environmental methyl mercury has been shown to be highly neurotoxic, especially to the developing brain. Because mercury has a high affinity for thiol (sulfhydryl (-SH)) groups, the thiol-containing antioxidant, glutathione (GSH), provides the major intracellular defense against mercury-induced neurotoxicity. Cultured neuroblastoma cells were found to have lower levels of GSH and increased sensitivity to thimerosol toxicity compared to glioblastoma cells that have higher basal levels of intracellular GSH. Thimerosal-induced cytotoxicity was associated with depletion of intracellular GSH in both cell lines. Pretreatment with 100 microM glutathione ethyl ester or N-acetylcysteine (NAC), but not methionine, resulted in a significant increase in intracellular GSH in both cell types. Further, pretreatment of the cells with glutathione ethyl ester or NAC prevented cytotoxicity with exposure to 15 microM Thimerosal. Although Thimerosal has been recently removed from most children's vaccines, it is still present in flu vaccines given to pregnant women, the elderly, and to children in developing countries. The potential protective effect of GSH or NAC against mercury toxicity warrants further research as possible adjunct therapy to individuals still receiving Thimerosal-containing vaccinations.

http://www.ncbi.nlm.nih.gov/pubmed/15527868

"Although Thimerosal has been recently removed from most children's vaccines, it is still present in flu vaccines given to pregnant women, the elderly, and to children in developing countries."

Archives Of Environmental Occupational Health • January 2005

Genetic influences on the retention of inorganic mercury

Author information

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Abstract

Mercury is eliminated as glutathione (GSH) conjugates. GSH production is mediated by glutamyl-cysteine ligase (GCL), and conjugation by glutathione S-transferases (GST). This study tested if polymorphisms in GCL and GST genes modify mercury retention in humans exposed to elemental mercury vapor. Total mercury concentrations in whole blood, plasma and urine, and genotypes for GCLC, GCLM, GSTA1, GSTM1, GSTP1, and GSTT1 were determined in 309 gold miners, gold buyers and controls. The presence of the GCLM-588T allele was associated with increased blood, plasma and urine mercury levels. These results indicate that genotypes with decreased GSH availability for mercury conjugation affect the metabolism of inorganic mercury.

http://www.ncbi.nlm.nih.gov/pubmed/?term=16961004

“These results indicate that genotypes with decreased glutathione availability for mercury conjugation affect the metabolism of inorganic mercury.”

Medical Science Monitor • April 2005

A two-phased population epidemiological study of the safety of thimerosal-containing vaccines: a follow-up analysis

Author information

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Abstract

BACKGROUND

Thimerosal is an ethylmercury-containing preservative in vaccines. Toxicokinetic studies have shown children received doses of mercury from thimerosal-containing vaccines (TCVs) that were in excess of safety guidelines. Previously, an ecological study showing a significant association between TCVs and neurodevelopmental disorders (NDs) in the US was published in this journal.

MATERIAL/METHODS

A two phased population-based epidemiological study was undertaken. Phase one evaluated reported NDs to the Vaccine Adverse Event Reporting System (VAERS) following thimerosal-containing Diphtheria-Tetanus-acellular-Pertussis (DTaP) vaccines in comparison to thimerosal-free DTaP vaccines administered from 1997 through 2001. Phase two evaluated the automated Vaccine Safety Datalink (VSD) for cumulative exposures to mercury from TCVs at 1-, 2-, 3-, and 6-months-of-age for infants born from 1992 through 1997 and the eventual risk of developing NDs.

RESULTS

Phase one showed significantly increased risks for autism, speech disorders, mental retardation, personality disorders, and thinking abnormalities reported to VAERS following thimerosal-containing DTaP vaccines in comparison to thimerosal-free DTaP vaccines. Phase two showed significant associations between cumulative exposures to thimerosal and the following types of NDs: unspecified developmental delay, tics, attention deficit disorder (ADD), language delay, speech delay, and neurodevelopmental delays in general.

CONCLUSIONS

This study showed that exposure to mercury from TCVs administered in the US was a consistent significant risk factor for the development of NDs. It is clear from these data and other recent publications linking TCVs with NDs that additional ND research should be undertaken in the context of evaluating mercury-associated exposures and thimerosal-free vaccines should be made available.

http://www.ncbi.nlm.nih.gov/pubmed/?term=15795695

“This study showed that exposure to mercury from Thimerosal containing vaccines administered in the US was a consistent significant risk factor for the development of NDs.”

Neurotoxicology • June 2005

Mitochondrial mediated thimerosal-induced apoptosis in a human neuroblastoma cell line (SK-N-SH)

Author information

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Abstract

Environmental exposure to mercurials continues to be a public health issue due to their deleterious effects on immune, renal and neurological function. Recently the safety of thimerosal, an ethyl mercury-containing preservative used in vaccines, has been questioned due to exposure of infants during immunization. Mercurials have been reported to cause apoptosis in cultured neurons; however, the signaling pathways resulting in cell death have not been well characterized. Therefore, the objective of this study was to identify the mode of cell death in an in vitro model of thimerosal-induced neurotoxicity, and more specifically, to elucidate signaling pathways which might serve as pharmacological targets. Within 2 h of thimerosal exposure (5 microM) to the human neuroblastoma cell line, SK-N-SH, morphological changes, including membrane alterations and cell shrinkage, were observed. Cell viability, assessed by measurement of lactate dehydrogenase (LDH) activity in the medium, as well as the 3-[4,5-dimethylthiazol-2-yl]-2,5-diphenyltetrazolium bromide (MTT) assay, showed a time- and concentration-dependent decrease in cell survival upon thimerosal exposure. In cells treated for 24 h with thimerosal, fluorescence microscopy indicated cells undergoing both apoptosis and oncosis/necrosis. To identify the apoptotic pathway associated with thimerosal-mediated cell death, we first evaluated the mitochondrial cascade, as both inorganic and organic mercurials have been reported to accumulate in the organelle. Cytochrome c was shown to leak from the mitochondria, followed by caspase 9 cleavage within 8 h of treatment. In addition, poly(ADP-ribose) polymerase (PARP) was cleaved to form a 85 kDa fragment following maximal caspase 3 activation at 24 h. Taken together these findings suggest deleterious effects on the cytoarchitecture by thimerosal and initiation of mitochondrial-mediated apoptosis.

http://www.ncbi.nlm.nih.gov/pubmed/15869795

“Taken together these findings suggest deleterious effects on the cytoarchitecture by thimerosal and initiation of mitochondrial-mediated apoptosis.”

Toxicology Science • July 2005

Effects of thimerosal on NGF signal transduction and cell death in neuroblastoma cells

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Abstract

Signaling through neurotrophic receptors is necessary for differentiation and survival of the developing nervous system. The present study examined the effects of the organic mercury compound thimerosal on nerve growth factor signal transduction and cell death in a human neuroblastoma cell line (SH-SY5Y cells). Following exposure to 100 ng/ml NGF and increasing concentrations of thimerosal (1 nM-10 microM), we measured the activation of TrkA, MAPK, and PKC-delta. In controls, the activation of TrkA MAPK and PKC-delta peaked after 5 min of exposure to NGF and then decreased but was still detectable at 60 min. Concurrent exposure to increasing concentrations of thimerosal and NGF for 5 min resulted in a concentration-dependent decrease in TrkA and MAPK phosphorylation, which was evident at 50 nM for TrkA and 100 nM for MAPK. Cell viability was assessed by the LDH assay. Following 24-h exposure to increasing concentrations of thimerosal, the EC50 for cell death in the presence or absence of NGF was 596 nM and 38.7 nM, respectively. Following 48-h exposure to increasing concentrations of thimerosal, the EC50 for cell death in the presence and absence of NGF was 105 nM and 4.35 nM, respectively. This suggests that NGF provides protection against thimerosal cytotoxicity. To determine if apoptotic versus necrotic cell death was occurring, oligonucleosomal fragmented DNA was quantified by ELISA. Control levels of fragmented DNA were similar in both the presence and absence of NGF. With and without NGF, thimerosal caused elevated levels of fragmented DNA appearing at 0.01 microM (apoptosis) to decrease at concentrations >1 microM (necrosis). These data demonstrate that thimerosal could alter NGF-induced signaling in neurotrophin-treated cells at concentrations lower than those responsible for cell death.

Full Report

http://toxsci.oxfordjournals.org/content/86/1/132.long

“These data demonstrate that thimerosal could alter NGF-induced signaling in neurotrophin-treated cells at concentrations lower than those responsible for cell death.”

Toxicology And Applied Pharmacology • August 2005

The association between genetic polymorphisms of coproporphyrinogen oxidase and an atypical porphyrinogenic response to mercury exposure in humans

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Abstract

Previous studies have demonstrated highly specific urinary porphyrin profile (UPP) changes in response to mercury (Hg) exposure in animals and human subjects and have defined the biochemical etiology of this effect as selective alteration of the heme pathway enzymes, uroporphyrinogen decarboxylase (UROD), and coproporphyrinogen oxidase (CPOX) by Hg in the kidney. Ongoing validation studies in a population of dental practitioners with low-level occupational Hg exposure have demonstrated the predicted UPP change among approximately 85% of subjects. This study focused on the genetic etiology of an atypical porphyrinogenic response (APR) seen among the remaining 15% of Hg-exposed subjects, characterized by excess excretion of 4- and 5-carboxyl porphyrins and also of the atypical ketoisocoproporphyrin (KICP). Automated DNA-sequencing-based assays were developed to examine the 7 exons and flanking intron-exon boundaries of the CPOX gene. Among several polymorphisms identified, an A814C variant in exon 4 encoding a N272H substitution was found to be predominant among subjects with the APR. Studies suggest that this variant CPOX preferentially converts the upstream 5-carboxylporphyrin (5-CP) to KICP. By partially inhibiting the 5- to 4-decarboxylation step of UROD, Hg promotes 5-CP accumulation, accounting for excess KICP excretion and the APR in Hg-exposed subjects carrying the variant CPOX gene. This finding represents the first report of a polymorphism in a human gene that modifies the effect of Hg on a biological process. The APR might serve as a biomarker of both Hg exposure and susceptibility to Hg toxicity.

http://www.ncbi.nlm.nih.gov/pubmed/?term=15967199

“This finding represents the first report of a polymorphism in a human gene that modifies the effect of ethyl mercury on a biological process. The atypical porphyrinogenic response might serve as a biomarker of both mercury exposure and susceptibility to mercury toxicity.”

"The results indicate that methyl mercury

is not a suitable reference for risk assessment from exposure to thimerosal-derived ethyl mercury."

Environmental Health Perspectives • August 2005

Comparison of blood and brain mercury levels in infant monkeys exposed to methylmercury or vaccines containing thimerosal

Author information

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Thimerosal is a preservative that has been used in manufacturing vaccines since the 1930s. Reports have indicated that infants can receive ethylmercury (in the form of thimerosal) at or above the U.S. Environmental Protection Agency guidelines for methylmercury exposure, depending on the exact vaccinations, schedule, and size of the infant. In this study we compared the systemic disposition and brain distribution of total and inorganic mercury in infant monkeys after thimerosal exposure with those exposed to MeHg. Monkeys were exposed to MeHg (via oral gavage) or vaccines containing thimerosal (via intramuscular injection) at birth and 1, 2, and 3 weeks of age. Total blood Hg levels were determined 2, 4, and 7 days after each exposure. Total and inorganic brain Hg levels were assessed 2, 4, 7, or 28 days after the last exposure. The initial and terminal half-life of Hg in blood after thimerosal exposure was 2.1 and 8.6 days, respectively, which are significantly shorter than the elimination half-life of Hg after MeHg exposure at 21.5 days. Brain concentrations of total Hg were significantly lower by approximately 3-fold for the thimerosal-exposed monkeys when compared with the MeHg infants, whereas the average brain-to-blood concentration ratio was slightly higher for the thimerosal-exposed monkeys (3.5 +/- 0.5 vs. 2.5 +/- 0.3). A higher percentage of the total Hg in the brain was in the form of inorganic Hg for the thimerosal-exposed monkeys (34% vs. 7%). The results indicate that MeHg is not a suitable reference for risk assessment from exposure to thimerosal-derived Hg. Knowledge of the toxicokinetics and developmental toxicity of thimerosal is needed to afford a meaningful assessment of the developmental effects of thimerosal-containing vaccines.

Full Report

http://www.ncbi.nlm.nih.gov/pmc/articles/PMC1280342/

Editors note: most current risk assessments of biological thimerosal (ethyl mercury) use are based on the false assumption that ethyl mercury and methyl mercury behave similarly in vivo and in vitro

Environmental Toxicology And Pharmacology • September 2005

Low dose mercury toxicity and human health

Author information

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Abstract

Post Minamata incident there has been awareness about mercury toxicity even among the general public. Previous researches contributed a vast amount of data regarding acute mercury exposure, but gradually information about the low dose [Ninomiya, T., Ohmori, H., Hashimoto, K., Tsuruta, K., Ekino, S., 1995. Expansion of methylmercury poisoning outside minamata: an epidemiological study on chronic methylmercury poisoninig outside of Minamata. Environ. Res. 70 (1) 47-50; Lebel, J., Mergler, D., Lucotte, M., Amorim, M., Dolbec, J., Miranda, D., Arantes, G., Rheault, I., Pichet, P., 1996. Evidence of early nervous system dysfunction in Amazonian populations exposed to low-levels of methylmercury. Neurotoxicology 17 (1) 157-167] of mercury toxicity has been trickling in. With mercury contaminating rain-, ground- and sea-water no one is safe. Polluted water leads to mercury laced fish, meat and vegetable. In aquatic environments, inorganic mercury is microbiologically transformed into lipophilic organic compound 'methylmercury'. This transformation makes mercury more prone to biomagnification in food chains. Consequently, populations with traditionally high dietary intake of food originating from fresh or marine environment have highest dietary exposure to mercury. Extensive research done on locals across the globe have already established this, persons who routinely consume fish or a particular species of fish are at an increased risk of methylmercury poisoning. The easy access of the toxicant to man through multiple pathways air, water, food, cosmetic products and even vaccines increase the exposure. Foetus and children are more susceptible towards mercury toxicity. Mothers consuming diet containing mercury pass the toxicant to foetus and to infants through breast milk. Decreased performance in areas of motor function and memory has been reported among children exposed to presumably safe mercury levels. Similarly, disruption of attention, fine motor function and verbal memory was also found in adults on exposure to low mercury levels. It is an occupational hazard for dental staff, chloralkali factory workers and goldminers, etc. Mercury has been found to be a causative agent of various sorts of disorders, including neurological, nephrological, immunological, cardiac, motor, reproductive and even genetic. Recently heavy metal mediated toxicity has been linked to diseases like Alzeihemer's, Parkinson's, Autism, Lupus, Amyotrophic lateral sclerosis, etc. Besides this, it poses danger to wildlife. Therefore, it becomes imperative to spread the information regarding the threat of mercury exposure amongst the scientists and masses.

http://www.ncbi.nlm.nih.gov/pubmed/?term=21783611

"Recently heavy metal mediated toxicity has been linked to diseases like Alzeihemer's, Parkinson's, Autism, Lupus, Amyotrophic lateral sclerosis, etc. Besides this, it poses danger to wildlife. Therefore, it becomes imperative to spread the information regarding the threat of mercury exposure amongst the scientists and masses."

“Repetitive doses of thimerosal leads to neurobehavioral deteriorations ...”

Neuro Endocrinology Letters • October 2005

Mercury and autism: accelerating evidence?

Author information

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Abstract

The causes of autism and neurodevelopmental disorders are unknown. Genetic and environmental risk factors seem to be involved. Because of an observed increase in autism in the last decades, which parallels cumulative mercury exposure, it was proposed that autism may be in part caused by mercury. We review the evidence for this proposal. Several epidemiological studies failed to find a correlation between mercury exposure through thimerosal, a preservative used in vaccines, and the risk of autism. Recently, it was found that autistic children had a higher mercury exposure during pregnancy due to maternal dental amalgam and thimerosal-containing immunoglobulin shots. It was hypothesized that children with autism have a decreased detoxification capacity due to genetic polymorphism. In vitro, mercury and thimerosal in levels found several days after vaccination inhibit methionine synthetase (MS) by 50%. Normal function of MS is crucial in biochemical steps necessary for brain development, attention and production of glutathione, an important antioxidative and detoxifying agent. Repetitive doses of thimerosal leads to neurobehavioral deteriorations in autoimmune susceptible mice, increased oxidative stress and decreased intracellular levels of glutathione in vitro. Subsequently, autistic children have significantly decreased level of reduced glutathione. Promising treatments of autism involve detoxification of mercury, and supplementation of deficient metabolites.

http://www.ncbi.nlm.nih.gov/pubmed/16264412

International Journal Of Molecular Medicine • December 2005

Thimerosal induces neuronal cell apoptosis by causing cytochrome c and apoptosis-inducing factor release from mitochondria

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Abstract

There is a worldwide increasing concern over the neurological risks of thimerosal (ethylmercury thiosalicylate) which is an organic mercury compound that is commonly used as an antimicrobial preservative. In this study, we show that thimerosal, at nanomolar concentrations, induces neuronal cell death through the mitochondrial pathway. Thimerosal, in a concentration- and time-dependent manner, decreased cell viability as assessed by calcein-ethidium staining and caused apoptosis detected by Hoechst 33258 dye. Thimerosal-induced apoptosis was associated with depolarization of mitochondrial membrane, generation of reactive oxygen species, and release of cytochrome c and apoptosis-inducing factor (AIF) from mitochondria to cytosol. Although thimerosal did not affect cellular expression of Bax at the protein level, we observed translocation of Bax from cytosol to mitochondria. Finally, caspase-9 and caspase-3 were activated in the absence of caspase-8 activation. Our data suggest that thimerosal causes apoptosis in neuroblastoma cells by changing the mitochondrial microenvironment.

http://www.ncbi.nlm.nih.gov/pubmed/16273274

“Our data suggest that thimerosal causes apoptosis in neuroblastoma cells by changing the mitochondrial microenvironment.”

Medical Veritas • 2005

Mercury toxicity:
Genetic susceptibility and synergistic effects

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Abstract

Mercury toxicity and intoxication (poisoning) are realities that every American needs to face. Both the Environmental Protection Agency and National Academy of Science state that between 8 to 10% of American women have mercury levels that would render any child they gave birth to neurological disorders. One of six children in the USA have a neurodevelopmental disorder according to the Centers for Disease Control and Preven- tion. Yet our dentistry and medicine continue to expose all patients to mercury. This article discusses the obvious sources of mercury exposures that can be easily prevented. It also points out that genetic susceptibility and exposures to other materials that synergistically enhance mercury and ethyl- mercury toxicity need to be evaluated, and that by their existence prevent the actual determination of a "safe level" of mercury exposure for all. The mercury sources we consider are from dentistry and from drugs, mainly vaccines, that, in today's world are not only unnecessary sources, but also sources that are being increasingly recognized as being significantly deleterious to the health of many.

Excerpts

3. Synergistic effects:
Thimerosal, aluminum hydroxide and Neomycin

It is well documented in the literature that mercury toxicity is synergistic with other heavy metals such as cadmium and lead. It is also known that certain antibiotics greatly enhance the toxicity of thimerosal in ocular solutions and that antibiotics prevent test animals from effectively excreting mercury. The major known difference between males and females is their hormones. We therefore investigated the possible involvement of aluminum cation (found in vaccines), antibiotics (neomycin) and male versus female (estrogen versus testosterone) on the toxic effects of 50 nanomolar (nM) thimerosal on neurons in culture. Neurons can be cultured for 24 hours without much death (Fig. 6). Fifty nanomolar thimerosal alone (solid circles) will cause the death of about 70% of the neurons within 24 hours. The synergistic effects of aluminum, neomycin and tes- tosterone are shown (Fig. 6) and are as follows:

Aluminum: Aluminum hydroxide alone at 500 nM showed no significant death of cells at 6 hours, and only slight toxicity over the 24-hour period. Thimerosal at 50 nM effected only a slight increase in neuron death at 6 hours. However, in the presence of 50 nM thimerosal plus 500 nM aluminum hydroxide (open triangles [Δ]), the neuronal death increases to roughly 60%, an amazing increase and clearly demonstrates the synergistic effects of other metals on mercury toxicity and certainly thimerosal toxicity.

Neomycin: At 1.75 mcg neomycin alone (solid squares) did not cause a significant increase in neuronal death after 12 hours. In the presence of 50 nM thimerosal (open squares) the rate of death at same point increased from about 40% to 60%, a 20% increase in rate of death.

4. Hormonal effects: Testosterone and Estrogen

Testosterone and estrogen-like compounds give vastly dif- ferent results. Using female hormones we found them not toxic to the neurons alone and to be consistently protective against thimerosal toxicity. In fact, at high levels they could afford total protection for 24 hours against neuronal death in this test sys- tem (data not plotted). However, testosterone which appeared protective at very low levels (0.01 to 0.1 micromolar), dramati- cally increased neuron death at higher levels (0.5 to 1.0 micro- molar). In fact, 1.0 micromolar levels of testosterone that by itself did not significantly increase neuron death (red flattened oval), within 3 hours when added with 50 nanomolar thimerosal (solid circles) caused 100% neuron death. Fifty nanomolar thimerosal at this time point did not significantly cause any cell death.

"In fact,
1.0 micromolar levels of testosterone
that by itself did not significantly increase
neuron death, within 3 hours when
added with 50 nanomolar thimerosal
caused 100% neuron death."

Full Report

http://www.1796kotok.com/pdfs/haley.pdf

"... there are a number of other diseases that may have a chronic mercury toxicity component,

such as Alzheimer's disease, heart disease, obesity, ALS, asthma,

and other various forms of autoimmune disorders ..."

Medical Hypotheses • 2005

The potential importance of steroids in the treatment of autistic spectrum disorders and other disorders involving mercury toxicity

Author information

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Abstract

Autism is a neurodevelopmental disorder that according to the Centers for Disease Control and Prevention (CDC) affects 1 in 150 children in the United States. Autism is characterized by impairments in social relatedness and communication, repetitive behaviors, abnormal movements, and sensory dysfunction. Recently emerging evidence suggests that mercury, especially from childhood vaccines, appears to be a factor in the development of the autistic disorders, and that autistic children have higher than normal body-burdens of mercury. In considering mercury toxicity, it has previously been shown that testosterone significantly potentates mercury toxicity, whereas estrogen is protective. Examination of autistic children has shown that the severity of autistic disorders correlates with the amount of testosterone present in the amniotic fluid, and an examination of a case-series of autistic children has shown that some have plasma testosterone levels that were significantly elevated in comparison neurotypical control children. A review of some of the current biomedical therapies for autistics, such as glutathione and cysteine, chelation, secretin, and growth hormone, suggests that they may in fact lower testosterone levels. We put forward the medical hypothesis that autistic disorders, in fact, represents a form of testosterone mercury toxicity, and based upon this observation, one can design novel treatments for autistics directed towards higher testosterone levels in autistic children. We suggest a series of experiments that need to be conducted in order to evaluate the exact mechanisms for mercury-testosterone toxicity, and various types of clinical manipulations that may be employed to control testosterone levels. It is hoped by devising therapies that address the steroid hormone pathways, in addition to the current treatments that successful lower heavy metal body-burdens of mercury, will work synergistically to improve clinical outcomes. In light of the fact that there are a number of other diseases that may have a chronic mercury toxicity component, such as Alzheimer's disease, heart disease, obesity, ALS, asthma, and other various forms of autoimmune disorders, it is imperative that further research should be conducted to understand mercury-testosterone toxicity.

http://www.ncbi.nlm.nih.gov/pubmed/15780490

Toxicology Letters • February 2006

A cascade analysis of the interaction of mercury and coproporphyrinogen oxidase (CPOX) polymorphism on the heme biosynthetic pathway and porphyrin production

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Abstract

Mercury (Hg) exposure in various forms remains a persistent public health concern in many parts of the world. In previous studies, we have described a biomarker of mercury exposure characterized by increased urinary concentrations of specific porphyrins, pentacarboxyporphyrin (5-CP) and coproporphyrin (4-CP), and the atypical keto-isocoproporphyrin (KICP), based on selective interference with the fifth (uroporphyrinogen decarboxylase, UROD) and sixth (coproporphyrinogen oxidase, CPOX) enzymes of the heme biosynthetic pathway. Whereas this response occurs in a predictable manner among approximately 85% of subjects with Hg exposure, an atypical porphyrinogenic response (APR) has been observed in approximately 15% of Hg-exposed persons, in which the three porphyrins that are affected by Hg, i.e., 5-CP, 4-CP and, KICP, are excreted in substantial excess of that predicted on the basis of Hg exposure alone. This APR has been attributed to a specific polymorphism in exon 4 of the CPOX gene (CPOX4). In the present study, we sought to further confirm the hypothesis that the observed changes in porphyrin excretion patterns might serve as a biomarker of Hg exposure and potential toxicity by statistically modeling the cascading effects on porphyrin concentrations within the heme biosynthetic pathway of Hg exposure and CPOX4 polymorphism in a human population with long-term occupational exposure to elemental mercury. Our results are highly consistent with this hypothesis. After controlling for precursor porphyrin concentrations, we demonstrated that 5-CP and 4-CP are independently associated with Hg concentration, while KICP is associated only with the CPOX4. An unpredicted association of Hg with heptacarboxyporphyrin (7-CP) may indicate a previously unidentified point of mercury inhibition of UROD. These findings lend further support to the proposed utility of urinary porphyrin changes as a biomarker of exposure and potential toxicity in subjects with mercury exposure. Additionally, these findings demonstrate the successful application of a computational model for characterizing complex metabolic responses and interactions associated with both toxicant exposure and genetic variation in human subjects.

http://www.ncbi.nlm.nih.gov/pubmed/?term=16214298

“Mercury (Hg) exposure in various forms remains a persistent public health concern in many parts of the world ... these findings demonstrate the successful application of a computational model for characterizing complex metabolic responses and interactions associated with both toxicant exposure and genetic variation in human subjects.”

Neuro Endocrinology Letters • February 2006

Metal-specific lymphocyte reactivity is downregulated after dental metal replacement

Author information

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Abstract

OBJECTIVES

This study was done to evaluate the results and clinical relevance of an optimized lymphocyte proliferation test, MELISA, for metal-induced inflammation in patients with CFS-like symptoms. The treatment of patients consisted of the replacement of incompatible dental materials (RID) together with supportive anti-oxidant therapy.

DESIGN OF THE STUDY

513 patients were tested by MELISA at the beginning of the study. Out of this group, 248 patients were available for follow-up MELISA after RID.

METHODS

In MELISA, lymphocytes are isolated from the blood and cultivated with different metal salts in tissue culture medium containing 10% inactivated human AB+ serum or autologous serum. After 5 days, the presence of metal-reactive lymphocytes are measured by isotope labelling of newly formed DNA in growing lymphoblasts and evaluated by calculating the Stimulation Index.

RESULTS

Nickel was the most common sensitizer, followed by inorganic mercury, thimerosal, lead, cadmium, palladium and gold. After RID treatment, a decrease of metal-specific lymphocyte responses in patients who reacted to metals at the beginning of the study could be observed. The cultivation of lymphocytes in autologous and homologous serum did not significantly affect the results. Simultaneous, the health status of patients improved as well.

CONCLUSIONS

Replacement of incompatible dental materials resulted in down-regulation of metal-induced lymphocyte sensitivity in vitro, as well as in the improvement of health status of majority of patients with unspecific CFS-like symptoms.

http://www.ncbi.nlm.nih.gov/pubmed/16648791

“Replacement of incompatible dental materials resulted in down-regulation of metal-induced lymphocyte sensitivity in vitro, as well as in the improvement of health status of majority of patients with unspecific Chronic Fatigue-like symptoms.”

Oxford Journals
Toxicological Sciences • April 2006

Thimerosal Induces Apoptosis in a Neuroblastoma Model via the cJun N-Terminal Kinase Pathway

Author Information

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Abstract

The cJun N-terminal kinase (JNK)-signaling pathway is activated in response to a variety of stimuli, including environmental insults, and has been implicated in neuronal apoptosis. In this study, we investigated the role that the JNK pathway plays in neurotoxicity caused by thimerosal, an ethylmercury-containing preservative. SK-N-SH cells treated with thimerosal (0–10μM) showed an increase in the phosphorylated (active) form of JNK and cJun with 5 and 10μM thimerosal treatment at 2 and 4 h. To examine activator protein-1 (AP-1) transcription, cells were transfected with a pGL2 vector containing four AP-1 consensus sequences and then treated with thimerosal (0–2.5μM) for 24 h. Luciferase studies showed an increase in AP-1 transcriptional activity upon thimerosal administration. To determine the components of the AP-1 complex, cells were transfected with a dominant negative to either cFos (A-Fos) or cJun (TAM67). Reporter analysis showed that TAM67, but not A-Fos, decreased AP-1 transcriptional activity, indicating a role for cJun in this pathway. To assess which components are essential to apoptosis, cells were treated with a cell-permeable JNK inhibitor II (SP600125) or transfected with TAM67, and the downstream effectors of apoptosis were analyzed. Cells pretreated with SP600125 showed decreases in activation of caspases 9 and 3, decreases in degradation of poly(ADP-ribose) polymerase (PARP), and decreased levels of proapoptotic Bim, in comparison to cells treated with thimerosal alone. However, cells transfected with TAM67 showed no changes in those same components. Taken together, these results indicate that thimerosal-induced neurotoxicity occurs through the JNK-signaling pathway, independent of cJun activation, leading ultimately to apoptotic cell death.

http://toxsci.oxfordjournals.org/content/92/1/246.long

“Taken together, these results indicate that thimerosal-induced neurotoxicity occurs through the JNK-signaling pathway, independent of cJun activation, leading ultimately to apoptotic cell death.”

Medical Science Monitor • June 2006

An assessment of downward trends in neurodevelopmental disorders in the USA following removal of Thimerosal from childhood vaccines

Author Information

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Abstract

BACKGROUND
The US is in the midst of an epidemic of neurodevelopmental disorders (NDs). Thimerosal is an ethylmercury-containing compound added to some childhood vaccines. Several previous epidemiological studies conducted in the US have associated Thimerosal-containing vaccine (TCV) administration with NDs.

MATERIAL/METHODS
An ecological study was undertaken to evaluate NDs reported to the Vaccine Adverse Event Reporting System (VAERS) from 1991 through 2004 by date of receipt and by date of vaccine administration. The NDs examined included autism, mental retardation, and speech disorders. Statistical trend analysis was employed to evaluate the effects of removal of Thimerosal on the proportion of NDs reported to VAERS.

RESULTS
There was a peak in the proportion of ND reports received by VAERS in 2001-2002 and in the proportion of ND reports by date of vaccine administration in 1998. There were significant reductions in the proportion of NDs reported to VAERS as Thimerosal was begun to be removed from childhood vaccines in the US from mid-1999 onwards.

CONCLUSIONS
The present study provides the first epidemiological evidence showing that as Thimerosal was removed from childhood vaccines, the number of NDs has decreased in the US. The analysis techniques utilized attempted to minimize chance or bias/confounding. Additional research should be conducted to further evaluate the relationship between TCVs and NDs. This is especially true because the handling of vaccine safety data from the National Immunization Program of the CDC has been called into question by the Institute of Medicine of the National Academy of Sciences in 2005.

http://www.ncbi.nlm.nih.gov/pubmed/16733480

“The present study provides the first epidemiological evidence showing that as Thimerosal was removed from childhood vaccines, the number of neurodevelopmental disorders has decreased in the US.

Neuro Endocrinology Letters • August 2006

A meta-analysis epidemiological assessment of neurodevelopmental disorders following vaccines administered from 1994 through 2000 in the United States

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Abstract

BACKGROUND
Thimerosal is an ethylmercury-containing compound (49.6% mercury by weight) used as at the preservative level in vaccines (0.005% to 0.01%).

METHODS
Statistical modeling in a meta-analysis epidemiological assessment of the Vaccine Adverse Event Reporting System (VAERS) for neurodevelopment disorders (NDs) reported following Diphtheria-Tetanus-whole-cell-Pertussis (DTP) vaccines in comparison to Diphtheria-Tetanus-whole-cell-Pertussis-Haemophilus Influenzae Type b (DTPH) vaccines (administered: 1994-1997) and following Thimerosal-containing Diphtheria-Tetanus-acellular-Pertussis (DTaP), vaccines in comparison to Thimerosal-free DTaP vaccines (administered: 1997-2000), was undertaken.

RESULTS
Significantly increased adjusted (sex, age, vaccine type, vaccine manufacturer) risks of autism, speech disorders, mental retardation, personality disorders, thinking abnormalities, ataxia, and NDs in general, with minimal systematic error or confounding, were associated with TCV exposure.

CONCLUSION
It is clear from the results of the present epidemiological study and other recently published data associating mercury exposure with childhood NDs, additional ND research should be undertaken in the context of evaluating mercury-associated exposures, especially from Thimerosal-containing vaccines.

http://www.ncbi.nlm.nih.gov/pubmed/16807526

“It is clear from the results of the present epidemiological study and other recently published data associating mercury exposure with childhood neurological disorders.”

“Autism was recently associated with a urinary porphyrin pattern indicative of mercury toxicity ...”

Neurotoxicity Research • August 2006

A prospective assessment of porphyrins in autistic disorders: a potential marker for heavy metal exposure

Author information

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Abstract

Autism was recently associated with a urinary porphyrin pattern indicative of mercury toxicity in a large cohort of French children. The IRB of the Institute for Chronic Illnesses approved the present study. A total of 37 consecutive American patients (> or = 7 years-old) with autism spectrum disorders (ASDs) (Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition-DSM IV), born from 1983-1998, that presented to the Genetic Centers of America for outpatient genetic evaluations were prospectively examined for urinary prophryin levels (LabCorp, Inc.) from June 2005-June 2006. Imaging and laboratory testing were conducted on each patient to rule-out other causal factors for their ASDs. As controls, age-, sex-, and race-matched neurotypical ASD siblings were examined. An apparent dose-response effect was observed between autism severity and increased urinary coproporphyrins. Patients with non-chelated autism (2.25-fold, 83% had levels > 2 SD above the control mean) and non-chelated ASDs (2-fold, 58% had levels > 2 SD above the control mean), but not patients with non-chelated pervasive developmental delay-not otherwise specified (PDD-NOS) or Asperger’s disorder (1.4-fold, 46% had levels > 2 SD above the control mean), had significantly increased median coproporphyrin levels versus controls. A significant increase (1.7-fold) in median coproporphyrin levels was observed among non-chelated ASD patients versus chelated ASD patients. Porphyrins should be routinely clinically measured in ASDs, and potential ASD treatments should consider monitoring porphyrin levels. Additional research should be conducted to evaluate the potential role for mercury exposure in some ASDs.

http://www.ncbi.nlm.nih.gov/pubmed/17000470

"Significantly increased odds ratios for autism, speech disorders, mental retardation, infantile spasms, and thinking abnormalities reported to VAERS were found following DTP vaccines in comparison to DTPH vaccines with minimal bias or systematic error."

Journal Of Toxicology And Environmental Health Part A • August 2006

An evaluation of the effects of thimerosal on neurodevelopmental disorders reported following DTP and Hib vaccines in comparison to DTPH vaccine in the United States

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Abstract

Thimerosal is an ethylmercury (49.55% mercury by weight) preservative historically added to some vaccines. Toxicokinetic studies showed children in the United States received doses of mercury from Thimerosal-containing vaccines (TCVs) in excess of safety guidelines. In the United States during the 1990s, diphtheria-tetanus-pertussis (DTP) and Haemophilus influenzae type b (Hib) vaccines (maximally, 50 mug mercury per joint administration) and diphtheria-tetanus-pertussis-Haemophilus influenzae type b (DTPH) vaccines (25 mug mercury per administration) were given to children in the same childhood vaccination schedule at 2, 4, 6, and 15-18 mo, so that children receiving DTP and Hib vaccines may have maximally received an additional 100 mug more mercury exposure from TCVs than children administered DTPH vaccines. A case-control epidemiological study of neurodevelopmental disorders (NDs) reported to the Vaccine Adverse Event Reporting System (VAERS) (online public access version; updated 31 August 2004) following administration of DTP vaccines in comparison DTPH vaccines manufactured by Lederle Laboratories (Pearl River, NY) from 1994 through 1998 was undertaken. Significantly increased odds ratios for autism, speech disorders, mental retardation, infantile spasms, and thinking abnormalities reported to VAERS were found following DTP vaccines in comparison to DTPH vaccines with minimal bias or systematic error. Additional ND research should be undertaken in the context of evaluating mercury-associated exposures, especially since in 2005 the Institute of Medicine issued a report calling into question handling of vaccine safety data by the National Immunization Program of the Centers for Disease Control and Prevention.

http://www.ncbi.nlm.nih.gov/pubmed/16766480

Environmental Toxicology And Pharmacology • September 2006

Thimerosal induces oxidative stress in HeLa S epithelial cells

Author information

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Abstract

Thimerosal is one of the most widely used preservatives and is found in a variety of biological products, including vaccines, contact lens cleaning solutions, and cosmetics. It has been reported to have harmful effects on epithelial tissues, such as causing conjunctivitis or contact dermatitis. However, the molecular mechanism of its toxicity has not been characterized using epithelial tissues. In the present study, we report that reactive oxygen species play a key role in thimerosal-induced cytotoxicity in HeLa S epithelial cells. Thimerosal significantly reduced HeLa S cell viability and it was associated with a decrease in intracellular glutathione levels. Flow cytometric cell cycle analysis showed a marked increase in the hypodiploidic cell population, indicating apoptosis of thimerosal-treated cells. The apoptotic cell death of epithelial cells was confirmed by observing a significant increase of caspase-3 activity in the cytosolic fraction of the treated cells. Thimerosal also induced a concentration-dependent increase of genomic DNA fragmentation, a biochemical hallmark of apoptosis. Hoechst 33342 nuclear staining demonstrated apoptotic-fragmented multinuclei in thimerosal-treated cells. All the thimerosal-mediated toxic responses observed in the present study were almost completely suppressed by pretreating cells with N-acetyl-l-cysteine, a radical scavenger. Taken together, these results suggest for the first time that epithelial cytotoxicity of thimerosal is mediated by oxidative stress.

http://www.ncbi.nlm.nih.gov/pubmed/?term=21783709

“[thimerosal] has been reported
to have harmful effects on epithelial tissues,
such as causing conjunctivitis or contact dermatitis.
Thimerosal also induced a concentration-dependent
increase of genomic DNA fragmentation,
a biochemical hallmark of apoptosis.
Taken together, these results suggest
for the first time that epithelial cytotoxicity
of thimerosal is mediated by oxidative stress.”

“... some autism spectrum disorders may result from ... exposure to mercury.”

Neuro Endocrinology Letters • December 2006

A clinical trial of combined anti-androgen and anti-heavy metal therapy in autistic disorders

Author information

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Abstract

BACKGROUND
A medical hypothesis has suggested that some autism spectrum disorders (ASDs) may result from interactions between the methionine cycle-transsulfuration and androgen pathways following exposure to mercury.

METHODS
The IRB of the Institute for Chronic Illnesses approved the present study. A novel treatment was utilized combining LUPRON (leuprolide acetate, TAP Pharmaceuticals, Inc.) and CHEMET (meso-2, 3-dimercaptosuccinic acid--DMSA, McNeil Consumer Products Company) on 11 consecutive children with ASDs.

RESULTS
A significant ($p<0.01$) overall improvement from the 70-79th percentile of severity (median baseline score=87) at baseline to the 40-49th percentile of severity (median end of study period score=63) at the end of the study was observed for patients treated for a median of approximately 4 months. Significant improvements in sociability, cognitive awareness, behavior, and clinical symptoms/behaviors of hyperandrogenemia were also observed. Significant decreases in blood androgens and increases in urinary heavy metal concentrations were observed. Minimal drug adverse effects were found.

CONCLUSION
This study provides the first clinical evidence for the benefit that combined anti-androgen and anti-heavy metal therapy may have on some children with ASDs. Additional studies should examine androgen and heavy metal mechanisms of action in ASDs, and future ASD treatment protocols should consider androgens and heavy metals.

http://www.ncbi.nlm.nih.gov/pubmed/17187010

[an example of disagreement within the research community]

Critical Reviews In Toxicology • December 2006

The toxicology of mercury and its chemical compounds

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Abstract

This review covers the toxicology of mercury and its compounds. Special attention is paid to those forms of mercury of current public health concern. Human exposure to the vapor of metallic mercury dates back to antiquity but continues today in occupational settings and from dental amalgam. Health risks from methylmercury in edible tissues of fish have been the subject of several large epidemiological investigations and continue to be the subject of intense debate. Ethylmercury in the form of a preservative, thimerosal, added to certain vaccines, is the most recent form of mercury that has become a public health concern. The review leads to general discussion of evolutionary aspects of mercury, protective and toxic mechanisms, and ends on a note that mercury is still an "element of mystery."

http://www.ncbi.nlm.nih.gov/pubmed/16973445

Critical Reviews In Toxicology • December 2007

Comments on the article "the toxicology of mercury and its chemical compounds" by Clarkson and Magos (2006)

Author information

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Abstract

Clarkson and Magos (2006) provide their perspectives on the toxicology of mercury vapor and dental amalgam. As scientists who are involved in preparing a German federal guideline regarding dental amalgam, we welcome additional scientific data on this issue. However, Clarkson and Magos do not present all the relevant studies in their review.

The additional data provided here show that: (a) Dental amalgam is the main source of human total mercury body burden, because individuals with amalgam have 2-12 times more mercury in their body tissues compared to individuals without amalgam; (b) there is not necessarily a correlation between mercury levels in blood, urine, or hair and in body tissues, and none of the parameters correlate with severity of symptoms; (c) the half-life of mercury deposits in brain and bone tissues could last from several years to decades, and thus mercury accumulates over time of exposure; (d) mercury, in particular mercury vapor, is known to be the most toxic nonradioactive element, and is toxic even in very low doses, and (e) some studies which conclude that amalgam fillings are safe for human beings have important methodological flaws.

Therefore, they have no value for assessing the safety of amalgam.

http://www.ncbi.nlm.nih.gov/pubmed/17661216

Toxicology • February 2007

Cell death and cytotoxic effects in YAC-1 lymphoma cells following exposure to various forms of mercury

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Abstract

The effects of 1 min-4 h exposures to four Hg compounds (mercuric chloride [HgCl2], methyl mercuric chloride [CH3HgCl], p-chloromercuribenzoate [p-CMB] and thimerosal [TMS; ethylmercurithiosalicylate]) on cell death, microtubules, actin, CD3 receptor expression, protein tyrosine phosphorylation (PTyr-P) and intracellular calcium ([Ca2+]i) levels were investigated in YAC-1 lymphoma cells using flow cytometry. YOPRO-1 (YP) and propidium iodide (PI) dye uptake indicated all forms of Hg tested were toxic at concentrations ranging from 25.8-48.4 microM, with two distinct patterns of effects. Early apoptosis was prolonged for CH3HgCl- and TMS-treated cells, with more than 50% remaining YP+/PI- after 4h. Both CH3HgCl and TMS induced complete loss of beta-tubulin fluorescence, indicative of microtubule depolymerization and inhibition of tubulin synthesis and/or beta-tubulin degradation, while F-actin fluorescence diminished to a lesser degree and only after loss beta-tubulin. CH3HgCl and TMS induced an almost immediate two-fold increase in CD3 fluorescence, with levels returning to baseline within minutes. With continued exposure, CD3 fluorescence was reduced to approximately 50% of baseline values. Both compounds also increased PTyr-P two- to three-fold immediately, with levels returning to baseline at 4h. Similarly, two- to three-fold increases in [Ca2+]i were noted after 1 min exposure. [Ca2+]i increased progressively, reaching levels five- to eight-fold greater than control values. In contrast, dye uptake was delayed with HgCl2 and p-CMB, although cell death proceeded rapidly, with almost all non-viable cells being late apoptotic (YP+/PI+) by 4h. p-CMB produced early reductions in F-actin, and after 4h, complete loss of F-actin with only partial reduction of total beta-tubulin was seen with both p-CMB and HgCl2. HgCl2 reduced CD3 expression and PTyr-P slightly within minutes, while p-CMB produced similar effects on CD3 only at 4h, at which time PTyr-P was increased two- to three-fold. Both compounds increased [Ca2+]i within minutes, though levels remained under twice the baseline concentration after 15 min exposure. With continued exposure, [Ca2+]i increased to levels two- to five-fold greater than control values. These findings indicate the two groups of Hg compounds may induce cell death by distinct pathways, reflecting interactions with different cellular targets leading to cell death.

http://www.ncbi.nlm.nih.gov/pubmed/?term=17210217

“These findings indicate the two groups of mercury compounds may induce cell death by distinct pathways, reflecting interactions with different cellular targets leading to cell death.”

Integrative Medicine • Vol. 6, No. 2 • April 2007

Heavy-Metal Toxicity—With Emphasis on Mercury

by John Neustadt, ND, and Steve Pieczenik, MD, PhD

• Recommended Report •

http://montanaim.com/pubs/Heavy_Metals_Article.pdf

“8 of 9 patients examined were exposed to significant mercury
from Thimerosal-containing biologic/vaccine preparations during their fetal/infant developmental periods,
and subsequently, between 12 and 24 mo of age, these previously normally developing children suffered
mercury toxic encephalopathies that manifested with clinical symptoms
consistent with regressive Autistic Spectrum Disorders.”

Journal Of Toxicology And Environmental Health Part A • May 2007

A case series of children with apparent mercury toxic encephalopathies manifesting with clinical symptoms of regressive autistic disorders

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Institute of Chronic Illnesses, Inc., Silver Spring, Maryland, USA

Abstract

Impairments in social relatedness and communication, repetitive behaviors, and stereotypic abnormal movement patterns characterize autism spectrum disorders (ASDs). It is clear that while genetic factors are important to the pathogenesis of ASDs, mercury exposure can induce immune, sensory, neurological, motor, and behavioral dysfunctions similar to traits defining or associated with ASDs. The Institutional Review Board of the Institute for Chronic Illnesses (Office for Human Research Protections, U.S. Department of Health and Human Services, IRB number IRB00005375) approved the present study. A case series of nine patients who presented to the Genetic Centers of America for a genetic/developmental evaluation are discussed. Eight of nine patients (one patient was found to have an ASD due to Rett’s syndrome) (a) had regressive ASDs; (b) had elevated levels of androgens; (c) excreted significant amounts of mercury post chelation challenge; (d) had biochemical evidence of decreased function in their glutathione pathways; (e) had no known significant mercury exposure except from Thimerosal-containing vaccines/Rho(D)-immune globulin preparations; and (f) had alternate causes for their regressive ASDs ruled out. There was a significant dose-response relationship between the severity of the regressive ASDs observed and the total mercury dose children received from Thimerosal-containing vaccines/Rho (D)-immune globulin preparations. Based upon differential diagnoses, 8 of 9 patients examined were exposed to significant mercury from Thimerosal-containing biologic/vaccine preparations during their fetal/infant developmental periods, and subsequently, between 12 and 24 mo of age, these previously normally developing children suffered mercury toxic encephalopathies that manifested with clinical symptoms consistent with regressive ASDs. Evidence for mercury intoxication should be considered in the differential diagnosis as contributing to some regressive ASDs.

http://www.ncbi.nlm.nih.gov/pubmed/17454560

Journal Of Maternal, Fetal And Neonatal Medicine • May 2007

A prospective study of thimerosal-containing Rho(D)-immune globulin administration as a risk factor for autistic disorders

Author information

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Abstract

BACKGROUND
This study evaluated the relationship between prenatal mercury exposure from thimerosal (49.55% mercury by weight)-containing Rho(D)-immune globulins (TCRs) and autism spectrum disorders (ASDs).

METHODS
The Institutional Review Board of the Institute for Chronic Illnesses approved the present study. A total of 53 consecutive non-Jewish Caucasian patients with ASDs (Diagnostic and statistical manual of mental disorders, fourth ed. - DSM IV) born between 1987 and 2001 who presented to the Genetic Centers of America for outpatient genetic/developmental evaluations were prospectively collected from June 1, 2005 through March 31, 2006. Imaging and laboratory testing were conducted on each patient to rule out other causal factors for their ASDs. As race-matched controls, the frequency of Rh negativity was determined from 926 non-Jewish Caucasian pregnant women who had presented for outpatient prenatal genetics care to the Genetic Centers of America between 1980 and 1989.

RESULTS
Children with ASDs (28.30%) were significantly more likely (odds ratio 2.35, 95% confidence interval 1.17-4.52, $p < 0.01$) to have Rh-negative mothers than controls (14.36%). Each ASD patient's mother was determined to have been administered a TCR during her pregnancy.

CONCLUSION
The results provide insights into the potential role prenatal mercury exposure may play in some children with ASDs.

http://www.ncbi.nlm.nih.gov/pubmed/17674242

"Each Autisic Spectrum Disorder patient's mother was determined to have been administered a Thimerosal-containing vaccine during her pregnancy ... The results provide insights into the potential role prenatal mercury exposure may play in some children with Autisic Spectrum Disorders."

American Journal Of Perinatology • August 2007

Exposure to mercury during the first six months via human milk and vaccines: modifying risk factors

Author information

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Abstract

Breastfeeding is the best natural protection infants have against morbidity and mortality, and the development of safe and effective vaccines has made it possible to immunize children against infectious disease. Both of these mechanisms for ensuring good health in children may be compromised by contact with mercury (Hg). Maternal exposure to environmental Hg during pregnancy can predispose nursing children to neurodevelopmental disorders. Despite the World Health Organization assurance that thimerosal-preserved vaccines are safe to use in infants, the United States, the European Union, and dozens of other countries have eliminated thimerosal as a vaccine preservative and stopped the immunization of children with such vaccines. Because of the increase in environmental pollution and the need to produce cheap and safe vaccines, there is a need to address the uncertainty of vaccine-ethylmercury risk of toxicity and Hg exposure during breastfeeding.

http://www.ncbi.nlm.nih.gov/pubmed/17564957

“Maternal exposure to environmental mercury during pregnancy can predispose nursing children to neurodevelopmental disorders.”

European Journal Of Pediatrics • September 2007

Hair mercury in breast-fed infants exposed to thimerosal-preserved vaccines

Author information

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Abstract

Because of uncertainties associated with a possible rise in neuro-developmental deficits among vaccinated children, thimerosal-preserved vaccines have not been used since 2004 in the USA (with the exception of thimerosal-containing influenza vaccines which are routinely recommended for administration to pregnant women and children), and the EU but are widely produced and used in other countries. We investigated the impact of thimerosal on the total Hg in hair of 82 breast-fed infants during the first 6 months of life. The infants received three doses of the hepatitis-B vaccine (at birth, 1 and 6 months) and three DTP (diphtheria, tetanus, and pertussis) doses at 2, 4 and 6 months, according to the immunization schedule recommended by the Ministry of Health of Brazil. The thimerosal in vaccines provided an ethylmercury (EtHg) exposure of 25 microgHg at birth, 30, 60 and 120 days, and 50 microgHg at 180 days. The exposure to vaccine-EtHg represents 80% of that expected from total breast milk-Hg in the first month but only 40% of the expected exposure integrated in the 6 months of breastfeeding. However, the Hg exposure corrected for body weight at the day of immunization was much higher from thimerosal- EtHg (5.7 to 11.3 microgHg/kg b.w.) than from breastfeeding (0.266 microgHg/kg b.w.). While mothers showed a relative decrease (-57%) in total hair-Hg during the 6 months lactation there was substantial increase in the infant's hair-Hg (446%). We speculate that dose and parenteral mode of thimerosal-EtHg exposure modulated the relative increase in hair-Hg of breast-fed infants at 6 months of age.

http://www.ncbi.nlm.nih.gov/pubmed/17237965

"Because of uncertainties associated with a possible rise in neuro-developmental deficits among vaccinated children, thimerosal-preserved vaccines have not been used since 2004 in the USA (with the exception of thimerosal-containing influenza vaccines which are routinely recommended for administration to pregnant women and children) ..."

Journal Of Toxicology And Environmental Health Part A • October 2007

A prospective study of mercury toxicity biomarkers in autistic spectrum disorders

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Abstract

Porphyrins are derivatives formed in the heme synthesis pathway and porphyrins afford a measure of xenobiotic exposure. The steps in the heme pathway most vulnerable to heavy metal inhibition are uroporphyrin decarboxylase (UROD) and coproporphyrinogen oxidase (CPOX) reactions. Mercury toxicity was associated with elevations in urinary coproporphyrin (cP), pentacarboxyporphyrin (5cxP), and precoproporphyrin (prcP) (also known as keto-isocoproporphyrin) levels. Two cohorts of autistic patients in the United States and France had urine porphyrin levels associated with mercury toxicity. A prospective study of urinary porphyrin testing at LabCorp (United States) and the Laboratoire Philippe Auguste (France) involving 71 autism spectrum disorder (ASD) patients, neurotypical sibling controls, and general population controls was undertaken. ASD patients had significant elevations in urinary levels of cP, 5cxP, and prcP relative to controls, and > 50% of ASD patients had urinary cP levels more than 2 standard deviations above the mean values for neurotypical sibling controls. Significant reductions in urinary 5cxP and cP levels were observed in ASD patients following chelation. A significant correlation was found between urinary porphyrins measured at LabCorp and those measured at the Laboratoire Philippe Auguste on individual ASD patients. The established developmental neurotoxicity attributed to mercury and biochemical/genomic evidence for mercury susceptibility/toxicity in ASDs indicates a causal role for mercury. Urinary porphyrin testing is clinically available, relatively inexpensive, and noninvasive. Porphyrins need to be routinely measured in ASDs to establish if mercury toxicity is a causative factor and to evaluate the effectiveness of chelation therapy.

http://www.ncbi.nlm.nih.gov/pubmed/17885929

“The established developmental neurotoxicity attributed to mercury and biochemical/genomic evidence for mercury susceptibility/toxicity in Autistic Spectrum Disorders indicates a causal role for mercury”

Toxicological Sciences • October 2007

Modeling Neurodevelopment Outcomes and Ethylmercury Exposure from Thimerosal-Containing Vaccines

Author Information

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Dear Editor

The neurotoxic effects of ethylmercury (EtHg) accidentally consumed in Iraq were sufficient to withdraw ethylmercury-containing fungicides as seed dressing. Despite that, not only did thimerosal continue to be used in pharmaceutical preparations but also toxicological interest in EtHg-derived substances diminished considerably and was never addressed with regard to the small quantities used as a vaccine preservative. Thimerosal-containing vaccines (TCV) have no record of overt clinical neurological consequences due to EtHg, and the plausibility of subtle neurotoxic effects in children has been recognized only recently by the United States and other industrialized countries. In this context, we welcome the interesting work of Berman et al. (2008); it is clear that this assiduous study (in immunologically susceptible mice) took into consideration doses and schedules of TCV-Hg concentrations that had been used in infants in the United States. Their mice model does not, however, cover the full extent of modifying factors associated with TCV-Hg exposure in the majority of immature and newborns around the world that still have to depend on TCV.

According to Berman et al. (2008), the United States vaccination scheduled exposed a total of 125 µgHg distributed at 2, 2, and 6 months through TCV (hepatitis B and DTP). This type of vaccine is no longer used in industrialized countries but it is still used all over the world. We know that thimerosal concentrations vary among brands of vaccines and also that immunization schedules vary depending on a country's health policy; not only that but new outbreaks of disease introduce additional new vaccines (which may contain thimerosal) during the first year of life. As an example, the public health services of Brazil, like other countries, still uses several brands of hepatitis B vaccine (containing thimerosal as preservative) with concentrations ranging from 12.5 to 50 µgHg per 0.5 ml shot. Another salient difference between countries that use TCV (like Brazil) and the United States is that in the former country hepatitis B inoculation starts within the first 12–24 h after birth (Marques et al., 2007) and is administered to low-birth weight ≥2000 g (Ministério, da Saúde, 2006 and premature babies who are also recommended a fourth shot as an additional booster (DI/DH/CVE, 2006). In such situations, not only toxicokinetics (TK) but especially toxicodynamics (TD) of EtHg are entirely different between a 1-day-old (with different stages of immaturity and birth weight) and a 60-day-old child (as modeled).

The newborn presents several physiological degrees of immaturity in the excretory system (kidneys and bile formation) and target organ (central nervous system, CNS) that are important modifiers of EtHg TK and TD. These features are inversely accentuated by gestational age and birth weight. Under such circumstances, unbound circulating EtHg in a newborn (and immature) may not be eliminated as fast as in a 2-month-old baby and thus will be readier to cross the more vulnerable blood-brain barrier (BBB). The newborn BBB increases in effectiveness with age; therefore, the free EtHg can more easily penetrate the immature CNS (Dorea, 2007). As a consequence, the smaller the body size and blood volume, the more altered the TD and TK of EtHg. Indeed, Stajich et al. (2000) showed that preterm infants do not metabolize Hg efficiently. Collectively, studies show that larger babies have significantly higher mean liver metallothionein than smaller babies (Dorea, 2007).

Factors associated with protein-binding capacity, excretion mechanisms, and enzyme activities are immature in the neonate and modulate differences in adverse effects between newborns and infants exposed to neurotoxic substances. During the period of immaturity, not only plasma albumin but also total protein concentrations decrease (Dorea, 2007). The best example in differences between neurotoxic effects is the type of albumin and competition for binding sites (due to increased circulatory concentrations of bilirubin). Albumin binding (to bilirubin) is less effective during the first postnatal days and, as a consequence, excess free bilirubin can cross the BBB at early stages of the postnatal CNS immaturity and cause brainstem abnormalities; albumin priming can be effective in attenuating effects caused by unbound bilirubin (Dorea, 2007).

We do not dispute the conclusions drawn by Berman et al. regarding Hg and the neurobiology of autism; however, we think it is possible to take their findings one step further in regards to thimerosal neurotoxicity. We contend that these findings are appropriate for U.S.-like scenarios (as intended by the authors) but are not sufficient to address the current TCV schedules in the majority of newborns and infants around the world. TCV are used worldwide in vaccination schedules that include more of these vaccines at an earlier age. Unfortunately, the differences that set newborns (especially low-birth-weights and prematures) apart from 2-month-old infants have not yet been modeled in experimental studies and remain neglected in TK and TD knowledge of TCV-EtHg exposure. We hope that studies like Berman et al. (2008) can inspire conventional toxicology to address uncertainties regarding current serial EtHg exposure in newborns and infants that have to take TCV.

http://toxsci.oxfordjournals.org/content/103/2/414.long#ref-1

“the hair sample analysis results offer some support for the idea that persons with autism may be less efficient and more variable at eliminating mercury from the blood.”

Journal Of Child Neurology • November 2007

Blood levels of mercury are related to diagnosis of autism: a reanalysis of an important data set

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Abstract

The question of what is leading to the apparent increase in autism is of great importance. Like the link between aspirin and heart attack, even a small effect can have major health implications. If there is any link between autism and mercury, it is absolutely crucial that the first reports of the question are not falsely stating that no link occurs. We have reanalyzed the data set originally reported by Ip et al. in 2004 and have found that the original p value was in error and that a significant relation does exist between the blood levels of mercury and diagnosis of an autism spectrum disorder. Moreover, the hair sample analysis results offer some support for the idea that persons with autism may be less efficient and more variable at eliminating mercury from the blood.

http://www.ncbi.nlm.nih.gov/pubmed/18006963

The Journal Of Toxicology And Environmental Health Part B - Critical Reviews • December 2007

A review of Thimerosal (Merthiolate) and its ethylmercury breakdown product: specific historical considerations regarding safety and effectiveness

Author Information

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Abstract

Thimerosal (Merthiolate) is an ethylmercury-containing pharmaceutical compound that is 49.55% mercury and that was developed in 1927. Thimerosal has been marketed as an antimicrobial agent in a range of products, including topical antiseptic solutions and antiseptic ointments for treating cuts, nasal sprays, eye solutions, vaginal spermicides, diaper rash treatments, and perhaps most importantly as a preservative in vaccines and other injectable biological products, including Rho(D)-immune globulin preparations, despite evidence, dating to the early 1930s, indicating Thimerosal to be potentially hazardous to humans and inffective as an antimicrobial agent. Despite this, Thimerosal was not scrutinized as part of U.S. pharmaceutical products until the 1980s, when the U.S. Food and Drug Administration finally recognized its demonstrated ineffectiveness and toxicity in topical pharmaceutical products, and began to eliminate it from these. Ironically, while Thimerosal was being eliminated from topicals, it was becoming more and more ubiquitous in the recommended immunization schedule for infants and pregnant women. Furthermore, Thimerosal continues to be administered, as part of mandated immunizations and other pharmaceutical products, in the United States and globally. The ubiquitous and largely unchecked place of Thimerosal in pharmaceuticals, therefore, represents a medical crisis.

http://www.ncbi.nlm.nih.gov/pubmed/18049924

“The ubiquitous and largely unchecked place of Thimerosal in pharmaceuticals, therefore, represents a medical crisis.”

Anales de la Facultad de Medicina • 2007

Neurotoxic effects of thimerosal at vaccines doses on the encephalon and development in 7 day-old hamsters

Laurente, Jonny, et al.

Objectives
To determine if thimerosal administration in amounts equivalent to vaccines content produces neurotoxic effects on the encephalon in postnatal hamsters and on experimentation animals' development.

Design
Experimental, prospective, bietapic study.

Setting
San Fernando Faculty of Medicine, Universidad Nacional Mayor de San Marcos.

Biologic material
Seven-day old hamsters.

Material
We divided 45 postnatal hamsters in three groups: group A (n = 15), group B (n = 15) and group C (n = 15). We administered three intramuscular equivalent doses of sucrose and thimerosal in 20 µL of physiological serum respectively to groups B and C on birth-days 7 (0,227 µg), 9 (0,216 µg) and 11 (0,220 µg). Group A received only 20 µL of saline solution.

Main outcome measures
Body weight, encephalon weight, hamster's stature and encephalon histopathological alterations.

Results
Anova and student t tests showed statistical significance in favor of low body weight, low encephalon weight and smaller stature in group C with respect to groups A and B hamsters ($p<0,000$). □2 statistical significance in relation to the presence of histopathological alterations in group C was also obtained ($p<0,000$). We observed greater relative risk of encephalic alterations in group C.

Conclusions
The administration of thimerosal in doses equivalent to vaccines content was associated with low corporal weight, low encephalon weight and smaller stature in postnatal hamsters. Neurotoxic effects were also produced at encephalic level, at hippocampus (regions CA1, CA3, DG), cerebral cortex and cerebellum (Purkinje cells and granuloses cells) with decrease in neuronal density, neuronal necrosis, axonal dismyelinization and gliosis. In addition, risk increase in developing any of these alterations was high in the animal group receiving thimerosal.

http://www.scielo.org.pe/scielo.php?pid=S1025-55832007000300003&script=sci_abstract&tlng=en

"The administration of thimerosal in doses equivalent to vaccines content was associated with low corporal weight, low encephalon weight and smaller stature in postnatal hamsters. Neurotoxic effects were also produced at encephalic level, at hippocampus (regions CA1, CA3, DG), cerebral cortex and cerebellum (Purkinje cells and granuloses cells) with decrease in neuronal density, neuronal necrosis, axonal dismyelinization and gliosis. In addition, risk increase in developing any of these alterations was high in the animal group receiving thimerosal."

Pediatrics • February 2008

Mercury levels in newborns and infants after receipt of thimerosal-containing vaccines

Author information

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Abstract

OBJECTIVES

Thimerosal is a mercurial preservative that was widely used in multidose vaccine vials in the United States and Europe until 2001 and continues to be used in many countries throughout the world. We conducted a pharmacokinetic study to assess blood levels and elimination of ethyl mercury after vaccination of infants with thimerosal-containing vaccines.

METHODS

Blood, stool, and urine samples were obtained before vaccination and 12 hours to 30 days after vaccination from 216 healthy children: 72 newborns (group 1), 72 infants aged 2 months (group 2), and 72 infants aged 6 months (group 3). Total mercury levels were measured by atomic absorption. Blood mercury pharmacokinetics were calculated by pooling the data on the group and were based on a 1-compartment first-order pharmacokinetics model.

RESULTS

For groups 1, 2, and 3, respectively, (1) mean +/- SD weights were 3.4 +/- 0.4, 5.1 +/- 0.6, and 7.7 +/- 1.1 kg; (2) maximal mean +/- SD blood mercury levels were 5.0 +/- 1.3, 3.6 +/- 1.5, and 2.8 +/- 0.9 ng/mL occurring at 0.5 to 1 day after vaccination; (3) maximal mean +/- SD stool mercury levels were 19.1 +/- 11.8, 37.0 +/- 27.4, and 44.3 +/- 23.9 ng/g occurring on day 5 after vaccination for all groups; and (4) urine mercury levels were mostly nondetectable. The blood mercury half-life was calculated to be 3.7 days and returned to prevaccination levels by day 30.

CONCLUSIONS

The blood half-life of intramuscular ethyl mercury from thimerosal in vaccines in infants is substantially shorter than that of oral methyl mercury in adults. Increased mercury levels were detected in stools after vaccination, suggesting that the gastrointestinal tract is involved in ethyl mercury elimination. Because of the differing pharmacokinetics of ethyl and methyl mercury, exposure guidelines based on oral methyl mercury in adults may not be accurate for risk assessments in children who receive thimerosal-containing vaccines.

http://www.ncbi.nlm.nih.gov/pubmed/?term=18245396

“Because of the differing pharmacokinetics of ethyl and methyl mercury, exposure guidelines based on oral methyl mercury in adults may not be accurate for risk assessments in children who receive thimerosal-containing vaccines.”

Chemical Research In Toxicology • February 2008

Thiol-modulated mechanisms of the cytotoxicity of thimerosal and inhibition of DNA topoisomerase II alpha

Author information

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Abstract

Thimerosal is an organic mercury compound that is widely used as a preservative in vaccines and other solution formulations. The use of thimerosal has caused concern about its ability to cause neurological abnormalities due to mercury accumulation during a normal schedule of childhood vaccinations. While the chemistry and the biological effects of methylmercury have been well-studied, those of thimerosal have not. Thimerosal reacted rapidly with cysteine, GSH, human serum albumin, and single-stranded DNA to form ethylmercury adducts that were detectable by mass spectrometry. These results indicated that thimerosal would be quickly metabolized in vivo because of its reactions with protein and nonprotein thiols. Thimerosal also potently inhibited the decatenation activity of DNA topoisomerase II alpha, likely through reaction with critical free cysteine thiol groups. Thimerosal, however, did not act as a topoisomerase II poison and the lack of cross-resistance with a K562 cell line with a decreased level of topoisomerase II alpha (K/VP.5 cells) suggested that inhibition of topoisomerase II alpha was not a significant mechanism for the inhibition of cell growth. Depletion of intracellular GSH with buthionine sulfoximine treatment greatly increased the K562 cell growth inhibitory effects of thimerosal, which showed that intracellular glutathione had a major role in protecting cells from thimerosal. Pretreatment of thimerosal with glutathione did not, however, change its K562 cell growth inhibitory effects, a result consistent with the rapid exchange of the ethylmercury adduct among various thiol-containing cellular reactants. Thimerosal-induced single and double strand breaks in K562 cells were consistent with a rapid induction of apoptosis. In conclusion, these studies have elucidated some of the chemistry and biological activities of the interaction of thimerosal with topoisomerase II alpha and protein and nonprotein thiols and with DNA.

http://www.ncbi.nlm.nih.gov/pubmed/18197631

"Thimerosal-induced single and double strand breaks in K562 cells were consistent with a rapid induction of apoptosis. In conclusion, these studies have elucidated some of the chemistry and biological activities of the interaction of thimerosal with topoisomerase II alpha and protein and nonprotein thiols and with DNA."

"This study associates Thimerosal-containing Rho(D) immune globulins exposure with some Neurodevelopmental Disorders in children."

Neuro Endocrinology Letters • April 2008

Neurodevelopmental disorders, maternal Rh-negativity, and Rho(D) immune globulins: a multi-center assessment

Author information

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Abstract

BACKGROUND
Many formulations of Thimerosal (49.55% mercury by weight)-containing Rho(D) immune globulins (TCRs) were routinely administered to Rh-negative mothers in the US prior to 2002.

OBJECTIVES
It was hypothesized: (1) if prenatal Rho(D)-immune globulin preparation exposure was a risk factor for neurodevelopmental disorders (NDs) then more children with NDs would have Rh-negative mothers compared to controls; and (2) if Thimerosal in the Rho(D)-immune globulin preparations was the ingredient associated with NDs, following the removal of Thimerosal from all manufactured Rho(D)-immune globulin preparations from 2002 in the US the frequency of maternal Rh-negativity among children with NDs should be similar to control populations.

METHODS
Maternal Rh-negativity was assessed at two sites (Clinic A-Lynchburg, VA; Clinic B-Rockville and Baltimore, MD) among 298 Caucasian children with NDs and known Rh-status. As controls, maternal Rh-negativity frequency was determined from 124 Caucasian children (born 1987-2001) without NDs at Clinic A, and the Rh-negativity frequency was determined from 1,021 Caucasian pregnant mothers that presented for prenatal genetic care at Clinic B (1980-1989). Additionally, 22 Caucasian patients with NDs born from 2002 onwards (Clinics A and B) were assessed for maternal Rh-negativity.

RESULTS
There were significant and comparable increases in maternal Rh-negativity among children with NDs (Clinic: A=24.2%), autism spectrum disorders (Clinic: A=28.3%, B=25.3%), and attention-deficit-disorder/attention-deficit-hyperactivity-disorder (Clinic: A=26.3%) observed at both clinics in comparison to both control groups (Clinic: A=12.1%, B=13.9%) employed. Children with NDs born post-2001 had a maternal Rh-negativity frequency (13.6%) similar to controls.

CONCLUSION
This study associates TCR exposure with some NDs in children.

http://www.ncbi.nlm.nih.gov/pubmed/18404135

Journal Of Neurological Science • August 2008

Thimerosal exposure in infants and neurodevelopmental disorders: an assessment of computerized medical records in the Vaccine Safety Datalink

Author information

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Abstract

The study evaluated possible associations between neurodevelopmental disorders (NDs) and exposure to mercury (Hg) from Thimerosal-containing vaccines (TCVs) by examining the automated Vaccine Safety Datalink (VSD). A total of 278,624 subjects were identified in birth cohorts from 1990-1996 that had received their first oral polio vaccination by 3 months of age in the VSD. The birth cohort prevalence rate of medically diagnosed International Classification of Disease, 9th revision (ICD-9) specific NDs and control outcomes were calculated. Exposures to Hg from TCVs were calculated by birth cohort for specific exposure windows from birth-7 months and birth-13 months of age. Poisson regression analysis was used to model the association between the prevalence of outcomes and Hg doses from TCVs. Consistent significantly increased rate ratios were observed for autism, autism spectrum disorders, tics, attention deficit disorder, and emotional disturbances with Hg exposure from TCVs. By contrast, none of the control outcomes had significantly increased rate ratios with Hg exposure from TCVs. Routine childhood vaccination should be continued to help reduce the morbidity and mortality associated with infectious diseases, but efforts should be undertaken to remove Hg from vaccines. Additional studies should be conducted to further evaluate the relationship between Hg exposure and NDs.

http://www.ncbi.nlm.nih.gov/pubmed/18482737

“Consistent significantly increased rate ratios were observed for autism, autism spectrum disorders, tics, attention deficit disorder, and emotional disturbances with ethyl mercury exposure from thimerosal containing vaccines.”

Indian Journal Of Medical Research • October 2008

A comprehensive review of mercury provoked autism

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Abstract

Emerging evidence supports the theory that some autism spectrum disorders (ASDs) may result from a combination of genetic/biochemical susceptibility, specifically a reduced ability to excrete mercury (Hg), and exposure to Hg at critical developmental periods. Elemental/inorganic Hg is released into the air/water where it becomes methylated and accumulates in animal tissues. The US population is primarily exposed to methyl-Hg by fish consumption. In addition, many pharmaceuticals have been, and some continue to be, a ubiquitous source of danger because they contain mercurials. Mercurials may be found in drugs for the eye, ear, nose, throat, and skin; in bleaching creams; as preservatives in cosmetics, tooth pastes, lens solutions, vaccines, allergy test and immunotherapy solutions; in antiseptics, disinfectants, and contraceptives; in fungicides and herbicides; in dental fillings and thermometers; and many other products. Hg has been found to cause immune, sensory, neurological, motor, and behavioural dysfunctions similar to traits defining/associated with ASDs, and that these similarities extend to neuroanatomy, neurotransmitters, and biochemistry. Furthermore, a review of molecular mechanisms indicates that Hg exposure can induce death, disorganization and/or damage to selected neurons in the brain similar to that seen in recent ASD brain pathology studies, and this alteration may likely produce the symptoms by which ASDs are diagnosed. Finally, a review of treatments suggests that ASD patients who undergo protocols to reduce Hg and/or its effects show significant clinical improvements in some cases. In conclusion, the overwhelming preponderance of the evidence favours acceptance that Hg exposure is capable of causing some ASDs.

http://www.ncbi.nlm.nih.gov/pubmed/19106436

“In conclusion,

the overwhelming preponderance of the evidence

favours acceptance that ethyl mercury exposure

is capable of causing some Autistic Spectrum Disorders.”

Alternative Therapies In Health And Medicine • November 2008

A possible central mechanism in autism spectrum disorders, part 1

Author information

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Abstract

The autism spectrum disorders (ASD) are a group of related neurodevelopmental disorders that have been increasing in incidence since the 1980s. Despite a considerable amount of data being collected from cases, a central mechanism has not been offered. A careful review of ASD cases discloses a number of events that adhere to an immunoexcitotoxic mechanism. This mechanism explains the link between excessive vaccination, use of aluminum and ethylmercury as vaccine adjuvants, food allergies, gut dysbiosis, and abnormal formation of the developing brain. It has now been shown that chronic microglial activation is present in autistic brains from age 5 years to age 44 years. A considerable amount of evidence, both experimental and clinical, indicates that repeated microglial activation can initiate priming of the microglia and that subsequent stimulation can produce an exaggerated microglial response that can be prolonged. It is also known that one phenotypic form of microglia activation can result in an outpouring of neurotoxic levels of the excitotoxins, glutamate and quinolinic acid. Studies have shown that careful control of brain glutamate levels is essential to brain pathway development and that excesses can result in arrest of neural migration, as well as dendritic and synaptic loss. It has also been shown that certain cytokines, such as TNF-alpha, can, via its receptor, interact with glutamate receptors to enhance the neurotoxic reaction. To describe this interaction I have coined the term immunoexcitotoxicity, which is described in this article.

http://www.ncbi.nlm.nih.gov/pubmed/?term=19043938

“This mechanism explains the link between excessive vaccination, use of aluminum and ethylmercury as vaccine adjuvants, food allergies, gut dysbiosis, and abnormal formation of the developing brain.”

Current Medicinal Chemistry • December 2008

Kawasaki’s disease, acrodynia, and mercury

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Abstract

A superantigen or autoimmunity has been hypothesized to be the main cause of the Kawasaki’s Disease but the etiology is unknown. Medical literature, epidemiological findings, and some case reports have suggested that mercury may play a pathogenic role. Several patients with Kawasaki’s Disease have presented with elevated urine mercury levels compared to matched controls. Most symptoms and diagnostic criteria which are seen in children with acrodynia, known to be caused by mercury, are similar to those seen in Kawasaki’s Disease. Genetic depletion of glutathione S-transferase , a susceptibility marker for Kawasaki’s Disease, is known to be also a risk factor for acrodynia and may also increase susceptibility to mercury. Coinciding with the largest increase (1985-1990) of thimerosal (49.6% ethyl mercury) in vaccines, routinely given to infants in the U.S. by 6 months of age (from 75microg to 187.5microg), the rates of Kawasaki’s Disease increased ten times, and, later (1985-1997), by 20 times. Since 1990 88 cases of patients developing Kawasaki’s Disease some days after vaccination have been reported to the Centers of Disease Control (CDC) including 19% manifesting symptoms the same day. The presented pathogenetic model may lead to new preventive- and therapeutic strategies for Kawasaki’s disease.

http://www.ncbi.nlm.nih.gov/pubmed/19075648

“Coinciding with the largest increase (1985-1990) of thimerosal in vaccines, routinely given to infants in the U.S. by 6 months of age (from 75microg to 187.5microg), the rates of Kawasaki’s Disease increased ten times, and, later (1985-1997), by 20 times. Since 1990 eighty-eight cases of patients developing Kawasaki’s Disease some days after vaccination have been reported to the Centers of Disease Control (CDC) including 19% manifesting symptoms the same day.”

Journal Of Toxicology And Environmental Health Part A • 2008

An investigation of porphyrinuria in Australian children with autism

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Abstract

Two recent studies, from France (Nataf et al., 2006) and the United States (Geier & Geier, 2007), identified atypical urinary porphyrin profiles in children with an autism spectrum disorder (ASD). These profiles serve as an indirect measure of environmental toxicity generally, and mercury (Hg) toxicity specifically, with the latter being a variable proposed as a causal mechanism of ASD (Bernard et al., 2001; Mutter et al., 2005). To examine whether this phenomenon occurred in a sample of Australian children with ASD, an analysis of urinary porphyrin profiles was conducted. A consistent trend in abnormal porphyrin levels was evidenced when data was compared with those previously reported in the literature. The results are suggestive of environmental toxic exposure impairing heme synthesis. Three independent studies from three continents have now demonstrated that porphyrinuria is concomitant with ASD, and that Hg may be a likely xenobiotic to produce porphyrin profiles of this nature.

http://www.ncbi.nlm.nih.gov/pubmed/18704827

“These profiles serve as an indirect measure of environmental toxicity generally, and mercury toxicity specifically, with the latter being a variable proposed as a causal mechanism of Autistic Spectrum Disorder (Bernard et al., 2001; Mutter et al., 2005).”

"... present observations are compatible with increased oxidative stress and a decreased detoxification capacity, particularly of mercury, in patients diagnosed with Autistic Spectrum Disorders."

Neurochemical Research • February 2009

A prospective study of transsulfuration biomarkers in autistic disorders

Author information

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Abstract

The goal of this study was to evaluate transsulfuration metabolites in participants diagnosed with autism spectrum disorders (ASDs). Transsulfuration metabolites, including: plasma reduced glutathione (GSH), plasma oxidized glutathione (GSSG), plasma cysteine, plasma taurine, plasma sulfate, and plasma free sulfate among participants diagnosed with ASDs (n = 38) in comparison to age-matched neurotypical controls were prospectively evaluated. Testing was conducted using Vitamin Diagnostics, Inc. (CLIA-approved). Participants diagnosed with ASDs had significantly ($P < 0.001$) decreased plasma reduced GSH, plasma cysteine, plasma taurine, plasma sulfate, and plasma free sulfate relative to controls. By contrast, participants diagnosed with ASDs had significantly ($P < 0.001$) increased plasma GSSG relative to controls. The present observations are compatible with increased oxidative stress and a decreased detoxification capacity, particularly of mercury, in patients diagnosed with ASDs. Patients diagnosed with ASDs should be routinely tested to evaluate transsulfuration metabolites, and potential treatment protocols should be evaluated to potentially correct the transsulfuration abnormalities observed.

http://www.ncbi.nlm.nih.gov/pubmed/18612812

Experimental And Toxicological Pathology • March 2009

Gender-selective toxicity of thimerosal

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Abstract

A recent report shows a correlation of the historical use of thimerosal in therapeutic immunizations with the subsequent development of autism; however, this association remains controversial. Autism occurs approximately four times more frequently in males compared to females; thus, studies of thimerosal toxicity should take into consideration gender-selective effects. The present study was originally undertaken to determine the maximum tolerated dose (MTD) of thimersosal in male and female CD1 mice. However, during the limited MTD studies, it became apparent that thimerosal has a differential MTD that depends on whether the mouse is male or female. At doses of 38.4-76.8mg/kg using 10% DMSO as diluent, seven of seven male mice compared to zero of seven female mice tested succumbed to thimerosal. Although the thimerosal levels used were very high, as we were originally only trying to determine MTD, it was completely unexpected to observe a difference of the MTD between male and female mice. Thus, our studies, although not directly addressing the controversy surrounding thimerosal and autism, and still preliminary due to small numbers of mice examined, provide, nevertheless, the first report of gender-selective toxicity of thimerosal and indicate that any future studies of thimerosal toxicity should take into consideration gender-specific differences.

http://www.ncbi.nlm.nih.gov/pubmed/18771903

“Thus, our studies, although not directly addressing the controversy surrounding thimerosal and autism, and still preliminary due to small numbers of mice examined, provide, nevertheless, the first report of gender-selective toxicity of thimerosal and indicate that any future studies of thimerosal toxicity should take into consideration gender-specific differences.”

[autism occurs at a 4-1 ratio for boys to girls. Four boys to every one girl are damaged with autism]

Health Place • March 2009

Proximity to point sources of environmental mercury release as a predictor of autism prevalence

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Abstract

The objective of this study was to determine if proximity to sources of mercury pollution in 1998 were related to autism prevalence in 2002. Autism count data from the Texas Educational Agency and environmental mercury release data from the Environmental Protection Agency were used. We found that for every 1000 pounds of industrial release, there was a corresponding 2.6% increase in autism rates ($p<.05$) and a 3.7% increase associated with power plant emissions($P<.05$). Distances to these sources were independent predictors after adjustment for relevant covariates. For every 10 miles from industrial or power plant sources, there was an associated decreased autism Incident Risk of 2.0% and 1.4%, respectively ($p<.05$). While design limitations preclude interpretation of individual risk, further investigations of environmental risks to child development issues are warranted.

http://www.ncbi.nlm.nih.gov/pubmed/18353703

“We found that for every 1000 pounds of industrial release, there was a corresponding 2.6% increase in autism rates ($p<.05$) and a 3.7% increase associated with power plant emissions($P<.05$). For every 10 miles from industrial or power plant sources, there was an associated decreased autism Incident Risk of 2.0% and 1.4%, respectively ($p<.05$).”

Journal Of Neurological Science • May 2009

Biomarkers of environmental toxicity and susceptibility in autism

Author information

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Abstract

Autism spectrum disorders (ASDs) may result from a combination of genetic/biochemical susceptibilities in the form of a reduced ability to excrete mercury and/or increased environmental exposure at key developmental times. Urinary porphyrins and transsulfuration metabolites in participants diagnosed with an ASD were examined. A prospective, blinded study was undertaken to evaluate a cohort of 28 participants with an ASD diagnosis for Childhood Autism Rating Scale (CARS) scores, urinary porphyrins, and transsulfuration metabolites. Testing was conducted using Vitamin Diagnostics, Inc. (CLIA-approved) and Laboratoire Philippe Auguste (ISO-approved). Participants with severe ASDs had significantly increased mercury intoxication-associated urinary porphyrins (pentacarboxyporphyrin, precoproporphyrin, and coproporphyrin) in comparison to participants with mild ASDs, whereas other urinary porphyrins were similar in both groups. Significantly decreased plasma levels of reduced glutathione (GSH), cysteine, and sulfate were observed among study participants relative to controls. In contrast, study participants had significantly increased plasma oxidized glutathione (GSSG) relative to controls. Mercury intoxication-associated urinary porphyrins were significantly correlated with increasing CARS scores and GSSG levels, whereas other urinary porphyrins did not show these relationships. The urinary porphyrin and CARS score correlations observed among study participants suggest that mercury intoxication is significantly associated with autistic symptoms. The transsulfuration abnormalities observed among study participants indicate that mercury intoxication was associated with increased oxidative stress and decreased detoxification capacity.

http://www.ncbi.nlm.nih.gov/pubmed/18817931

“The urinary porphyrin and CARS score correlations observed among study participants suggest that mercury intoxication is significantly associated with autistic symptoms.”

Toxicology And Environmental Chemistry • June 2009

Mitochondrial dysfunction, impaired oxidative-reduction activity, degeneration, and death in human neuronal and fetal cells induced by low-level exposure to thimerosal and other metal compounds

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Abstract

Thimerosal (ethylmercurithiosalicylic acid), an ethylmercury (EtHg)-releasing compound (49.55% mercury (Hg)), was used in a range of medical products for more than 70 years. Of particular recent concern, routine administering of Thimerosal-containing biologics/childhood vaccines have become significant sources of Hg exposure for some fetuses/infants. This study was undertaken to investigate cellular damage among in vitro human neuronal (SH-SY-5Y neuroblastoma and 1321N1 astrocytoma) and fetal (nontransformed) model systems using cell vitality assays and microscope-based digital image capture techniques to assess potential damage induced by Thimerosal and other metal compounds (aluminum (Al) sulfate, lead (Pb)(II) acetate, methylmercury (MeHg) hydroxide, and mercury (Hg)(II) chloride) where the cation was reported to exert adverse effects on developing cells. Thimerosal-associated cellular damage was also evaluated for similarity to pathophysiological findings observed in patients diagnosed with autistic disorders (ADs). Thimerosal-induced cellular damage as evidenced by concentration- and time-dependent mitochondrial damage, reduced oxidative-reduction activity, cellular degeneration, and cell death in the in vitro human neuronal and fetal model systems studied. Thimerosal at low nanomolar (nM) concentrations induced significant cellular toxicity in human neuronal and fetal cells. Thimerosal-induced cytoxicity is similar to that observed in AD pathophysiologic studies. Thimerosal was found to be significantly more toxic than the other metal compounds examined. Future studies need to be conducted to evaluate additional mechanisms underlying Thimerosal-induced cellular damage and assess potential co-exposures to other compounds that may increase or decrease Thimerosal-mediated toxicity.

Full Report: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3924342/

“Thimerosal at low nanomolar concentrations induced significant cellular toxicity in human neuronal and fetal cells. Thimerosal-induced cytoxicity is similar to that observed in Autistic Disorder pathophysiologic studies. Thimerosal was found to be significantly more toxic than the other metal compounds examined.”

American Journal Of Perinatology • August 2009

Neonate exposure to thimerosal mercury from hepatitis B vaccines

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Abstract

Infant exposure to ethylmercury (EtHg) has not only increased but is starting earlier as a result of the current immunization schedule that uses thimerosal-containing vaccines (TCVs). Although vaccination schedule varies considerably between countries, infants in less-developed countries continue to be exposed to EtHg derived from more affordable TCVs. We studied the exposure of newborns to EtHg from hepatitis B vaccines; hospital records (21,685) were summarized for the years 2001 to 2005 regarding date of birth, vaccination date, and birth weight. Most of the vaccinations occurred in the first 24 hours postdelivery; over the 5 years, there was an increase in vaccinations within hours of birth (same day), from 7.4% (2001) to 87.8% (2005). Nearly 94.6% of infants are now being vaccinated within the first 24 hours. Range of mercury exposure spread from 4.2 to 21.1 microg mercury/kg body weight for those receiving TCVs with the highest thimerosal concentration; these exposure levels are conservative for 2% of children receiving vaccines within 2 to 3 postnatal days, when they are still going through physiological postnatal weight loss. Because of the particular timing (transitioning from in utero to ex utero metabolism) and specific aspects of exposure (i.e., parenteral mode, bypassing gastroenteric barriers) and dose (related to vaccine manufacturer and with variation in birth weight), this study reveals critical issues that can modulate toxicokinetics and toxicodynamics of organomercurials in neonates.

http://www.ncbi.nlm.nih.gov/pubmed/?term=19283656

“Infant exposure to ethylmercury (EtHg) has not only increased but is starting earlier as a result of the current immunization schedule that uses thimerosal-containing vaccines (TCVs) ... this study reveals critical issues that can modulate toxicokinetics and toxicodynamics of organomercurials in neonates.”

Toxicology In Vitro • September 2009

Increase in intracellular Zn2+ concentration by thimerosal in rat thymocytes: intracellular Zn2+ release induced by oxidative stress

Author information

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Abstract

Thimerosal (TMR), an ethylmercury-containing preservative in pharmaceutical products, was recently reported to increase intracellular Zn(2+) concentration. Therefore, some health concerns about the toxicity of TMR remain because of physiological and pathological roles of Zn(2+). To reveal the property of TMR-induced increase in intracellular Zn(2+) concentration, the effect of TMR on FluoZin-3 fluorescence, an indicator of intracellular Zn(2+), of rat thymocytes was examined. TMR at concentrations ranging from 0.3 microM to 10 microM increased the intensity of FluoZin-3 fluorescence in a concentration-dependent manner under external Ca(2+)- and Zn(2+)-free condition. The threshold concentration was 0.3-1 microM. The increase in the intensity was significant when TMR concentration was 1 microM or more. N,N,N',N'-Tetrakis(2-pyridylmethyl)ethylenediamine (TPEN), a chelator for intracellular Zn(2+), completely attenuated the TMR-induced augmentation of FluoZin-3 fluorescence. Hydrogen peroxide (H(2)O(2)) and N-ethylmaleimide, reducing cellular thiol content, significantly increased FluoZin-3 fluorescence intensity and decreased 5-chloromethylfluorescein (5-CMF) fluorescence intensity, an indicator for cellular thiol. The correlation coefficient between TMR-induced augmentation of FluoZin-3 fluorescence and attenuation of 5-CMF fluorescence was -0.882. TMR also attenuated the 5-CMF fluorescence in the presence of TPEN. Simultaneous application of H(2)O(2) and TMR synergistically augmented the FluoZin-3 fluorescence. It is suggested that TMR increases intracellular Zn(2+) concentration via decreasing cellular thiol content.

http://www.ncbi.nlm.nih.gov/pubmed/?term=19497362

“It is suggested that Thimerosal increases intracellular Zn(2+) concentration via decreasing cellular thiol content.”

Biometals • December 2009

Assessment of chronic mercury exposure within the U.S. population, National Health and Nutrition Examination Survey 1999–2006

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Abstract

The purpose of this study was to assess chronic mercury exposure within the US population. Time trends were analyzed for blood inorganic mercury (I-Hg) levels in 6,174 women, ages 18-49, in the NHANES, 1999-2006 data sets. Multivariate logistic regression distinguished a significant, direct correlation within the US population between I-Hg detection and years since the start of the survey (OR = 1.49, P < 0.001). Within this population, I-Hg detection rose sharply from 2% in 1999-2000 to 30% in 2005-2006. In addition, the population averaged mean I-Hg concentration rose significantly over that same period from 0.33 to 0.39 μ/L (Anova, P < 0.001). In a separate analysis, multivariate logistic regression indicated that I-Hg detection was significantly associated with age (OR = 1.02, P < 0.001). Furthermore, multivariate logistic regression revealed significant associations of both I-Hg detection and mean concentration with biomarkers for the main targets of mercury deposition and effect: the liver, immune system, and pituitary. This study provides compelling evidence that I-Hg deposition within the human body is a cumulative process, increasing with age and in the population over time, since 1999, as a result of chronic mercury exposure. Furthermore, our results indicate that I-Hg deposition is associated with the significant biological markers for main targets of exposure, deposition, and effect. Accumulation of focal I-Hg deposits within the human body due to chronic mercury exposure provides a mechanism which suggests a time dependent rise in the population risks for associated disease.

http://www.ncbi.nlm.nih.gov/pubmed/?term=19697139

“Within this population, inorganic mercury detection rose sharply from 2% in 1999-2000 to 30% in 2005-2006. In addition, the population averaged mean inorganic mercury concentration rose significantly over that same period from 0.33 to 0.39 μ/L (Anova, P < 0.001).”

“... thimerosal administration to suckling or adult rats impairs sensitivity to pain ...”

Brain Research • December 2009

Neonatal administration of a vaccine preservative, thimerosal, produces lasting impairment of nociception and apparent activation of opioid system in rats

Author information

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Abstract

Thimerosal (THIM), an organomercury preservative added to many child vaccines is a suspected factor in pathogenesis of neurodevelopmental disorders. We examined the pharmacokinetics of Hg in the brain, liver and kidneys after i.m. THIM injection in suckling rats and we tested THIM effect on nociception. THIM solutions were injected to Wistar and Lewis rats in a vaccination-like mode on PN days 7, 9, 11 and 15 in four equal doses. For Wistar rats these were: 12, 48, 240, 720, 1440, 2160, 3000 microg Hg/kg and for Lewis: 54, 216, 540 and 1080 microg Hg/kg. Pharmacokinetic analysis revealed that Hg from THIM injections accumulates in the rat brain in significant amounts and remains there longer than 30 days after the injection. At the 6th week of age animals were examined for pain sensitivity using the hot plate test. THIM treated rats of both strains and sexes manifested statistically significantly elevated pain threshold (latency for paw licking, jumping) on a hot plate (56 degrees C). Wistar rats were more sensitive to this effect than Lewis rats. Protracted THIM-induced hypoalgesia was reversed by naloxone (5 mg/kg, i.p.) injected before the hot plate test, indicative of involvement of endogenous opioids. This was confirmed by augmented catalepsy after morphine (2.5 mg/kg, s.c.) injection. Acute THIM injection to 6-week-old rats also produced hypoalgesia, but this effect was transient and was gone within 14 days. Present findings show that THIM administration to suckling or adult rats impairs sensitivity to pain, apparently due to activation the endogenous opioid system.

http://www.ncbi.nlm.nih.gov/pubmed/19747466

Acta Neurobiologia Experimentalis • 2009

A prospective study of prenatal mercury exposure from maternal dental amalgams and autism severity

Author information

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Abstract

Dental amalgams containing 50% mercury (Hg) have been used in dentistry for the last 150 years, and Hg exposure during key developmental periods was associated with autism spectrum disorders (ASDs). This study examined increased Hg exposure from maternal dental amalgams during pregnancy among 100 qualifying participants born between 1990-1999 and diagnosed with DSM-IV autism (severe) or ASD (mild). Logistic regression analysis (age, gender, race, and region of residency adjusted) by quintile of maternal dental amalgams during pregnancy revealed the ratio of autism:ASD (severe:mild) were about 1 (no effect) for < or =5 amalgams and increased for > or =6 amalgams. Subjects with > or =6 amalgams were 3.2-fold significantly more likely to be diagnosed with autism (severe) in comparison to ASD (mild) than subjects with < or =5 amalgams. Dental amalgam policies should consider Hg exposure in women before and during the child-bearing age and the possibility of subsequent fetal exposure and adverse outcomes.

Full Report

http://www.ncbi.nlm.nih.gov/pubmed/19593333

“Hg [ethyl mercury] exposure during key developmental periods was associated with autism spectrum disorders ... Subjects with > or =6 amalgams were 3.2-fold significantly more likely to be diagnosed with autism (severe) in comparison to ASD (mild) than subjects with < or =5 amalgams.”

“A significant correlation was observed between increasing cP levels and CARS scores.”

Journal Of Toxicology And Environmental Health Part A • 2009

A prospective blinded evaluation of urinary porphyrins verses the clinical severity of autism spectrum disorders

Author information

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Abstract

A prospective, blinded study evaluated the relationship between autism spectrum disorder (ASD) severity measured by Childhood Autism Rating Scale (CARS) scores and urinary porphyrins among a cohort of participants (n = 26). LabCorp (CLIA-approved) tested for uroporphyrins, heptacarboxylporphyrins, hexacarboxylporphyrins, pentacarboxylporphyrins, coproporphyrin (cP) I, and cP III levels. Participants with severe ASD had significantly increased cP I, cP III, and total cP levels in comparison to participants with mild ASD. A significant correlation was observed between increasing cP levels and CARS scores. Significant correlations were also noted for comparative urinary porphyrin testing between LabCorp and the Laboratoire Philippe Auguste (ISO-approved) for total cP. Finally, total cP measured at LabCorp was found to significantly correlate with precoproporphryin (a specific porphyrin marker for mercury toxicity) measured at the Laboratoire Philippe Auguste. Since urinary porphyrin testing is clinically available, relatively inexpensive, and noninvasive, it may be used to help suggest whether heavy metal toxicity is associated with ASD.

http://www.ncbi.nlm.nih.gov/pubmed/20077233

Toxicology And Applied Pharmacology • March 2010

Mercury toxicokinetics dependency on strain and gender

Author information

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Abstract

Mercury (Hg) exposure from dental amalgam fillings and thimerosal in vaccines is not a major health hazard, but adverse health effects cannot be ruled out in a small and more susceptible part of the exposed population. Individual differences in toxicokinetics may explain susceptibility to mercury. Inbred, H-2-congenic A.SW and B10.S mice and their F1- and F2-hybrids were given HgCl2 with 2.0 mg Hg/L drinking water and traces of (203)Hg. Whole-body retention (WBR) was monitored until steady state after 5 weeks, when the organ Hg content was assessed. Despite similar Hg intake, A.SW males attained a 20-30% significantly higher WBR and 2- to 5-fold higher total renal Hg retention/concentration than A.SW females and B10.S mice. A selective renal Hg accumulation but of lower magnitude was seen also in B10.S males compared with females. Differences in WBR and organ Hg accumulation are therefore regulated by non-H-2 genes and gender. Lymph nodes lacked the strain- and gender-dependent Hg accumulation profile of kidney, liver and spleen. After 15 days without Hg A.SW mice showed a 4-fold higher WBR and liver Hg concentration, but 11-fold higher renal Hg concentration, showing the key role for the kidneys in explaining the slower Hg elimination in A.SW mice. The trait causing higher mercury accumulation was not dominantly inherited in the F1 hybrids. F2 mice showed a large inter-individual variation in Hg accumulation, showing that multiple genetic factors influence the Hg toxicokinetics in the mouse. The genetically heterogeneous human population may therefore show a large variation in mercury toxicokinetics.

http://www.ncbi.nlm.nih.gov/pubmed/19732784

“The genetically heterogeneous human population may therefore show a large variation in mercury toxicokinetics.”

Journal Of Neuroinflammation • March 2010

Mercury induces inflammatory mediator release from human mast cells

Author information

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Abstract

BACKGROUND

Mercury is known to be neurotoxic, but its effects on the immune system are less well known. Mast cells are involved in allergic reactions, but also in innate and acquired immunity, as well as in inflammation. Many patients with Autism Spectrum Disorders (ASD) have "allergic" symptoms; moreover, the prevalence of ASD in patients with mastocytosis, characterized by numerous hyperactive mast cells in most tissues, is 10-fold higher than the general population suggesting mast cell involvement. We, therefore, investigated the effect of mercuric chloride (HgCl2) on human mast cell activation.

METHODS

Human leukemic cultured LAD2 mast cells and normal human umbilical cord blood-derived cultured mast cells (hCBMCs) were stimulated by HgCl2 (0.1-10 microM) for either 10 min for beta-hexosaminidase release or 24 hr for measuring vascular endothelial growth factor (VEGF) and IL-6 release by ELISA.

RESULTS

HgCl2 induced a 2-fold increase in beta-hexosaminidase release, and also significant VEGF release at 0.1 and 1 microM (311 +/- 32 pg/106 cells and 443 +/- 143 pg/106 cells, respectively) from LAD2 mast cells compared to control cells (227 +/- 17 pg/106 cells, $n = 5$, $p < 0.05$). Addition of HgCl2 (0.1 microM) to the proinflammatory neuropeptide substance P (SP, 0.1 microM) had synergestic action in inducing VEGF from LAD2 mast cells. HgCl2 also stimulated significant VEGF release (360 +/- 100 pg/106 cells at 1 microM, $n = 5$, $p < 0.05$) from hCBMCs compared to control cells (182 +/- 57 pg/106 cells), and IL-6 release (466 +/- 57 pg/106 cells at 0.1 microM) compared to untreated cells (13 +/- 25 pg/106 cells, $n = 5$, $p < 0.05$). Addition of HgCl2 (0.1 microM) to SP (5 microM) further increased IL-6 release.

CONCLUSIONS

HgCl2 stimulates VEGF and IL-6 release from human mast cells. This phenomenon could disrupt the blood-brain-barrier and permit brain inflammation. As a result, the findings of the present study provide a biological mechanism for how low levels of mercury may contribute to ASD pathogenesis.

Full Report:

http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2850891/

"... the findings of the present study provide a biological mechanism for how low levels of mercury may contribute to Autistic Spectrum Disorder pathogenesis."

"... association between premature puberty and exposure to mercury from thimerosal-containing vaccines ..."

Indian Journal Of Medical Research • April 2010

Thimerosal exposure & increasing trends of premature puberty in the vaccine safety datalink

Author information

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Abstract

BACKGROUND & OBJECTIVES

The US Agency for Toxic Substances and Disease Registry (ATSDR) reports that mercury (Hg) is a known endocrine disruptor and it adversely affects the steroid synthesis pathway in animals and humans, and may interact to enhance the risk for a child developing premature puberty. An association between premature puberty and exposure to Hg from thimerosal-containing vaccines (TCVs) was evaluated in computerized medical records within the Vaccine Safety Datalink (VSD).

METHODS

A total of 278,624 subjects were identified in birth cohorts from 1990-1996. The birth cohort prevalence rates of medically diagnosed International Classification of Disease, 9(th) revision (ICD-9) premature puberty and control outcomes were calculated. Exposures to Hg from TCVs were calculated by birth cohort for specific exposure windows from birth-7 months and birth-13 months of age. Poisson regression analysis was used to model the association between the prevalence of outcomes and Hg doses from TCVs.

RESULTS

Significantly increased ($P<0.0001$) rate ratios were observed for premature puberty for a 100 microg difference in Hg exposure from TCVs in the birth-7 months (rate ratio=5.58) and birth-13 months (rate ratio=6.45) of age exposure windows. By contrast, none of the control outcomes had significantly increased rate ratios with Hg exposure from TCVs.

INTERPRETATION & CONCLUSIONS

Routine childhood vaccination should be continued to help reduce the morbidity and mortality associated with infectious diseases, but efforts should be undertaken to remove Hg from vaccines. Additional studies should be done to evaluate the relationship between Hg exposure and premature puberty.

Full report available at this link: http://www.ncbi.nlm.nih.gov/pubmed/20424300

Indian Journal Of Medical Research • April 2010

Exposure to low-dose mercury (from thimerosal) & premature puberty - a new avenue for research with the vaccine safety datalink

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Abstract

The paper by Geier et al1 addresses the plausible association of premature puberty after a typical pattern of exposure to ethylmercury in thimerosal-containing vaccines (TCVs) taken by young children in the USA before TCVs were discontinued. Both precocious puberty and low-level mercury are per se high-profile topics of public health interest. Given that TCVs are still currently given to pregnant women, infants and young children around the world, the paper raises a unique opportunity for discussing the role of mercury- based preservatives.

The study took advantage of the vaccine-safety datalink (VSD) system of the USA. Black et al2 summarized the advantage of the VSD over the former Vaccine Adverse Event Reporting System (VAERS) in use until 1991 in the USA. Until then, potential vaccine safety issues could only be evaluated by the passive data collected through the VAERS. The current VSD system links outcome and vaccine exposure information, demographic and other covariate information, from the automated clinical databases within several Health Maintenance Organizations (HMOs). As pointed out by Black et al2 this data bank can be utilized to screen for possible associations of events after vaccination and also, as in the case of Geier et al1, to evaluate hypotheses. Geier et al1 analyzed the data from 1990 to 1996 (n = 278,624) and explored a possible link of premature puberty to TCV received at young ages by comparing this outcome to outcomes not related to mercury exposure (controls). It is worth mentioning the disproportionate percentage of males (7%) in the sample. If encountered in future studies, this information confirms gender differences in thimerosal toxicity3. Constitutional differences in gender determine hormonal balance and represent a biologic variable4 to be considered in reproductive and neurologic outcomes.

Premature sexual development is a topic of current interest because of social and attendant health- associated issues, especially for girls. Unwanted teenage pregnancy and sexually transmitted diseases are among the important social and biological issues affecting poor countries and disadvantaged segments of rich countries. Reports from different parts of the world indicate that precocious gynaecological-age is significantly associated with early sexual initiation5 and with teenage pregnancy6,7. Additionally, as reviewed by Karaolis-Danckert et al8, an accelerated age of puberty onset may influence the life-time risk for breast and testicular cancer, insulin resistance, and adiposity. It is becoming clear that environmental factors are strongly associated with precocious puberty9. Studies indicate that increasing rates of precocious puberty are among the endocrine-system related effects of endocrine-disruptor chemicals found in the environment10.

Generally described as endocrine disruptors, there are a broad range of these substances capable of affecting the endocrine system. Some of these can act specifically on the reproductive system having estrogenic, anti-estrogenic, androgenic, and anti- androgenic activity. Besides that, these chemicals can also interfere with the hypthalamo-pituitary unit, and also disrupt estrous cyclicity. The endocrine-disrupting activity of these pollutants on developmental toxicology depends on timing and dosage. However, since these occur as mixtures, it is not yet possible to know if their end-point effects are additive or antagonistic. Therefore, this type of exposure is difficult to study because of the variety of possible outcomes10. A wide range of endocrine disruptors listed by Abaci et al18 include biocides (herbicides, fungicides, insecticides, nematocides), and industrial compounds made up of organic substances and metals (that includes mercury).

Full report available at this link: http://www.ncbi.nlm.nih.gov/pubmed/20424297

Toxicology • August 2010

Sensitization effect of thimerosal is mediated in vitro via reactive oxygen species and calcium signaling

Author information

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Abstract

Thimerosal, a mercury derivative composed of ethyl mercury chloride (EtHgCl) and thiosalicylic acid (TSA), is widely used as a preservative in vaccines and cosmetic products and causes cutaneous reactions. Since dendritic cells (DCs) play an essential role in the immune response, the sensitization potency of chemicals was studied in vitro using U937, a human promyelomonocytic cell line that is used as a surrogate of monocytic differentiation and activation. Currently, this cell line is under ECVAM (European Center for the Validation of Alternative Methods) validation as an alternative method for discriminating chemicals. Thimerosal and mercury derivatives induced in U937 an overexpression of CD86 and interleukin (IL)-8 secretion similarly to 1-chloro-2,4-dinitrobenzene (DNCB), a sensitizer used as a positive control for DC activation. Non-sensitizers, dichloronitrobenzene (DCNB), TSA and sodium dodecyl sulfate (SDS), an irritant, had no effect. U937 activation was prevented by cell pretreatment with N-acetyl-L-cysteine (NAC) but not with thiol-independent antioxidants except vitamin E which affected CD86 expression by preventing lipid peroxidation of cell membranes. Thimerosal, EtHgCl and DNCB induced glutathione (GSH) depletion and reactive oxygen species (ROS) within 15 min; another peak was detected after 2h for mercury compounds only. MitoSOX, a specific mitochondrial fluorescent probe, confirmed that ROS were essentially produced by mitochondria in correlation with its membrane depolarization. Changes in mitochondrial membrane permeability induced by mercury were reversed by NAC but not by thiol-independent antioxidants. Thimerosal and EtHgCl also induced a calcium (Ca2+) influx with a peak at 3h, suggesting that Ca2+ influx is a secondary event following ROS induction as Ca2+ influx was suppressed after pretreatment with NAC but not with thiol-independent antioxidants. Ca2+ influx was also suppressed when culture medium was deprived of Ca2+ confirming the specificity of the measure. In conclusion, these data suggest that thimerosal induced U937 activation via oxidative stress from mitochondrial stores and mitochondrial membrane depolarization with a primordial effect of thiol groups. A cross-talk between ROS and Ca2+ influx was demonstrated.

http://www.ncbi.nlm.nih.gov/pubmed/20457211

“In conclusion, these data suggest that thimerosal induced U937 activation via oxidative stress from mitochondrial stores and mitochondrial membrane depolarization with a primordial effect of thiol groups. A cross-talk between ROS and Ca2+ in ux was demonstrated.”

Environmental Health Perspectives • October 2010

Urinary porphyrin excretion in neurotypical and autistic children

Author information

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Abstract

BACKGROUND
Increased urinary concentrations of pentacarboxyl-, precopro- and copro-porphyrins have been associated with prolonged mercury (Hg) exposure in adults, and comparable increases have been attributed to Hg exposure in children with autism (AU).

OBJECTIVES
This study was designed to measure and compare urinary porphyrin concentrations in neurotypical (NT) children and same-age children with autism, and to examine the association between porphyrin levels and past or current Hg exposure in children with autism.

METHODS
This exploratory study enrolled 278 children 2-12 years of age. We evaluated three groups: AU, pervasive developmental disorder-not otherwise specified (PDD-NOS), and NT. Mothers/caregivers provided information at enrollment regarding medical, dental, and dietary exposures. Urine samples from all children were acquired for analyses of porphyrin, creatinine, and Hg. Differences between groups for mean porphyrin and Hg levels were evaluated. Logistic regression analysis was conducted to determine whether porphyrin levels were associated with increased risk of autism.

RESULTS
Mean urinary porphyrin concentrations are naturally high in young children and decline by as much as 2.5-fold between 2 and 12 years of age. Elevated copro- ($p < 0.009$), hexacarboxyl- ($p < 0.01$) and pentacarboxyl- ($p < 0.001$) porphyrin concentrations were significantly associated with AU but not with PDD-NOS. No differences were found between NT and AU in urinary Hg levels or in past Hg exposure as determined by fish consumption, number of dental amalgam fillings, or vaccines received.

CONCLUSIONS
These findings identify disordered porphyrin metabolism as a salient characteristic of autism. Hg exposures were comparable between diagnostic groups, and a porphyrin pattern consistent with that seen in Hg-exposed adults was not apparent.

Full Report

http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2957928/

“Increased urinary concentrations of pentacarboxyl-, precopro- and copro-porphyrins have been associated with prolonged mercury (Hg) exposure in adults, and comparable increases have been attributed to Hg exposure in children with autism.”

“These data document that exposure to thimerosal during early postnatal life produces lasting alterations in the densities of brain opioid receptors along with other neuropathological changes, which may disturb brain development.”

Neurochemistry Research • November 2010

Neonatal administration of thimerosal causes persistent changes in mu opioid receptors in the rat brain

Author information

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Abstract

Thimerosal added to some pediatric vaccines is suspected in pathogenesis of several neurodevelopmental disorders. Our previous study showed that thimerosal administered to suckling rats causes persistent, endogenous opioid-mediated hypoalgesia. Here we examined, using immunohistochemical staining technique, the density of μ-opioid receptors (MORs) in the brains of rats, which in the second postnatal week received four i.m. injections of thimerosal at doses 12, 240, 1,440 or 3,000 μg Hg/kg. The periaqueductal gray, caudate putamen and hippocampus were examined. Thimerosal administration caused dose-dependent statistically significant increase in MOR densities in the periaqueductal gray and caudate putamen, but decrease in the dentate gyrus, where it was accompanied by the presence of degenerating neurons and loss of synaptic vesicle marker (synaptophysin). These data document that exposure to thimerosal during early postnatal life produces lasting alterations in the densities of brain opioid receptors along with other neuropathological changes, which may disturb brain development.

Full Report

http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2957583/

"our data demonstrated that the toxicokinetics of Thimerosal (ethyl mercury)

is completely different from that of methyl mercury."

Archives of Toxicology • Inorganic Compounds • November 2010

Identification and distribution of mercury species in rat tissues following administration of thimerosal or methylmercury

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Abstract

Methylmercury (Met-Hg) is one the most toxic forms of Hg, with a considerable range of harmful effects on humans. Sodium ethyl mercury thiosalicylate, thimerosal (TM) is an ethylmercury (Et-Hg)-containing preservative that has been used in manufacturing vaccines in many countries. Whereas the behavior of Met-Hg in humans is relatively well known, that of ethylmercury (Et-Hg) is poorly understood. The present study describes the distribution of mercury as (-methyl, -ethyl and inorganic mercury) in rat tissues (brain, heart, kidney and liver) and blood following administration of TM or Met-Hg. Animals received one dose/day of Met-Hg or TM by gavage (0.5 mg Hg/kg). Blood samples were collected after 6, 12, 24, 48, 96 and 120 h of exposure. After 5 days, the animals were killed, and their tissues were collected. Total blood mercury (THg) levels were determined by ICP-MS, and methylmercury (Met-Hg), ethylmercury (Et-Hg) and inorganic mercury (Ino-Hg) levels were determined by speciation analysis with LC-ICP-MS. Mercury remains longer in the blood of rats treated with Met-Hg compared to that of TM-exposed rats. Moreover, after 48 h of the TM treatment, most of the Hg found in blood was inorganic. Of the total mercury found in the brain after TM exposure, 63% was in the form of Ino-Hg, with 13.5% as Et-Hg and 23.7% as Met-Hg. In general, mercury in tissues and blood following TM treatment was predominantly found as Ino-Hg, but a considerable amount of Et-Hg was also found in the liver and brain. Taken together, our data demonstrated that the toxicokinetics of TM is completely different from that of Met-Hg. Thus, Met-Hg is not an appropriate reference for assessing the risk from exposure to TM-derived Hg. It also adds new data for further studies in the evaluation of TM toxicity.

http://link.springer.com/article/10.1007%2Fs00204-010-0538-4

Clinica Chimica Acta • November 2010

Making sense of epidemiological studies of young children exposed to thimerosal in vaccines

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Abstract

OBJECTIVE:
To compare epidemiological studies dealing with neurological issues (compatible with Hg toxicity) linked to exposing newborns and infants to intramuscular doses of preservative-Hg resulting from vaccination with thimerosal-containing vaccines (TCV).

METHODS:
Major databases were searched for studies that addressed neurodevelopment outcomes other than autism. Eight studies were identified and compared.

RESULTS:
Information extracted from the studies done in the USA, the UK, and Italy is important in understanding the complex interplay of variables but insufficient to establish non-toxicity for infants and young children still receiving TCV: a) there is ambiguity in some studies reporting neurodevelopment outcomes that seem to depend on confounding variables; b) the risk of neurotoxicity due to low doses of thimerosal is plausible at least for susceptible infants; c) there is a need to address these issues in less developed countries still using TCV in pregnant mothers, newborns, and young children.

CONCLUSIONS:
Since the use of TCV is still inevitable in many countries, this increases the need to protect vulnerable infants and promote actions that strengthen neurodevelopment. Developing countries should intensify campaigns that include breastfeeding among efforts to help prime the central nervous system to tolerate exposure to neurotoxic substances, especially thimerosal-Hg.

http://www.ncbi.nlm.nih.gov/pubmed/20638374?dopt=Abstract

“Since the use of thimerosal-containing vaccines is still inevitable in many countries, this increases the need to protect vulnerable infants ...”

“The neurotoxic effects of both mercurials are interwoven with their modulatory actions on GABA(A) and NMDA receptors, which most likely involve binding to these macromolecules.”

Journal Of Physiological Pharmacology • December 2010

Intermingled modulatory and neurotoxic effects of thimerosal and mercuric ions on electrophysiological responses to GABA and NMDA in hippocampal neurons

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Abstract

The organomercurial, thimerosal, is at the center of medical controversy as a suspected factor contributing to neurodevelopmental disorders in children. Many neurotoxic effects of thimerosal have been described, but its interaction with principal excitatory and inhibitory neurotransmiter systems is not known. We examined, using electrophysiological recordings, thimerosal effects on GABA and NMDA-evoked currents in cultured hippocampal neurons. After brief (3 to 10 min) exposure to thimerosal at concentrations up to 100 μM, there was no significant effect on GABA or NMDA-evoked currents. However, following exposure for 60-90 min to 1 or 10 μM thimerosal, there was a significant decrease in NMDA-induced currents ($p<0.05$) and GABAergic currents ($p<0.05$). Thimerosal was also neurotoxic, damaging a significant proportion of neurons after 60-90 min exposure; recordings were always conducted in the healthiest looking neurons. Mercuric chloride, at concentrations 1 μM and above, was even more toxic, killing a large proportion of cells after just a few minutes of exposure. Recordings from a few sturdy cells revealed that micromolar mercuric chloride markedly potentiated the GABAergic currents ($p<0.05$), but reduced NMDA-evoked currents ($p<0.05$). The results reveal complex interactions of thimerosal and mercuric ions with the GABA(A) and NMDA receptors. Mercuric chloride act rapidly, decreasing electrophysiological responses to NMDA but enhancing responses to GABA, while thimerosal works slowly, reducing both NMDA and GABA responses. The neurotoxic effects of both mercurials are interwoven with their modulatory actions on GABA(A) and NMDA receptors, which most likely involve binding to these macromolecules.

http://www.ncbi.nlm.nih.gov/pubmed/21224507

"... results show an association between the apparent level of mercury toxicity as measured by recognized urinary porphyrin biomarkers of mercury toxicity and the magnitude of the specific hallmark features of autism ..."

Biometals • December 2010

A biomarker of mercury body-burden correlated with diagnostic domain specific clinical symptoms of autism spectrum disorder

Author information

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Abstract

The study purpose was to compare the quantitative results from tests for urinary porphyrins, where some of these porphyrins are known biomarkers of heavy metal toxicity, to the independent assessments from a recognized quantitative measurement, the Autism Treatment Evaluation Checklist (ATEC), of specific domains of autistic disorders symptoms (Speech/Language, Sociability, Sensory/Cognitive Awareness, and Health/Physical/Behavior) in a group of children having a clinical diagnosis of autism spectrum disorder (ASD). After a Childhood Autism Rating Scale (CARS) evaluation to assess the development of each child in this study and aid in confirming their classification, and an ATEC was completed by a parent, a urinary porphyrin profile sample was collected and sent out for blinded analysis. Urinary porphyrins from twenty-four children, 2-13 years of age, diagnosed with autism or PDD-NOS were compared to their ATEC scores as well as their scores in the specific domains (Speech/Language, Sociability, Sensory/Cognitive Awareness, and Health/Physical/Behavior) assessed by ATEC. Their urinary porphyrin samples were evaluated at Laboratoire Philippe Auguste (which is an ISO-approved clinical laboratory). The results of the study indicated that the participants' overall ATEC scores and their scores on each of the ATEC subscales (Speech/Language, Sociability, Sensory/Cognitive Awareness, and Health/Physical/Behavior) were linearly related to urinary porphyrins associated with mercury toxicity. The results show an association between the apparent level of mercury toxicity as measured by recognized urinary porphyrin biomarkers of mercury toxicity and the magnitude of the specific hallmark features of autism as assessed by ATEC.

http://www.ncbi.nlm.nih.gov/pubmed/20532957

"... there has been a great deal of information

... that repetitive mercury exposure during pregnancy, through thimerosal,

dental amalgam, and fish consumption, and after birth, through thimerosal-containing vaccinations ...

is one potential factor in autism."

Education and Training in Autism and Developmental Disabilities • 2010

Mercury and Autism: A Review

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Abstract

The prevalence of autism has increased approximately four times in children in nearly one decade (California Health and Human Services Agency, 2003). It has been reported that explanations such as immigration, shifts in the interpretation of diagnostic criteria, improved identification, or diagnostic accuracies cannot explain the observed increase (Geier & Geier, 2005). One potential cause that has alarmed many has been the presence of thimersol, the mercury-based preservative found among immunizations. Although many refute this, concern has been leveled by many families and professionals concerning the potential impact of mercury poisoning as a causal factor. Researchers have proposed that autism may be in part caused by mercury, because there was cumulative mercury exposure through dental amalgam, fish consumption, environment pollution, and additionally, through increased thimerosal-containing vaccines for both mothers and newborns (Mutter, Naumann, Schneider, Walach, & Haley, 2005). The purpose of this study is to review the information from studies concerning the relationship between mercury exposure and autism.

Conclusion

To sum up, there has been a great deal of information from different studies that seems to indicate that repetitive mercury exposure during pregnancy, through thimerosal, dental amalgam, and fish consumption, and after birth, through thimerosal-containing vaccinations and pollution, in genetically susceptible individuals is one potential factor in autism. Certainly this question continues to stir debate among professionals across the medical and behavioral sciences. It serves as a grey area for many families as they seek to quell their anxiety invoked by this debate by discovering the facts. The purpose of this article was to synthesize the findings relative to this question to hopefully serve as a resource to educators as we seek to become more well-informed on this timely issue. As the prevalence rate for autism in children continues to rise, more research is needed to better understand causal factors. It is also crucial that quality reviews be conducted to synthesize a body of knowledge pertaining to these questions if the puzzle is to be solved pertaining to the link between mercury exposure and autism.

http://www.daddcec.org/Portals/0/CEC/Autism_Disabilities/Research/Publications/Education_Training_Development_Disabilities/2010v45_Journals/ETDD_201003v45n1p107-115_Mercury_Autism_A_Review.pdf

Acta Neurobiologiea Experimentalis • 2010

Age-dependent lower or higher levels of hair mercury in autistic children than in healthy controls

Author information

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Abstract

An association between autism and early life exposure to mercury is a hotly debated issue. In this study, 91 autistic Polish children, male and female, 3-4 and 7-9 years old, were compared to 75 age- and sex-matched healthy children with respect to: demographic, perinatal, clinical and developmental measures, parental age, birth order, morphometric measures, vaccination history, and hair mercury content. In demographic and perinatal measures there were no consistent differences between the autistic and control groups. Autistic children had a significantly greater prevalence of adverse reactions after vaccinations and abnormal development than controls. Between 45 and 80% of autistic children experienced developmental regress. Autistic children significantly differed from healthy peers in the concentrations of mercury in hair: younger autistics had lower levels, while older - higher levels than their respective controls. The results suggest that autistic children differ from healthy children in metabolism of mercury, which seems to change with age.

http://www.ncbi.nlm.nih.gov/pubmed/?term=20628443

“The results suggest that autistic children differ from healthy children in metabolism of mercury, which seems to change with age.”

Acta Neurobiologiea Experimentalis • 2010

Sorting out the spinning of autism: heavy metals and the question of incidence

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Abstract

The reasons for the rise in autism prevalence are a subject of heated professional debate. Featuring a critical appraisal of some research used to question whether rising levels of autism are related to environmental exposure to toxins (Soden et al. 2007, Barbaresi et al. 2009, Thompson et al. 2007) we aim to evaluate the actual state of scientific knowledge. In addition, we surveyed the empirical research on the topic of autism and heavy metal toxins. In our opinion empirical investigations are finding support for a link with heavy metal toxins. The various causes that have led to the increase in autism diagnosis are likely multi-faceted, and understanding the causes is one of the most important health topics today. We argue that scientific research does not support rejecting the link between the neurodevelopmental disorder of autism and toxic exposures.

http://www.ncbi.nlm.nih.gov/pubmed/?term=20628440

“In our opinion empirical investigations are finding support for a link with heavy metal toxins. We argue that scientific research does not support rejecting the link between the neurodevelopmental disorder of autism and toxic exposures.”

Journal Of Toxicology And Environmental Health Part A • 2010

Delayed acquisition of neonatal reflexes in newborn primates receiving a thimerosal-containing hepatitis B vaccine: influence of gestational age and birth weight

Author information

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Abstract

This study examined whether acquisition of neonatal reflexes in newborn rhesus macaques was influenced by receipt of a single neonatal dose of hepatitis B vaccine containing the preservative thimerosal (Th). Hepatitis B vaccine containing a weight-adjusted Th dose was administered to male macaques within 24 h of birth (n = 13). Unexposed animals received saline placebo (n = 4) or no injection (n = 3). Infants were tested daily for acquisition of nine survival, motor, and sensorimotor reflexes. In exposed animals there was a significant delay in the acquisition of root, snout, and suck reflexes, compared with unexposed animals. No neonatal responses were significantly delayed in unexposed animals. Gestational age (GA) and birth weight (BW) were not significantly correlated. Cox regression models were used to evaluate main effects and interactions of exposure with BW and GA as independent predictors and time-invariant covariates. Significant main effects remained for exposure on root and suck when controlling for GA and BW, such that exposed animals were relatively delayed in time-to-criterion. Interaction models indicated there were various interactions between exposure, GA, and BW and that inclusion of the relevant interaction terms significantly improved model fit. This, in turn, indicated that lower BW and/or lower GA exacerbated the adverse effects following vaccine exposure. This primate model provides a possible means of assessing adverse neurodevelopmental outcomes from neonatal Th-containing hepatitis B vaccine exposure, particularly in infants of lower GA or BW. The mechanisms underlying these effects and the requirements for Th requires further study.

http://www.ncbi.nlm.nih.gov/pubmed/?term=20711932

“This primate model provides a possible means of assessing adverse neurodevelopmental outcomes from neonatal Thimerosal-containing hepatitis B vaccine exposure, particularly in infants ...”

Acta Neurobiologia Experimentalis • 2010

Blood mercury levels in autism spectrum disorder: Is there a threshold level?

Author information

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Abstract

Mercury (Hg) may significantly impact the pathogenesis of autism spectrum disorders (ASDs). Lab results generated by Vitamin Diagnostics (CLIA-approved) from 2003-2007, were examined among subjects diagnosed with an ASD (n=83) in comparison to neurotypical controls (n=89). Blood Hg levels were determined by analyzing Hg content in red blood cells (RBC) using cold vapor analysis, and consistent Hg measurements were observed between Vitamin Diagnostics and the University of Rochester. Adjusted (age, gender, and date of collection) mean Hg levels were 1.9-fold significantly (P<.0001) increased among subjects diagnosed with an ASD (21.4 microg/L) in comparison to controls (11.4 microg/L). Further, an adjusted significant (P<.0005) threshold effect >15 microg/L) was observed for Hg levels on the risk of a subject being diagnosed with an ASD in comparison to controls (odds ratio=6.4). The weight of scientific evidence supports Hg as a causal factor in subjects diagnosed with an ASD.

Full Report: http://www.ncbi.nlm.nih.gov/pubmed/20628441

“The weight of scientific evidence supports ethyl mercury as a causal factor in subjects diagnosed with an Autistic Spectrum Disorder”

“These findings document neurotoxic effects of thimerosal,

at doses equivalent to those used in infant vaccines ...”

Folia Neuropathology • 2010

Lasting neuropathological changes in rat brain after intermittent neonatal administration of thimerosal

Author information

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Abstract

Thimerosal, an organomercurial added as a preservative to some vaccines, is a suspected iatrogenic factor, possibly contributing to paediatric neurodevelopmental disorders including autism. We examined the effects of early postnatal administration of thimerosal (four i.m. injections, 12 or 240 μg THIM-Hg/kg, on postnatal days 7, 9, 11 and 15) on brain pathology in Wistar rats. Numerous neuropathological changes were observed in young adult rats which were treated postnatally with thimerosal. They included: ischaemic degeneration of neurons and “dark” neurons in the prefrontal and temporal cortex, the hippocampus and the cerebellum, pathological changes of the blood vessels in the temporal cortex, diminished synaptophysin reaction in the hippocampus, atrophy of astroglia in the hippocampus and cerebellum, and positive caspase-3 reaction in Bergmann astroglia. These findings document neurotoxic effects of thimerosal, at doses equivalent to those used in infant vaccines or higher, in developing rat brain, suggesting likely involvement of this mercurial in neurodevelopmental disorders.

http://www.ncbi.nlm.nih.gov/pubmed/?term=21225508

"... investigators have long recognized that Hg is a neurodevelopmental poison;

it can cause problems in neuronal cell migration and division,

and can ultimately cause cell degeneration and death."

Acta Neurobiologia Experimentalis • 2010

The biological basis of autism spectrum disorders: Understanding causation and treatment by clinical geneticists

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Abstract

Autism spectrum disorders (ASDs) also known as pervasive developmental disorders (PDD) are a behaviorally defined group of neurodevelopmental disorders that are usually diagnosed in early childhood. ASDs disproportionately affect male children. Mercury (Hg) a heavy metal, is widespread and persistent in the environment. Mercury is a ubiquitous source of danger in fish, drugs, fungicides/herbicides, dental fillings, thermometers, and many other products. Elevated Hg concentrations may remain in the brain from several years to decades following exposure. This is important because investigators have long recognized that Hg is a neurodevelopmental poison; it can cause problems in neuronal cell migration and division, and can ultimately cause cell degeneration and death. Case-reports of patients have described developmental regressions with ASD symptoms following fetal and/or early childhood Hg exposure, and epidemiological studies have linked exposure to Hg with an elevated risk of a patient being diagnosed with an ASD. Immune, sensory, neurological, motor, and behavioral dysfunctions similar to traits defining or associated with ASDs were reported following Hg intoxication with similarities extending to neuroanatomy, neurotransmitters, and biochemistry. The sexual dimorphism of ASDs may result from synergistic neurotoxicity caused by the interaction of testosterone and Hg; in contrast, estrogen is protective, mitigating the toxicity of Hg. Mercury exposure may significantly increase androgen levels, and as a result, patients diagnosed with an ASD may significantly benefit from anti-androgen therapy. Finally, the clinical geneticist has a wealth of biomarkers to evaluate and treat patients diagnosed with an ASD.

Access to full report: http://www.ncbi.nlm.nih.gov/pubmed/20628444

Neurotoxicity Research • January 2011

Correlations Between Gene Expression and Mercury Levels in Blood of Boys With and Without Autism

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Abstract

Gene expression in blood was correlated with mercury levels in blood of 2- to 5-year-old boys with autism (AU) compared to age-matched typically developing (TD) control boys. This was done to address the possibility that the two groups might metabolize toxicants, such as mercury, differently. RNA was isolated from blood and gene expression assessed on whole genome Affymetrix Human U133 expression microarrays. Mercury levels were measured using an inductively coupled plasma mass spectrometer. Analysis of covariance (ANCOVA) was performed and partial correlations between gene expression and mercury levels were calculated, after correcting for age and batch effects. To reduce false positives, only genes shared by the ANCOVA models were analyzed. Of the 26 genes that correlated with mercury levels in both AU and TD boys, 11 were significantly different between the groups ($P(Diagnosis*Mercury) \leq 0.05$). The expression of a large number of genes ($n = 316$) correlated with mercury levels in TD but not in AU boys ($P \leq 0.05$), the most represented biological functions being cell death and cell morphology. Expression of 189 genes correlated with mercury levels in AU but not in TD boys ($P \leq 0.05$), the most represented biological functions being cell morphology, amino acid metabolism, and antigen presentation. These data and those in our companion study on correlation of gene expression and lead levels show that AU and TD children display different correlations between transcript levels and low levels of mercury and lead. These findings might suggest different genetic transcriptional programs associated with mercury in AU compared to TD children.

http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3006666/

"These data and those in our companion study on correlation of gene expression and lead levels show that Autistic and Typically Developing children display different correlations between transcript levels and low levels of mercury and lead. These findings might suggest different genetic transcriptional programs associated with mercury in Autistic compared to Typically Developing children."

Journal Of Occupational Medicine And Toxicology • January 2011

Is dental amalgam safe for humans? The opinion of the scientific committee of the European Commission

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Abstract

It was claimed by the Scientific Committee on Emerging and Newly Identified Health Risks (SCENIHR)) in a report to the EU-Commission that "....no risks of adverse systemic effects exist and the current use of dental amalgam does not pose a risk of systemic disease..." [1, available from: http://ec.europa.eu/health/ph_risk/committees/04_scenihr/docs/scenihr_o_016.pdf].SCENIHR disregarded the toxicology of mercury and did not include most important scientific studies in their review. But the real scientific data show that:(a) Dental amalgam is by far the main source of human total mercury body burden. This is proven by autopsy studies which found 2-12 times more mercury in body tissues of individuals with dental amalgam. Autopsy studies are the most valuable and most important studies for examining the amalgam-caused mercury body burden.(b) These autopsy studies have shown consistently that many individuals with amalgam have toxic levels of mercury in their brains or kidneys.(c) There is no correlation between mercury levels in blood or urine, and the levels in body tissues or the severity of clinical symptoms. SCENIHR only relied on levels in urine or blood.(d) The half-life of mercury in the brain can last from several years to decades, thus mercury accumulates over time of amalgam exposure in body tissues to toxic levels. However, SCENIHR state that the half-life of mercury in the body is only "20-90 days".(e) Mercury vapor is about ten times more toxic than lead on human neurons and with synergistic toxicity to other metals.(f) Most studies cited by SCENIHR which conclude that amalgam fillings are safe have severe methodical flaws.

Full Report

http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3025977/

"The half-life of mercury in the brain can last from several years to decades, thus mercury accumulates over time of amalgam exposure in body tissues to toxic levels. However, SCENIHR state that the half-life of mercury in the body is only "20-90 days". Mercury vapor is about ten times more toxic than lead on human neurons and with synergistic toxicity to other metals. Most studies cited by SCENIHR which conclude that amalgam fillings are safe have severe methodical flaws."

Toxicology And Environmental Chemistry • February 2011

Toxicity biomarkers among US children compared to a similar cohort in France: a blinded study measuring urinary porphyrins

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Abstract

The purpose of this blinded study was to evaluate potential environmental toxicity in a cohort of neurotypical children (n = 28) living in a suburban area of north-central Texas in the United States (US) with a comparable age- and gender-matched cohort of neurotypical children (n = 28) living in a suburban area of southeastern France using urinary porphyrin testing: uroporphyrin (uP), heptacarboxyporphyrin (7cxP), hexacarboxyporphyrin (6cxP), pentacarboxyporphyrin (5cxP), precoproporphyrin (prcP), and coproporphyrin (cP). Results showed significantly elevated 6cxP, prcP (an atypical, mercury-specific porphyrin), and cP levels, and increasing trends in 5cxP levels, among neurotypical children in the USA compared to children in France. Data suggest that in US neurotypical children, there is a significantly increased body-burden of mercury (Hg) compared to the body-burden of Hg in the matched neurotypical children in France. The presence of lead contributing to the higher levels of cP also needs to be considered. Further, other factors including genetics can not be completely ruled out.

Full Report

http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3898545/

"Data suggest that in US neurotypical children, there is a significantly increased body-burden of mercury compared to the body-burden of mercury in the matched neurotypical children in France."

Biometals • April 2011

A significant relationship between mercury exposure from dental amalgams a nd urinary porphyrins: a further assessment of the Casa Pia children's dental amalgam trial

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Abstract

Previous studies noted specific changes in urinary porphyrin excretion patterns associated with exposure to mercury (Hg) in animals and humans. In our study, urinary porphyrin concentrations were examined in normal children 8-18 years-old from a reanalysis of data provided from a randomized, prospective clinical trial that was designed to evaluate the potential health consequences of prolonged exposure to Hg from dental amalgam fillings (the parent study). Our analysis examined dose-dependent correlations between increasing Hg exposure from dental amalgams and urinary porphyrins utilizing statistical models with adjustments for the baseline level (i.e. study year 1) of the following variables: urinary Hg, each urinary porphyrin measure, gender, race, and the level of lead (Pb) in each subject's blood. Significant dose-dependent correlations between cumulative exposure to Hg from dental amalgams and urinary porphyrins associated with Hg body-burden (pentacarboxyporphyrin, precoproporphyrin, and coproporphyrin) were observed. Overall, 5-10% increases in Hg-associated porphyrins for subjects receiving an average number of dental amalgam fillings in comparison to subjects receiving only composite fillings were observed over the 8-year course of the study. In contrast, no significant correlations were observed between cumulative exposure to Hg from dental amalgams and urinary porphyrins not associated with Hg body-burden (uroporphyrin, heptacarboxyporphyrin, and hexacarboxyporphyrin). In conclusion, our study, in contrast to the no-effect results published from the parent study, further establishes the sensitivity and specificity of specific urinary porphyrins as a biomarker for low-level Hg body-burden, and also reveals that dental amalgams are a significant chronic contributor to Hg body-burden.

http://www.ncbi.nlm.nih.gov/pubmed/?term=21053054

"In conclusion, our study, in contrast to the no-effect results published from the parent study, further establishes the sensitivity and specificity of specific urinary porphyrins as a biomarker for low-level mercury body-burden, and also reveals that dental amalgams are a significant chronic contributor to mercury body-burden."

“Recent studies suggest that children diagnosed with an autism spectrum disorder have significantly increased levels of urinary porphyrins associated with mercury (Hg) toxicity ...”

Pediatrics International • April 2011

Toxicity biomarkers in autism spectrum disorder: a blinded study of urinary porphyrins

Author information

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Abstract

BACKGROUND

Recent studies suggest that children diagnosed with an autism spectrum disorder (ASD) have significantly increased levels of urinary porphyrins associated with mercury (Hg) toxicity, including pentacarboxyporphyrin (5cxP), precoproporphyrin (prcP), and coproporphyrin (cP), compared to typically developing controls. However, these initial studies were criticized because the controls were not age- and gender-matched to the children diagnosed with an ASD.

METHODS

Urinary porphyrin biomarkers in a group of children (2-13 years of age) diagnosed with an ASD (n= 20) were compared to matched (age, gender, race, location, and year tested) group of typically developing controls (n= 20).

RESULTS

Participants diagnosed with an ASD had significantly increased levels of 5cxP, prcP, and cP in comparison to controls. No significant differences were found in non-Hg associated urinary porphyrins (uroporphyrins, hexacarboxyporphyrin, and heptacarboxyporphyrin). There was a significantly increased odds ratio for an ASD diagnosis relative to controls among study participants with precoproporphyrin (odds ratio = 15.5, $P < 0.01$) and coproporphyrin (odds ratio = 15.5, $P < 0.01$) levels in the second through fourth quartiles in comparison to the first quartile.

CONCLUSION

These results suggest that the levels of Hg-toxicity-associated porphyrins are higher in children with an ASD diagnosis than controls. Although the pattern seen (increased 5cxP, prcP, and cP) is characteristic of Hg toxicity, the influence of other factors, such as genetics and other metals cannot be completely ruled out.

http://www.ncbi.nlm.nih.gov/pubmed/20626635

“Mercury (Hg) is recognized as a ubiquitous environmental neurotoxin and there is mounting evidence linking it to neurodevelopmental disorders, including autism.”

Toxicology And Environmental Chemistry • May 2011

The plausibility of a role for mercury in the etiology of autism: a cellular perspective

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Abstract

Autism is defined by a behavioral set of stereotypic and repetitious behavioral patterns in combination with social and communication deficits. There is emerging evidence supporting the hypothesis that autism may result from a combination of genetic susceptibility and exposure to environmental toxins at critical moments in development. Mercury (Hg) is recognized as a ubiquitous environmental neurotoxin and there is mounting evidence linking it to neurodevelopmental disorders, including autism. Of course, the evidence is not derived from experimental trials with humans but rather from methods focusing on biomarkers of Hg damage, measurements of Hg exposure, epidemiological data, and animal studies. For ethical reasons, controlled Hg exposure in humans will never be conducted. Therefore, to properly evaluate the Hg-autism etiological hypothesis, it is essential to first establish the biological plausibility of the hypothesis. This review examines the plausibility of Hg as the primary etiological agent driving the cellular mechanisms by which Hg-induced neurotoxicity may result in the physiological attributes of autism. Key areas of focus include: (1) route and cellular mechanisms of Hg exposure in autism; (2) current research and examples of possible genetic variables that are linked to both Hg sensitivity and autism; (3) the role Hg may play as an environmental toxin fueling the oxidative stress found in autism; (4) role of mitochondrial dysfunction; and (5) possible role of Hg in abnormal neuroexcitory and excitotoxity that may play a role in the immune dysregulation found in autism. Future research directions that would assist in addressing the gaps in our knowledge are proposed.

Full Report

http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3173748/

Neurochemical Research • June 2011

Integrating experimental (in vitro and in vivo) neurotoxicity studies of low-dose thimerosal relevant to vaccines

Author information

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Abstract

There is a need to interpret neurotoxic studies to help deal with uncertainties surrounding pregnant mothers, newborns and young children who must receive repeated doses of Thimerosal-containing vaccines (TCVs). This review integrates information derived from emerging experimental studies (in vitro and in vivo) of low-dose Thimerosal (sodium ethyl mercury thiosalicylate). Major databases (PubMed and Web-of-science) were searched for in vitro and in vivo experimental studies that addressed the effects of low-dose Thimerosal (or ethylmercury) on neural tissues and animal behaviour. Information extracted from studies indicates that: (a) activity of low doses of Thimerosal against isolated human and animal brain cells was found in all studies and is consistent with Hg neurotoxicity; (b) the neurotoxic effect of ethylmercury has not been studied with co-occurring adjuvant-Al in TCVs; (c) animal studies have shown that exposure to Thimerosal-Hg can lead to accumulation of inorganic Hg in brain, and that (d) doses relevant to TCV exposure possess the potential to affect human neuro-development. Thimerosal at concentrations relevant for infants' exposure (in vaccines) is toxic to cultured human-brain cells and to laboratory animals. The persisting use of TCV (in developing countries) is counterintuitive to global efforts to lower Hg exposure and to ban Hg in medical products; its continued use in TCV requires evaluation of a sufficiently nontoxic level of ethylmercury compatible with repeated exposure (co-occurring with adjuvant-Al) during early life.

http://www.ncbi.nlm.nih.gov/pubmed/21350943

"... activity of low doses of Thimerosal against isolated human and animal brain cells was found in all studies and is consistent with mercury neurotoxicity ... animal studies have shown that exposure to Thimerosal-Hg can lead to accumulation of inorganic mercury in brain, and that doses relevant to Thimerosal-containing vaccine exposure possess the potential to affect human neuro-development."

Biological Trace Elements Research • June 2011

Automated speciation of mercury in the hair of breastfed infants exposed to ethylmercury from thimerosal-containing vaccines

Author information

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Abstract

A simplified thiourea-based chromatography method, originally developed for methyl and inorganic mercury, was adapted to separate methylmercury (MeHg), ethylmercury (EtHg), and inorganic mercury (Hg(II)) in infants' hair. Samples were weighed and leached with an acidic thiourea solution. Leachates were concentrated on a polymeric resin prior to analysis by Hg-thiourea liquid chromatography/cold vapor atomic fluorescence spectrometry. All but one sample showed small amounts of EtHg, and four of the six analyzed samples had proportionally higher Hg(II) as a percent of total Hg. Breastfed infants from riverine Amazonian communities are exposed to mercury in breast milk (from high levels of maternal sources that include both fish consumption and dental amalgam) and to EtHg in vaccines (from thimerosal). The method proved sensitive enough to detect and quantify acute EtHg exposure after shots of thimerosal-containing vaccines. Based on work with MeHg and Hg(II), estimated detection limits for this method are 0.050, 0.10, and 0.10 ng g□¹ for MeHg, Hg(II), and EtHg, respectively, for a 20-mg sample. Specific limits depend on the amount of sample extracted and the amount of extract injected.

http://www.ncbi.nlm.nih.gov/pubmed/?term=20419397

"The method proved sensitive enough to detect and quantify acute Ethyl Mercury exposure after shots of thimerosal-containing vaccines."

"... significant elevation in the concentration of copper, lead and mercury ..."

Biological Trace Element Research • August 2011

Level of trace elements (copper, zinc, magnesium and selenium) and toxic elements (lead and mercury) in the hair and nail of children with autism

Author information

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Abstract

Autism is a multi-factorial pathology observed in children with altered levels of essential and elevated levels of toxic elements. There are also studies reporting a decrease in nutritional trace elements in the hair and nail of autistic children with healthy controls; moreover, bioelements have been shown to play an important role in the central nervous system. Therefore, the purpose of the present study was to assess the levels of trace elements like copper (Cu), zinc (Zn), magnesium (Mg), and selenium (Se) and toxic elements like mercury (Hg), and lead (Pb) in the hair and nail samples of autistic children and to evaluate whether the level of these elements could be correlated with the severity of autism. The subjects of the study were 45 autistic children with different grades of severity (low (LFA), medium (MFA), and high (HFA) functioning autism) according to Childhood Autism Rating Scale, n = 15 children in each group and 50 healthy children (age and sex matched). The boys and girls ratio involved in this study was 4:1, and they were 4-12 years of age. The study observed a valid indication of Cu body burden in the autistic children. The children with different grades of autism showed high significance ($p < 0.001$) in the level of copper in their hair and nail samples when compared to healthy controls. The level of Cu in the autistic children could be correlated with their degree of severity (more the Cu burden severe is autism). The study showed a significant elevation ($p < 0.001$) in the levels of toxic metals Pb and Hg in both hair and nail samples of autistic children when compared to healthy control group. The elevation was much pronounced in LFA group subjects when compared among autistic groups MFA and HFA. The levels of trace elements Mg and Se were significantly decreased ($p < 0.001$) in autistic children when compared to control. The trace element Zn showed significant variation in both hair and nails of LFA group children when compared to control group and other study groups. The significant elevation in the concentration of Cu, Pb, and Hg and significant decrease in the concentration of Mg and Se observed in the hair and nail samples of autistic subjects could be well correlated with their degrees of severity.

http://www.ncbi.nlm.nih.gov/pubmed/20625937

The Science Of The Total Environment • September 2011

Mercury exposure and risks from dental amalgam in the US population post-2000

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Abstract

Dental amalgam is 50% metallic mercury (Hg) by weight and Hg vapour continuously evolves from in-place dental amalgam, causing increased Hg content with increasing amalgam load in urine, faeces, exhaled breath, saliva, blood, and various organs and tissues including the kidney, pituitary gland, liver, and brain. The Hg content also increases with maternal amalgam load in amniotic fluid, placenta, cord blood, meconium, various foetal tissues including liver, kidney and brain, in colostrum and breast milk. Based on 2001 to 2004 population statistics, 181.1 million Americans carry a grand total of 1.46 billion restored teeth. Children as young as 26 months were recorded as having restored teeth. Past dental practice and recently available data indicate that the majority of these restorations are composed of dental amalgam. Employing recent US population-based statistics on body weight and the frequency of dentally restored tooth surfaces, and recent research on the incremental increase in urinary Hg concentration per amalgam-filled tooth surface, estimates of Hg exposure from amalgam fillings were determined for 5 age groups of the US population. Three specific exposure scenarios were considered, each scenario incrementally reducing the number of tooth surfaces assumed to be restored with amalgam. Based on the least conservative of the scenarios evaluated, it was estimated that some 67.2 million Americans would exceed the Hg dose associated with the reference exposure level (REL) of 0.3 µg/m(3) established by the US Environmental Protection Agency; and 122.3 million Americans would exceed the dose associated with the REL of 0.03 µg/m(3) established by the California Environmental Protection Agency. Exposure estimates are consistent with previous estimates presented by Health Canada in 1995, and amount to 0.2 to 0.4 µg/day per amalgam-filled tooth surface, or 0.5 to 1 µg/day/amalgam-filled tooth, depending on age and other factors.

http://www.ncbi.nlm.nih.gov/pubmed/?term=21782213

“Based on the least conservative of the scenarios evaluated, it was estimated that some 67.2 million Americans would exceed the mercury dose associated with the reference exposure level (REL) of 0.3 µg/m(3) established by the US Environmental Protection Agency; and 122.3 million Americans would exceed the dose associated with the REL of 0.03 µg/m(3) established by the California Environmental Protection Agency.”

“These data document that early postnatal Thimerosal administration

causes lasting neurobehavioral impairments and neurochemical alterations in the brain ...”

Behavioral Brain Research • September 2011

Persistent behavioral impairments and alterations of brain dopamine system after early postnatal administration of thimerosal in rats

Author information

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Abstract

The neurotoxic organomercurial thimerosal (THIM), used for decades as vaccine preservative, is a suspected factor in the pathogenesis of some neurodevelopmental disorders. Previously we showed that neonatal administration of THIM at doses equivalent to those used in infant vaccines or higher, causes lasting alterations in the brain opioid system in rats. Here we investigated neonatal treatment with THIM (at doses 12, 240, 1440 and 3000 μg Hg/kg) on behaviors, which are characteristically altered in autism, such as locomotor activity, anxiety, social interactions, spatial learning, and on the brain dopaminergic system in Wistar rats of both sexes. Adult male and female rats, which were exposed to the entire range of THIM doses during the early postnatal life, manifested impairments of locomotor activity and increased anxiety/neophobia in the open field test. In animals of both sexes treated with the highest THIM dose, the frequency of prosocial interactions was reduced, while the frequency of asocial/antisocial interactions was increased in males, but decreased in females. Neonatal THIM treatment did not significantly affect spatial learning and memory. THIM-exposed rats also manifested reduced haloperidol-induced catalepsy, accompanied by a marked decline in the density of striatal D2 receptors, measured by immunohistochemical staining, suggesting alterations to the brain dopaminergic system. Males were more sensitive than females to some neurodisruptive/neurotoxic actions of THIM. These data document that early postnatal THIM administration causes lasting neurobehavioral impairments and neurochemical alterations in the brain, dependent on dose and sex. If similar changes occur in THIM/mercurial-exposed children, they could contribute do neurodevelopmental disorders.

http://www.ncbi.nlm.nih.gov/pubmed/?term=21549155

Neuroscience Letters • October 2011

Chronic inorganic mercury exposure induces sex-specific changes in central TNF expression: importance in autism?

Author information

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Abstract

Mercury is neurotoxic and increasing evidence suggests that environmental exposure to mercury may contribute to neuropathologies including Alzheimer's disease and autism spectrum disorders. Mercury is known to disrupt immunocompetence in the periphery, however, little is known about the effects of mercury on neuroimmune signaling. Mercury-induced effects on central immune function are potentially very important given that mercury exposure and neuroinflammation both are implicated in certain neuropathologies (i.e., autism). Furthermore, mounting evidence points to the involvement of glial activation in autism. Therefore, we utilized an in vivo model to assess the effects of mercury exposure on neuroimmune signaling. In prairie voles, 10 week mercury exposure (60ppm HgCl(2) in drinking water) resulted in a male-specific increase in TNF protein expression in the cerebellum and hippocampus. These findings are consistent with our previously reported male-specific mercury-induced deficits in social behavior and further support a role for heavy metals exposure in neuropathologies such as autism. Subsequent studies should further evaluate the mechanism of action and biological consequences of heavy metals exposure. Additionally, these observations highlight the potential of neuroimmune markers in male voles as biomarkers of environmental mercury toxicity.

Full Report

http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3443965/

"These findings are consistent with our previously reported male-specific mercury-induced deficits in social behavior and further support a role for heavy metals exposure in neuropathologies such as autism."

"... statistically significant differences in the mean urine levels of aluminum, barium, cerium, mercury ..."

Maedica Bucharest • October 2011

Heavy metals and trace elements in hair and urine of a sample of arab children with autistic spectrum disorder

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Abstract

General information: Autism is a severe developmental disorder which involves social withdrawal, communication deficits, and stereotypic/repetitive behavior. The pathophysiological etiologies which precipitate autism symptoms remain elusive and controversial in many cases, but both genetic and environmental factors (and their interactions) have been implicated. While autism is considered multicausal, environmental factors have received significant attention. International discussion has ocused on neurotoxins such as mercury and lead, suggesting that these and other toxic metals contribute to the development of the disorder. An epidemiological study released in 2006 (Palmer et al.) linking Toxic Release Inventory (TRI) data on mercury to special education data in Texas reported a 61% increase in autism prevalence rates (or 17% adjusted) per 1000 pounds of mercury released into the environment (1). We attempted to further evaluate whether exposure to variable environmental contributes to the genesis of autistic spectrum disorder, and thus is a factor increasing the risk for developing autism symptoms in utero or in early childhood.

PURPOSE

The purpose of this study is to examine possible environmental risk factors and sources of exposure to mercury and other heavy metals in children with autism spectrum disorder versus controls. Through laboratory diagnostics we are able to distinguish between present and past exposure (i.e. hair analysis measurements reflect past exposure), urinary excretion levels of unprovoked urine represent immediate exposure. By assessing a spectrum of trace elements and heavy metals in hair and urine of both autistic and control groups, we focused on the participants≈ past and present exposure.

METHODOLOGY

The participants were 25 Autistic Spectrum Disorder (ASD) children (22 boys and 3 girls) between the age of 3 and 9 years. They were either diagnosed previously by other psychiatrist, psychologist, and developmental pediatrician or suspected by their parents as being autistic. All children were attendants to the Child Psychiatric Clinic in Erfan Psychiatric Hospital in Jeddah, KSA. Samples were collected during the period of June 2006 to March 2008. A control group of 25 children without any psychiatric or medical disorders was age-matched and sex-matched. All parents signed informed consent forms. All autistic children were subjected to a full clinical child psychiatric sheet for the diagnosis of autism spectrum disorder and exclusion of other psychiatric disorders according to the Diagnostic and Statistical Manual of Mental Disorders, 4th Edition (DSM IV). The severity of autistic symptomatology was measured by the Childhood Autism Rating Scale (CARS) and Autism Behavior Checklist (ABC) using the Arabic versions. Both groups were subjected to the Questionnaire on Exposure to Heavy Metals, Physical Symptoms, and Child Development. Hair and baseline urine samples (i.e. unprovoked urine) were taken from both groups and sent to the German clinical and environmental laboratory Micro Trace Minerals Gmbh, for the detection of heavy metals and trace elements levels where metal testing was performed via ICP-MS spectroscopy utilizing cell technique.

RESULTS

By comparing the ASD Group to the Control Group, we found a statistically significant difference in the mean hair levels of arsenic, cadmium, barium, cerium and lead (p=0.01, 0.03, 0.003, 0.003, and 0.03 respectively), and in the mean hair levels of magnesium and zinc (p=0.001 and 0.003 respectively). There were also statistically significant differences in the mean urine levels of aluminum, barium, cerium, mercury, and lead (p=0.004, 002, 0.014, 0.006 and 0.004 respectively), and in the mean urine levels of copper and germanium (p=0.049 and 0.02 respectively). An agreement was found in both specimen (hair and urine) for barium and lead. The statistically significant differences in mean hair levels of arsenic, cadmium, and cerium were not supported by urine baseline levels. Also, the statistically significant magnesium and zinc levels of hair were not supported by urine levels. A disagreement was also found with copper and germanium concentrations.

Full Report: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3391939/

Journal Of Toxicology • 2011

Toxicity of volatile methylated species of bismuth, arsenic, tin, and mercury in Mammalian cells in vitro

Author information

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Abstract

The biochemical transformation of mercury, tin, arsenic and bismuth through formation of volatile alkylated species performs a fundamental role in determining the environmental processing of these elements. While the toxicity of inorganic forms of most of these compounds are well documented (e.g., arsenic, mercury) and some of them are of relatively low toxicity (e.g., tin, bismuth), the more lipid-soluble organometals can be highly toxic. In the present study we investigated the cyto- and genotoxicity of five volatile metal(loid) compounds: trimethylbismuth, dimethylarsenic iodide, trimethylarsine, tetramethyltin, and dimethylmercury. As far as we know, this is the first study investigating the toxicity of volatile metal(loid) compounds in vitro. Our results showed that dimethylmercury was most toxic to all three used cell lines (CHO-9 cells, CaCo, Hep-G2) followed by dimethylarsenic iodide. Tetramethyltin was the least toxic compound; however, the toxicity was also dependend upon the cell type. Human colon cells (CaCo) were most susceptible to the toxicity of the volatile compounds compared to the other cell lines. We conclude from our study that volatile metal(loid) compounds can be toxic to mammalian cells already at very low concentrations but the toxicity depends upon the metal(loid) species and the exposed cell type.

Full Report

http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3189616/

“We conclude from our study that volatile metal(loid) compounds can be toxic to mammalian cells already at very low concentrations but the toxicity depends upon the metal(loid) species and the exposed cell type.”

Journal Of Toxicology And Environmental Health Part A • 2011

Ancestry of pink disease (infantile acrodynia) identified as a risk factor for autism spectrum disorders

Author information

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Abstract

Pink disease (infantile acrodynia) was especially prevalent in the first half of the 20th century. Primarily attributed to exposure to mercury (Hg) commonly found in teething powders, the condition was developed by approximately 1 in 500 exposed children. The differential risk factor was identified as an idiosyncratic sensitivity to Hg. Autism spectrum disorders (ASD) have also been postulated to be produced by Hg. Analogous to the pink disease experience, Hg exposure is widespread yet only a fraction of exposed children develop an ASD, suggesting sensitivity to Hg may also be present in children with an ASD. The objective of this study was to test the hypothesis that individuals with a known hypersensitivity to Hg (pink disease survivors) may be more likely to have descendants with an ASD. Five hundred and twenty-two participants who had previously been diagnosed with pink disease completed a survey on the health outcomes of their descendants. The prevalence rates of ASD and a variety of other clinical conditions diagnosed in childhood (attention deficit hyperactivity disorder, epilepsy, Fragile X syndrome, and Down syndrome) were compared to well-established general population prevalence rates. The results showed the prevalence rate of ASD among the grandchildren of pink disease survivors (1 in 22) to be significantly higher than the comparable general population prevalence rate (1 in 160). The results support the hypothesis that Hg sensitivity may be a heritable/genetic risk factor for ASD.

http://www.ncbi.nlm.nih.gov/pubmed/21797771

“Pink disease was especially prevalent in the first half of the 20th century. Primarily attributed to exposure to mercury commonly found in teething powders, the condition was developed by approximately 1 in 500 exposed children.”

Journal Of Toxicology And Environmental Health • 2011

A positive association found between autism prevalence and childhood vaccination uptake across the U.S. population

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Abstract

The reason for the rapid rise of autism in the United States that began in the 1990s is a mystery. Although individuals probably have a genetic predisposition to develop autism, researchers suspect that one or more environmental triggers are also needed. One of those triggers might be the battery of vaccinations that young children receive. Using regression analysis and controlling for family income and ethnicity, the relationship between the proportion of children who received the recommended vaccines by age 2 years and the prevalence of autism (AUT) or speech or language impairment (SLI) in each U.S. state from 2001 and 2007 was determined. A positive and statistically significant relationship was found: The higher the proportion of children receiving recommended vaccinations, the higher was the prevalence of AUT or SLI. A 1% increase in vaccination was associated with an additional 680 children having AUT or SLI. Neither parental behavior nor access to care affected the results, since vaccination proportions were not significantly related (statistically) to any other disability or to the number of pediatricians in a U.S. state. The results suggest that although mercury has been removed from many vaccines, other culprits may link vaccines to autism. Further study into the relationship between vaccines and autism is warranted.

http://www.ncbi.nlm.nih.gov/pubmed/21623535

“The results suggest that although mercury has been removed from many vaccines, other culprits may link vaccines to autism.”

“Our data supports the historic evidence that heavy metals play a role in the development of Autistic Spectrum Disorder.”

Maedica Bucharest • January 2012

Toxic Metals and Essential Elements in Hair and Severity of Symptoms among Children with Autism

Author information

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Abstract

OBJECTIVE

The objective of this study was to assess the levels of ten toxic metals and essential elements in hair samples of children with autism, and to correlate the level of these elements with the severity of autism.

METHOD

The participants were 44 children, age 3 to 9 years, with Autistic Spectrum Disorder (ASD) according to Diagnostic and Statistical Manual of Mental Disorders 4th Edition, (DSM-IV). The severity of autistic symptomatology was measured by the Childhood Autism Rating Scale (CARS). Hair analysis was performed to evaluate the long term metal exposure and mineral level.

RESULTS

By comparing hair concentration of autistic vs nonautistic children, elevated hair concentrations were noted for aluminum, arsenic, cadmium, mercury, antimony, nickel, lead, and vanadium. Hair levels of calcium, iron, iodine, magnesium, manganese, molybdenum, zinc, and selenium were considered deficient. There was a significant positive correlation between lead & verbal communication ($p = 0.020$) and general impression ($p = 0.008$). In addition, there was a significant negative correlation between zinc & fear and nervousness ($p = 0.022$).

CONCLUSION

Our data supports the historic evidence that heavy metals play a role in the development of ASD. In combination with an inadequate nutritional status the toxic effect of metals increase along with the severity of symptoms.

Full Report
http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3484795/

Neurochemical Research • February 2012

Administration of thimerosal to infant rats increases overflow of glutamate and aspartate in the prefrontal cortex: protective role of dehydroepiandrosterone sulfate

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Abstract

Thimerosal, a mercury-containing vaccine preservative, is a suspected factor in the etiology of neurodevelopmental disorders. We previously showed that its administration to infant rats causes behavioral, neurochemical and neuropathological abnormalities similar to those present in autism. Here we examined, using microdialysis, the effect of thimerosal on extracellular levels of neuroactive amino acids in the rat prefrontal cortex (PFC). Thimerosal administration (4 injections, i.m., 240 μg Hg/kg on postnatal days 7, 9, 11, 15) induced lasting changes in amino acid overflow: an increase of glutamate and aspartate accompanied by a decrease of glycine and alanine; measured 10-14 weeks after the injections. Four injections of thimerosal at a dose of 12.5 μg Hg/kg did not alter glutamate and aspartate concentrations at microdialysis time (but based on thimerosal pharmacokinetics, could have been effective soon after its injection). Application of thimerosal to the PFC in perfusion fluid evoked a rapid increase of glutamate overflow. Coadministration of the neurosteroid, dehydroepiandrosterone sulfate (DHEAS; 80 mg/kg; i.p.) prevented the thimerosal effect on glutamate and aspartate; the steroid alone had no influence on these amino acids. Coapplication of DHEAS with thimerosal in perfusion fluid also blocked the acute action of thimerosal on glutamate. In contrast, DHEAS alone reduced overflow of glycine and alanine, somewhat potentiating the thimerosal effect on these amino acids. Since excessive accumulation of extracellular glutamate is linked with excitotoxicity, our data imply that neonatal exposure to thimerosal-containing vaccines might induce excitotoxic brain injuries, leading to neurodevelopmental disorders. DHEAS may partially protect against mercurials-induced neurotoxicity.

Abstract: http://www.ncbi.nlm.nih.gov/pubmed/?term=22015977

Full Report: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3264864/

“Since excessive accumulation of extracellular glutamate is linked with excitotoxicity, our data imply that neonatal exposure to thimerosal-containing vaccines might induce excitotoxic brain injuries, leading to neurodevelopmental disorders.”

PLoS One • 2012

Thimerosal-induced apoptosis in mouse C2C12 myoblast cells occurs through suppression of the PI3K/Akt/survivin pathway

Author information

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Abstract

BACKGROUND

Thimerosal, a mercury-containing preservative, is one of the most widely used preservatives and found in a variety of biological products. Concerns over its possible toxicity have reemerged recently due to its use in vaccines. Thimerosal has also been reported to be markedly cytotoxic to neural tissue. However, little is known regarding thimerosal-induced toxicity in muscle tissue. Therefore, we investigated the cytotoxic effect of thimerosal and its possible mechanisms on mouse C2C12 myoblast cells.

METHODOLOGY/PRINCIPAL FINDINGS

The study showed that C2C12 myoblast cells underwent inhibition of proliferation and apoptosis after exposure to thimerosal (125-500 nM) for 24, 48 and 72 h. Thimerosal caused S phase arrest and induced apoptosis as assessed by flow cytometric analysis, Hoechst staining and immunoblotting. The data revealed that thimerosal could trigger the leakage of cytochrome c from mitochondria, followed by cleavage of caspase-9 and caspase-3, and that an inhibitor of caspase could suppress thimerosal-induced apoptosis. Thimerosal inhibited the phosphorylation of Akt(ser473) and survivin expression. Wortmannin, a PI3K inhibitor, inhibited Akt activity and decreased survivin expression, resulting in increased thimerosal-induced apoptosis in C2C12 cells, while the activation of PI3K/Akt pathway by mIGF-I (50 ng/ml) increased the expression of survivin and attenuated apoptosis. Furthermore, the inhibition of survivin expression by siRNA enhanced thimerosal-induced cell apoptosis, while overexpression of survivin prevented thimerosal-induced apoptosis. Taken together, the data show that the PI3K/Akt/survivin pathway plays an important role in the thimerosal-induced apoptosis in C2C12 cells.

CONCLUSIONS/SIGNIFICANCE

Our results suggest that in C2C12 myoblast cells, thimerosal induces S phase arrest and finally causes apoptosis via inhibition of PI3K/Akt/survivin signaling followed by activation of the mitochondrial apoptotic pathway.

Full Report

http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3492179/

“Our results suggest that in C2C12 myoblast cells, thimerosal induces S phase arrest and finally causes apoptosis via inhibition of PI3K/Akt/survivin signaling followed by activation of the mitochondrial apoptotic pathway.”

Journal On Developmental Disabilities • 2012

A Link Between mercury exposure, Autism Spectrum Disorder, and other neurodevelopmental Disorders? Implications for thimerosal-containing Vaccines

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Abstract

Autism is a multisystem developmental disorder characterized by dysfunctional immunity and impaired brain function. Although autism is partly determined by genetic susceptability factors, reported dramatic increases in the prevalence of autism in developed countries have intensified scientific focus on environmental exposures. Pre and perinatal immunotoxic insults are now strongly suspected as contributors to this increase. Mercury (Hg) is both a neuro and an immuno toxin and continues to be used in some pediatric vaccines in the form of the preservative thimerosal. Although currently there are no direct human studies on the risks of Hg exposure from thimerosalcontaining vaccines (TCVs), animal studies show that doses relevant to human TCV exposure can result in adverse neurodevelopmental outcomes. To date, TCVs continue to be administered on a regular basis to potentially the most vulnerable populations: pregnant women and children. In light of existing experimental evidence, the rationale for using this known immunotoxic and neurotoxic substance in human vaccines should be reconsidered.

Given the dramatic and rapidly-growing reported prevalence of autism spectrum disorder (ASD) (Newschaffer, Falb, & Gurney, 2005), a clear answer to the etiology of this apparent epidemic would serve parents as well as the medical community entrusted with the health of all children. The focus of this commentary is on the possible involvement of thimerosal (49% ethylmercury (EtHg)) in neurodevelopmental disorders. In the past, thimerosal was used worldwide as a preservative in vaccines. Although this practice has largely been discontinued due to safety concerns (Offit & Jew, 2003), thimerosal continues to be used in less-developed and developing countries (Dórea, Marques, & Brandao, 2009)), as well as in the preservation of multi-dose vaccine vials in Canada and the United States (Centers for Disease Control and Prevention, 2011; Public Health Agency of Canada, 2011). The use of thimerosal-containing vaccines (TCVs) continues to be a highly contentious issue. The fact that a causal link between thimerosal exposure and neurodevelopmental disorders in children is not supported by many studies (Andrews et al., 2004; Hviid, Stellfeld, Wohlfahrd, & Melbye, 2003; Parker, Schwartz, Todd, & Pickering, 2004; Verstraeten et al., 2003) fails to put this issue at rest.

Full Report: http://www.oadd.org/docs/41011_JoDD_18-1_34-42_Tomljenovic_et_al.pdf

“Given the dramatic and rapidly-growing reported prevalence of autism spectrum disorder (ASD) (Newschaffer, Falb, & Gurney, 2005), a clear answer to the etiology of this apparent epidemic would serve parents as well as the medical community entrusted with the health of all children. The fact that a causal link between thimerosal exposure and neurodevelopmental disorders in children is not supported by many studies fails to put this issue at rest.”

Environmental Sources Of Mercury

Mercury Concentration	Form	Biological Significance
0.4ppb	MetHg	Median chronic intake of contaminated fish (0.4ug/kg body weight) causes delayed speech and autistic-like symptoms in male children (Corbett & Poor, 2008)
1.6ppb	MetHg	Provisional Tolerable Weekly Intake (PTWI) based on body weight for infants and pregnant women (1.6ug/kg; Food & Agricultural Association/World Health Organization 2006)
2.0ppb	Inorganic Mercury	US EPA limit for drinking water (US EPA, 2011)
200ppb	Various Types Of Mercury	Level in liquid that the US EPA classifies as hazardous waste based on toxocity characteristics (US EPA, 2010)
600ppb	EtHg	Concentration of mercury in vaccines containing trace amounts of thimerosal (0.3ug/0.5 ml. dose, or 600ug/L;Halsey, 1999)
25,000-50,000ppb	EtHg	Concentration in Thimerosal containing multi-dose influenza, meningococcal pneumococcal polysaccharide and diphtheria-tetanus vaccines (Offit & Jew, 2003)

Journal Of Toxicology • June 2012

Thimerosal-Derived Ethylmercury Is a Mitochondrial Toxin in Human Astrocytes: Possible Role of Fenton Chemistry in the Oxidation and Breakage of mtDNA

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Abstract

Thimerosal generates ethylmercury in aqueous solution and is widely used as preservative. We have investigated the toxicology of Thimerosal in normal human astrocytes, paying particular attention to mitochondrial function and the generation of specific oxidants. We find that ethylmercury not only inhibits mitochondrial respiration leading to a drop in the steady state membrane potential, but also concurrent with these phenomena increases the formation of superoxide, hydrogen peroxide, and Fenton/Haber-Weiss generated hydroxyl radical. These oxidants increase the levels of cellular aldehyde/ketones. Additionally, we find a five-fold increase in the levels of oxidant damaged mitochondrial DNA bases and increases in the levels of mtDNA nicks and blunt-ended breaks. Highly damaged mitochondria are characterized by having very low membrane potentials, increased superoxide/hydrogen peroxide production, and extensively damaged mtDNA and proteins. These mitochondria appear to have undergone a permeability transition, an observation supported by the five-fold increase in Caspase-3 activity observed after Thimerosal treatment.

http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3395253/

“We find that ethylmercury not only inhibits mitochondrial respiration leading to a drop in the steady state membrane potential, but also concurrent with these phenomena increases the formation of superoxide, hydrogen peroxide, and Fenton/Haber-Weiss generated hydroxyl radical. These oxidants increase the levels of cellular aldehyde/ketones. Additionally, we find a five-fold increase in the levels of oxidant damaged mitochondrial DNA bases and increases in the levels of mtDNA nicks and blunt-ended breaks.”

Cerebellum • June 2012

Maternal thimerosal exposure results in aberrant cerebellar oxidative stress, thyroid hormone metabolism, and motor behavior in rat pups; sex- and strain-dependent effects

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Abstract

Methylmercury (Met-Hg) and ethylmercury (Et-Hg) are powerful toxicants with a range of harmful neurological effects in humans and animals. While Met-Hg is a recognized trigger of oxidative stress and an endocrine disruptor impacting neurodevelopment, the developmental neurotoxicity of Et-Hg, a metabolite of thimerosal (TM), has not been explored. We hypothesized that TM exposure during the perinatal period impairs central nervous system development, and specifically the cerebellum, by the mechanism involving oxidative stress. To test this, spontaneously hypertensive rats (SHR) or Sprague-Dawley (SD) rat dams were exposed to TM (200 μg/kg body weight) during pregnancy (G10-G15) and lactation (P5-P10). Male and female neonates were evaluated for auditory and motor function; cerebella were analyzed for oxidative stress and thyroid metabolism. TM exposure resulted in a delayed startle response in SD neonates and decreased motor learning in SHR male (22.6%), in SD male (29.8%), and in SD female (55.0%) neonates. TM exposure also resulted in a significant increase in cerebellar levels of the oxidative stress marker 3-nitrotyrosine in SHR female (35.1%) and SD male (14.0%) neonates. The activity of cerebellar type 2 deiodinase, responsible for local intra-brain conversion of thyroxine to the active hormone, 3',3,5-triiodothyronine (T3), was significantly decreased in TM-exposed SHR male (60.9%) pups. This coincided with an increased (47.0%) expression of a gene negatively regulated by T3, Odf4 suggesting local intracerebellar T3 deficiency. Our data thus demonstrate a negative neurodevelopmental impact of perinatal TM exposure which appears to be both strain- and sex-dependent.

http://www.ncbi.nlm.nih.gov/pubmed/22015705

"Our data thus demonstrate a negative neurodevelopmental impact of perinatal Thimerosal exposure which appears to be both strain- and sex-dependent."

Journal Of Biomedics And Biotechnology • July 2012

Toxic effects of mercury on the cardiovascular and central nervous systems

Author information

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Abstract

Environmental contamination has exposed humans to various metal agents, including mercury. This exposure is more common than expected, and the health consequences of such exposure remain unclear. For many years, mercury was used in a wide variety of human activities, and now, exposure to this metal from both natural and artificial sources is significantly increasing. Many studies show that high exposure to mercury induces changes in the central nervous system, potentially resulting in irritability, fatigue, behavioral changes, tremors, headaches, hearing and cognitive loss, dysarthria, incoordination, hallucinations, and death. In the cardiovascular system, mercury induces hypertension in humans and animals that has wide-ranging consequences, including alterations in endothelial function. The results described in this paper indicate that mercury exposure, even at low doses, affects endothelial and cardiovascular function. As a result, the reference values defining the limits for the absence of danger should be reduced.

Full Report

http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3395437/

“The results described in this paper indicate that mercury exposure, even at low doses, affects endothelial and cardiovascular function.”

Journal Of Biomedicine And Biotechnology • September 2012

Mercury Toxicity

João B. T. Rocha, Michael Aschner, José G. Dórea,
Sandra Ceccatelli, Marcelo Farina and Luiz Carlos L. Silveira

Abstract

Mercury (Hg) is one of the most toxic elements in the periodic table. Although Hg is present in nature, it has also been released into the environment for centuries as a result of anthropogenic activities. Nowadays, there are efforts to reduce its anthropogenic use; however, its environmental presence is significant and will persist. We are pleased to present this special issue on mercury toxicity. The objective of collecting research findings in a single issue devoted to the toxicology of mercury was to compile reports on the latest findings on Hg's toxicity from renowned research groups across the world. This special issue affords the opportunity to bring together a wide range of review and research papers devoted both to basic and applied toxicity associated with various exposure scenarios and Hg species (dental material, iatrogenic ethylmercury, fish-methylmercury) along with comprehensive description on experimental models. While human studies demonstrated the noxious effects of these forms of Hg, experimental studies have assisted in defining mechanistic pathways central to Hg's toxicity in various tissues and organ systems.

The volume is dedicated in part to articles that provide new insights on important considerations of subtle effects of exposure to multiple forms of organic mercury (ethylmercury in thimerosal-containing vaccines and methylmercury (MeHg) derived from maternal fish consumption) and neurological outcomes in infants (J. G. Dórea et al.). In addition, hypersensitivity to low-dose Hg exposure from dental amalgam fillings is detailed, showing exquisite sensitivity to amalgam-derived Hg in sensitized individuals (H. McParland and S. Warnakulasuriya). Local effects of amalgam and Hg dental restoration represent the most important nonoccupational exposure to inorganic mercury, while fish consumption represents the most common source of MeHg exposure.

The impacts of exposure to fish-derived MeHg at levels below those considered to pose neurological risk (hair level: 50 μg/g) were explored by Japanese researchers in subjects of the Niigata mercury poisoning (K. Maruyama et al.). Experimental research papers from this issue confirmed and extended observations that exposure of immature rodents to different chemical forms of Hg is associated with differential bodily distribution Hg (M. Blanuša et al.; C.-F. Huang et al.). C.-F. Huang et al. demonstrated that exposure of developing rats to cinnabar (HgS) caused long-lasting neurobehavioral and neurochemical toxic effect, indicating that the use of this millenary component of traditional Chinese medicine continues to represent a toxicological concern. Using an important, yet little explored experimental mouse model, J. P. Bourdineaud and colleagues demonstrated that the ingestion of MeHg-adulterated fish led to higher neurotoxicity in comparison to the ingestion of the "free salt" of methylmercury chloride (MeHgCl). The scarcity of studies on this subject highlights the need for future studies to address these persistent toxicological issues.

The molecular, subcellular, cellular, and systemic toxicity of Hg was also addressed here in this volume. The cardiovascular toxicity of Hg in humans and rodents was reviewed by B. F. Azevedo et al. The impact of Hg exposure on endothelial cell physiology is well established; however, the limit of dietary-derived Hg needed to trigger cardiotoxic effects is still debatable. The negative impact of oral exposure to Hg(II) on reproductive performance of male rats was demonstrated by J. C. Heath and collaborators, highlighting the need for detailed studies to determine the nonobservable adverse effect level (NOAEL) of Hg(II) in the male reproductive system, as well as Hg deposition in target tissues. The comparative renal and hepatic toxicity of Hg(II) and MeHg in fish was addressed by V. Branco et al., demonstrating that both forms of mercury targeted the antioxidant selenoenzyme thioredoxin-reductase (TrxR) and reinforcing the central role of disrupted selenoprotein function in mercurial toxicity. The in vitro and in vivo targeting of the critical sulfhydryl-containing enzyme, Na+, K+-ATPase was reviewed by I. Kade and addressed by T. S. Huang et al., noting divergent effects in vitro and in vivo. The role of mitochondria and calcium in the neurotoxicity of MeHg was reviewed by D. Roos et al., providing evidence that Ca2+, glutamate, oxidative stress, and mitochondria play a central role in its neurotoxicity. The efficacy of the marine n-3 fatty acids, eicosapentaenoic acid (EPA), and docosahexaenoic acid (DHA) in attenuating MeHg-induced toxicity was studied in fish and mammalian cell cultures. O. J. Nøstbakken et al. demonstrated that DHA decreased MeHg uptake into mammalian cells but increased MeHg-induced apoptosis in fish cells.

We hope that the new findings on the subtle effects of combined exposure to iatrogenic ethylmercury (from thimerosal-containing vaccines) and maternal MeHg (from fish consumption), as well as the results of experimental studies and the critical reviews presented herein can shed novel information on mercury's absorption, distribution, metabolism, and excretion, as well as its ill effects at the cellular, molecular, and organismal levels. Understanding of these facets of research is required for derivation on environmental and health policies as well as guidance for the most promising future research venues. Finally, we would like to thank all the reviewers that have contributed their time and insight to this special issue as well as the journal's personnel (particularly Doaa Hassan) for their support and making possible the publication of this special issue.

Neurotoxicology And Teratology • November 2012

Neonatal exposure to Thimerosal from vaccines and child development in the first 3 years of life

Author information

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Abstract

BACKGROUND:
Despite the common use of Thimerosal as a preservative in childhood vaccines since the 1930s, there are not many studies on ethylmercury toxicokinetics and toxicodynamics in infants. The knowledge of ethylmercury's potential adverse effects is derived mostly from parallel methylmercury research or from animal and theoretical models.

AIM OF THE STUDY:
This study was designed to examine the relationship between neonatal exposure to Thimerosal-containing vaccine (TCV) and child development.

MATERIAL AND METHODS:
The study sample consisted of 196 infants born between January 2001 and March 2003 to mothers attending ambulatory prenatal clinics in the first and second trimesters of pregnancy in Krakow. Vaccination history (date and the type of the vaccine) was extracted from physicians' records. Child development was assessed using the Bayley Scales of Infant Development (BSID-II) measured in one-year intervals over 3years. General Linear Model (GLM) and Generalized Estimating Equation (GEE) models adjusted for potential confounders were used to assess the association.

RESULTS:
An adverse effect of neonatal TCV exposure was observed for the psychomotor development index (PDI) only in the 12th and 24th months of life (ß=-6.44, $p<0.001$ and ß=-5.89, $p<0.001$). No significant effect of neonatal TCV exposure was found in the 36th month. The overall deficit in the PDI attributable to neonatal TCV exposure measured over the course of the three-year follow-up (GEE) was significantly higher in TCV group (ß=-4.42, $p=0.001$). MDI scores did not show the adverse association with neonatal TCV exposure.

http://www.ncbi.nlm.nih.gov/pubmed/23069197

"Despite the common use of Thimerosal as a preservative in childhood vaccines since the 1930s, there are not many studies on ethylmercury toxicokinetics and toxicodynamics in infants. An adverse effect of neonatal TCV exposure was observed for the psychomotor development index ..."

American Journal Of Epidemiology • November 2012

Re: “Prenatal Exposure to Mercury and Infant Neurodevelopment in a Multicenter Cohort in Spain: Study of Potential Modifiers”

Author Information

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Abstract

In an interesting study, Llop et al. (1) addressed the vulnerability of the central nervous system to mercury during early development. Their findings suggested a negative association between total cord blood mercury levels and psychomotor development at approximately 14 months of age only in girls. Although I welcome these interesting findings, I would like to raise the issue of a source of organic mercury exposure during the perinatal period, namely ethylmercury in vaccines that contain Thimerosal (Noah Technologies Corporation, San Antonio, Texas). During recruitment of mothers (in November 2003) and infants born in 2004 in the study by Llop et al., Thimerosal-containing vaccines (TCVs) were still used in some European Union countries and probably in Spain (2). Therefore, it is reasonable to assume that additional mercury exposure could have occurred, at least for some of the sampled subjects. According to Spain’s vaccination schedule, some children could be exposed to TCV ethylmercury (mainly in diphtheria-tetanus-pertussis and hepatitis B vaccines); furthermore, during pregnancy, some mothers were also likely to be exposed to TCVs. Neither infant vaccines nor maternal exposure to TCVs, anti- Rho(D) immune globulin (to Rh-negative participants), or dental amalgams during pregnancy were mentioned in the otherwise assiduous study of Llop et al.

Assuming that there was a gradual discontinuation of TCVs in Spain, readers familiar with the changes occurring in vaccine type used in European Union countries during the early 2000s could benefit from a post hoc discussion of this confounding mercury source. The pertinence of this discussion is further justified by the recent reports that a subtle but significant association with psychomotor development can be shown in young children as a result of exposure to TCVs in Poland (3), Korea (4), and Brazil (5). Indeed, ecologic and epidemiologic studies in the United States, United Kingdom, and Italy (6) that addressed children’s neurodevelopment associated with ethylmercury exposure in TCVs indicated collectively that “a) there is ambiguity in some studies reporting neurodevelopment outcomes that seem to depend on confounding variables; b) the risk of neurotoxicity due to low doses of Thimerosal is plausible at least for susceptible infants” (6, p. 1580). Furthermore, recent findings have shown that neurologic responses in animals (mice, rats, and rhesus monkeys) exposed to ethylmercury from the hepatitis B vaccine in the early postnatal life presented statistically significant differences when compared with controls (7); there is also strong in vitro evidence of Thimerosal neurotoxicity in small doses relevant to TCVs (7).

Ethylmercury has a shorter half-life than does methylmercury; therefore, it is unlikely that it could contribute to total mercury levels in cord blood measured by Llop et al. (1). Nevertheless, ethylmercury exposure can be ascertained from vaccination cards (3–5). Information on the association of neurodevelopment and coexposure to multiple forms of mercury is limited, and despite the current widespread use of TCVs (in most countries), it is even scarcer for specific exposure to small amounts of ethylmercury (8). Therefore, only studies like that of Llop et al. (1) can offer the opportunity to explore possible cumulative insults resulting from maternal environmental (methylmercury) exposure and additional infant ethylmercury exposure due to differential (TCV) immunization. Although I do not question the statistical model, results, or interpretation of the study by Llop et al. (1), I hope to provoke a post hoc discussion highlighting possible ethylmercury exposure during pregnancy and postnatal periods via TCVs. Without proper testing, we will never discover whether additional TCV-related mercury exposure in early life can affect neurodevelopment tests.

“... a subtle but significant association with psychomotor development can be shown in young children as a result of exposure to Thimerosal containing vaccines in Poland, Korea, and Brazil ... there is also strong in vitro evidence of Thimerosal neurotoxicity in small doses relevant to Thimerosal containing vaccines.”

www.http://aje.oxfordjournals.org/content/early/2012/11/15/aje.kws386

Brain Development • March 2013

Prenatal exposure to organomercury, thimerosal, persistently impairs the serotonergic and dopaminergic systems in the rat brain: implications for association with developmental disorders

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Abstract

Thimerosal, an organomercury compound, has been widely used as a preservative. Therefore, concerns have been raised about its neurotoxicity. We recently demonstrated perturbation of early serotonergic development by prenatal exposure to thimerosal (Ida-Eto et al. (2011) [11]). Here, we investigated whether prenatal thimerosal exposure causes persistent impairment after birth. Analysis on postnatal day 50 showed significant increase in hippocampal serotonin following thimerosal administration on embryonic day 9. Furthermore, not only serotonin, striatal dopamine was significantly increased. These results indicate that embryonic exposure to thimerosal produces lasting impairment of brain monoaminergic system, and thus every effort should be made to avoid the use of thimerosal.

http://www.ncbi.nlm.nih.gov/pubmed/?term=22658806

“These results indicate that embryonic exposure to thimerosal produces lasting impairment of brain monoaminergic system, and thus every effort should be made to avoid the use of thimerosal.”

“... dental amalgams contribute to ongoing kidney damage ... in a dose-dependent fashion.”

Human Experiments In Toxicology • April 2013

A significant dose-dependent relationship between mercury exposure from dental amalgams and kidney integrity biomarkers: a further assessment of the Casa Pia children’s dental amalgam trial

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Abstract

Dental amalgams are a commonly used dental restorative material. Amalgams are about 50% mercury (Hg), and Hg is known to significantly accumulate in the kidney. It was hypothesized that because Hg accumulates in the proximal tubules (PTs), glutathione-S-transferases (GST)-a (suggestive of kidney damage at the level of PT) would be expected to be more related to Hg exposure than GST-π (suggestive of kidney damage at the level of the distal tubules). Urinary biomarkers of kidney integrity were examined in children of 8-18 years old, with and without dental amalgam fillings, from a completed clinical trial (parent study). Our study determined whether there was a significant dose-dependent correlation between increasing Hg exposure from dental amalgams and GST-a and GST-π as biomarkers of kidney integrity. Overall, the present study, using a different and more sensitive statistical model than the parent study, revealed a statistically significant dose-dependent correlation between cumulative exposure to Hg from dental amalgams and urinary levels of GST-a, after covariate adjustment; where as, a nonsignificant relationship was observed with urinary levels of GST-π. Furthermore, it was observed that urinary GST-a levels increased by about 10% over the 8-year course of the study among individuals with an average exposure to amalgams among the study subjects from the amalgam group, in comparison with study subjects with no exposure to dental amalgams. The results of our study suggest that dental amalgams contribute to ongoing kidney damage at the level of the PTs in a dose-dependent fashion.

http://www.ncbi.nlm.nih.gov/pubmed/22893351

“This suggests certain individuals with a mild mitochondrial defect

may be highly susceptible to mitochondrial specific toxins like the vaccine preservative thimerosal.”

Journal Of Toxicology • June 2013

B-lymphocytes from a population of children with autism spectrum disorder and their unaffected siblings exhibit hypersensitivity to thimerosal

Author information

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Abstract

The role of thimerosal containing vaccines in the development of autism spectrum disorder (ASD) has been an area of intense debate, as has the presence of mercury dental amalgams and fish ingestion by pregnant mothers. We studied the effects of thimerosal on cell proliferation and mitochondrial function from B-lymphocytes taken from individuals with autism, their nonautistic twins, and their nontwin siblings. Eleven families were examined and compared to matched controls. B-cells were grown with increasing levels of thimerosal, and various assays (LDH, XTT, DCFH, etc.) were performed to examine the effects on cellular proliferation and mitochondrial function. A subpopulation of eight individuals (4 ASD, 2 twins, and 2 siblings) from four of the families showed thimerosal hypersensitivity, whereas none of the control individuals displayed this response. The thimerosal concentration required to inhibit cell proliferation in these individuals was only 40% of controls. Cells hypersensitive to thimerosal also had higher levels of oxidative stress markers, protein carbonyls, and oxidant generation. This suggests certain individuals with a mild mitochondrial defect may be highly susceptible to mitochondrial specific toxins like the vaccine preservative thimerosal.

http://www.ncbi.nlm.nih.gov/pubmed/?term=23843785

"... decreased glutathione reserve capacity in children with an Autistic Spectrum Disorder could make them more susceptible to the toxic effects of Thimerosal routinely administered as part of mandated childhood immunization schedules."

International Journal Of Environmental Research And Public Health • August 2013

Thimerosal exposure and the role of sulfation chemistry and thiol availability in autism

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Abstract

Autism spectrum disorder (ASD) is a neurological disorder in which a significant number of the children experience a developmental regression characterized by a loss of previously acquired skills and abilities. Typically reported are losses of verbal, nonverbal, and social abilities. Several recent studies suggest that children diagnosed with an ASD have abnormal sulfation chemistry, limited thiol availability, and decreased glutathione (GSH) reserve capacity, resulting in a compromised oxidation/reduction (redox) and detoxification capacity. Research indicates that the availability of thiols, particularly GSH, can influence the effects of thimerosal (TM) and other mercury (Hg) compounds. TM is an organomercurial compound (49.55% Hg by weight) that has been, and continues to be, used as a preservative in many childhood vaccines, particularly in developing countries. Thiol-modulating mechanisms affecting the cytotoxicity of TM have been identified. Importantly, the emergence of ASD symptoms post-6 months of age temporally follows the administration of many childhood vaccines. The purpose of the present critical review is provide mechanistic insight regarding how limited thiol availability, abnormal sulfation chemistry, and decreased GSH reserve capacity in children with an ASD could make them more susceptible to the toxic effects of TM routinely administered as part of mandated childhood immunization schedules.

Full Report

http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3774468/

Journal Of Applied Toxicology • August 2013

Toxicity of ethylmercury (and Thimerosal): a comparison with methylmercury

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Abstract

Ethylmercury (etHg) is derived from the metabolism of thimerosal (o-carboxy-phenyl-thio-ethyl-sodium salt), which is the most widely used form of organic mercury. Because of its application as a vaccine preservative, almost every human and animal (domestic and farmed) that has been immunized with thimerosal-containing vaccines has been exposed to etHg. Although methylmercury (meHg) is considered a hazardous substance that is to be avoided even at small levels when consumed in foods such as seafood and rice (in Asia), the World Health Organization considers small doses of thimerosal safe regardless of multiple/repetitive exposures to vaccines that are predominantly taken during pregnancy or infancy. We have reviewed in vitro and in vivo studies that compare the toxicological parameters among etHg and other forms of mercury (predominantly meHg) to assess their relative toxicities and potential to cause cumulative insults. In vitro studies comparing etHg with meHg demonstrate equivalent measured outcomes for cardiovascular, neural and immune cells. However, under in vivo conditions, evidence indicates a distinct toxicokinetic profile between meHg and etHg, favoring a shorter blood half-life, attendant compartment distribution and the elimination of etHg compared with meHg. EtHg's toxicity profile is different from that of meHg, leading to different exposure and toxicity risks. Therefore, in real-life scenarios, a simultaneous exposure to both etHg and meHg might result in enhanced neurotoxic effects in developing mammals. However, our knowledge on this subject is still incomplete, and studies are required to address the predictability of the additive or synergic toxicological effects of etHg and meHg (or other neurotoxicants).

http://www.ncbi.nlm.nih.gov/pubmed/23401210

"the World Health Organization considers small doses of thimerosal safe regardless of multiple/repetitive exposures to vaccines that are predominantly taken during pregnancy or infancy ... in real-life scenarios, a simultaneous exposure to both etHg and meHg might result in enhanced neurotoxic effects in developing mammals. However, our knowledge on this subject is still incomplete, and studies are required to address the predictability of the additive or synergic toxicological effects of etHg and meHg (or other neurotoxicants)."

“Ethylmercury (EtHg) ... has received significant toxicological attention due to its presence in thimerosal-containing vaccines.”

Neuro Toxicology • September 2013

Comparative study on methyl- and ethylmercury-induced toxicity in C6 glioma cells and the potential role of LAT-1 in mediating mercurial-thiol complexes uptake

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Abstract

Various forms of mercury possess different rates of absorption, metabolism and excretion, and consequently, toxicity. Methylmercury (MeHg) is a highly neurotoxic organic mercurial. Human exposure is mostly due to ingestion of contaminated fish. Ethylmercury (EtHg), another organic mercury compound, has received significant toxicological attention due to its presence in thimerosal-containing vaccines. This study was designed to compare the toxicities induced by MeHg and EtHg, as well as by their complexes with cysteine (MeHg-S-Cys and EtHg-S-Cys) in the C6 rat glioma cell line. MeHg and EtHg caused significant ($p < 0.0001$) decreases in cellular viability when cells were treated during 30 min with each mercurial following by a washing period of 24 h (EC50 values of 4.83 and 5.05 μM, respectively). Significant cytotoxicity ($p < 0.0001$) was also observed when cells were treated under the same conditions with MeHg-S-Cys and EtHg-S-Cys, but the respective EC50 values were significantly increased (11.2 and 9.37 μM). l-Methionine, a substrate for the l-type neutral amino acid carrier transport (LAT) system, significantly protected against the toxicities induced by both complexes (MeHg-S-Cys and EtHg-S-Cys). However, no protective effects of l-methionine were observed against MeHg and EtHg toxicities. Corroborating these findings, l-methionine significantly decreased mercurial uptake when cells were exposed to MeHg-S-Cys ($p = 0.028$) and EtHg-S-Cys ($p = 0.023$), but not to MeHg and EtHg. These results indicate that the uptake of MeHg-S-Cys and EtHg-S-Cys into C6 cells is mediated, at least in part, through the LAT system, but MeHg and EtHg enter C6 cells by mechanisms other than LAT system.

http://www.sciencedirect.com/science/article/pii/S0161813X13000922

Biological Trace Element Research • September 2013

Mercury transfer during pregnancy and breastfeeding: hair mercury concentrations as biomarker

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Abstract

Hair mercury (HHg) concentration is a biomarker of exposure that is widely used to assess environmental contamination by fish methylmercury and neurodevelopment in children. In the Rio Madeira basin (Brazilian Amazon), total HHg concentrations in 649 mother-infant pairs were measured at birth (prenatal exposure) and after 6 months of exclusive breastfeeding; these mother-infant pairs were from high fish-eating communities (urban, n = 232; rural, n = 35; and Riverine, n = 262) and low fish-eating tin-miner settlers (n = 120). Differences in kinetics were seen between Hg exposure from fish consumption and environmental exposure to a tin-ore mining environment. Overall maternal HHg concentrations (at childbirth and after 6 months of lactation) were higher than those of infant HHg. However, the relative change in HHg after 6 months of lactation showed that mothers decreased HHg while infants increased HHg. The relative change showed a consistently higher increase for girls than boys with a statistical significance only in high fish-eating mothers. The correlation coefficients between maternal and newborn hair were high and statistically significant for mothers living in urban ($r = 0.66$, $p < 0.001$), rural ($r = 0.89$, $p < 0.001$), and Riverine ($r = 0.89$, $p < 0.001$) communities not for tin miner settlers ($r = 0.07$, $p = 0.427$). After 6 months of exclusive breastfeeding, correlation coefficients showed high correlation coefficients and statistical significance for all groups (urban, $r = 0.73$, $p < 0.001$; rural, $r = 0.88$, $p < 0.001$; Riverine, $r = 0.91$, $p < 0.001$) except for Tin miners ($r = -0.07$, $p = 0.428$). A linear model analysis was used to assess the longitudinal associations of maternal total HHg and total HHg at birth (0 days) and 6 months of age in exclusively breastfed infants. Regression analysis significantly predicted HHg in newborn from maternal HHg for high fish-eating maternal-infant pairs.

CONCLUSION:
The concentration of mercury accumulated in newborn tissues (in utero and during breastfeeding) relevant to both, maternal sources and infant exposure, can be reliably assessed from maternal hair.

http://www.ncbi.nlm.nih.gov/pubmed/23836367

“The concentration of mercury accumulated in newborn tissues (in utero and during breastfeeding) relevant to both, maternal sources and infant exposure, can be reliably assessed from maternal hair.”

Toxicological and Environmental Chemistry • September 2013

Thimerosal in childhood vaccines contributes to accumulating mercury toxicity in the kidney

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Abstract

Mercury (Hg) is a hazardous chemical that accumulates in many cells and tissues, thereby producing toxicity. The kidney is a key target organ for Hg accumulation and toxicity. The contributing factors to Hg accumulation in humans include: (1) elemental and inorganic Hg exposure, often occurring by inhalation of Hg vapors; (2) exposure to methyl Hg (meHg), for example, through contaminated seafood; and (3) exposure to ethyl mercury (etHg) via thimerosal-containing vaccines. Systematic investigations on the toxic effects of etHg/thimerosal on the nervous system were carried out, and etHg/thimerosal emerged as a possible risk factor for autism and other neurodevelopmental disorders. There is, however, little known about the mechanisms and molecular interactions underlying toxicity of etHg/thimerosal in the kidney, which is the focus of the current review. Susceptible populations such as infants, pregnant women, and the elderly are exposed to etHg through thimerosal-containing vaccines, and in-depth study of the potential adverse effects on the kidney is needed. In general, toxicity occurring in association with different forms of Hg is related to: intracellular thiol metabolism and oxidative stress reactions; mitochondrial function; intracellular distribution and build-up of calcium; apoptosis; expression of stress proteins; and also interaction with the cytoskeleton. Available evidence for the etHg-induced toxicity in the kidney was examined, and the main mechanisms and molecular interactions of cytotoxicity of etHg/thimerosal exposure in kidney described. Such accumulating knowledge may help to indicate molecular pathways that, if modulated, may better handle Hg-mediated toxicity.

“Systematic investigations on the toxic effects of ethyl mercury/thimerosal on the nervous system were carried out, and ethyl mercury/thimerosal emerged as a possible risk factor for autism and other neurodevelopmental disorders.”

https://www.researchgate.net/publication/260943204_Thimerosal_in_childhood_vaccines_contributes_to_accumulating_mercury_toxicity_in_the_kidney

International Journal Of Environmental Research And Public Health • October 2013

The kinetic signature of toxicity of four heavy metals and their mixtures on MCF7 breast cancer cell line

Author information

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Abstract

This study evaluated the kinetic signature of toxicity of four heavy metals known to cause severe health and environmental issues--cadmium (Cd), mercury (Hg) lead (Pb) arsenic (As)--and the mixture of all four metals (Mix) on MCF7 cancer cells, in the presence and absence of the antioxidant glutathione (GSH). The study was carried out using real time cell electronic sensing (RT-CES). RT-CES monitors in real time the electrical impedance changes at the electrode/culture medium interface due to the number of adhered cells, which is used as an index of cell viability. Cells were seeded for 24 h before exposure to the metals and their mixtures. The results showed that in the presence and absence of cellular glutathione, arsenic was the most cytotoxic of all five treatments, inducing cell death after 5 h of exposure. Lead was the least cytotoxic in both scenarios. In the presence of cellular GSH, the cytotoxic trend was As > Cd > MIX > Hg > Pb, while in the absence of GSH, the cytotoxic trend was As > Hg > MIX > Cd > Pb. The findings from this study indicate the significance of glutathione-mediated toxicity of the metals examined--particularly for mercury--and may be clinically relevant for disorders such as autism spectrum disorder where decreased glutathione-based detoxification capacity is associated with increased mercury intoxication.

Full Report

http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3822392/

“The findings from this study indicate the significance of glutathione-mediated toxicity of the metals examined—particularly for mercury—and may be clinically relevant for disorders such as autism spectrum disorder where decreased glutathione-based detoxification capacity is associated with increased mercury intoxication.”

World Journal Of Pediatrics • November 2013

Effect of thimerosal on the neurodevelopment of premature rats

Author information

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Abstract

BACKGROUND
This study was undertaken to determine the effect of thimerosal on the neurodevelopment of premature rats.

METHODS
Thimerosal was injected into premature SD rats at a dose of 32.8, 65.6, 98.4 or 131.2 μg/kg on postnatal day 1. Expression of dopamine D4 receptor (DRD4) and serotonin 2A receptor (5-HT2AR), apoptosis in the prefrontal cortex on post-injection day 49, and learning and memory function were studied and compared with those in a control group injected with saline.

RESULTS
Expression of DRD4 and 5-HT2AR and learning function decreased, and apoptosis increased significantly in the 131.2 μg/kg group ($P<0.001$). Memory function was significantly impaired by 65.6 ($P<0.05$), 98.4 and 131.2 μg/kg ($P<0.001$).

CONCLUSIONS
The negative adverse consequences on neurodevelopment observed in the present study are consistent with previous studies; this study raised serious concerns about adverse neurodevelopmental disorder such as autism in humans following the ongoing worldwide routine administration of thimerosalcontaining vaccines to infants.

http://www.ncbi.nlm.nih.gov/pubmed/?term=24235069

"The negative adverse consequences on neurodevelopment observed in the present study are consistent with previous studies; this study raised serious concerns about adverse neurodevelopmental disorder such as autism in humans following the ongoing worldwide routine administration of thimerosal containing vaccines to infants."

International Journal Of Environmental Research And Public Health • December 2013

Proposed toxic and hypoxic impairment of a brainstem locus in autism

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Abstract

Electrophysiological findings implicate site-specific impairment of the nucleus tractus solitarius (NTS) in autism. This invites hypothetical consideration of a large role for this small brainstem structure as the basis for seemingly disjointed behavioral and somatic features of autism. The NTS is the brain's point of entry for visceral afference, its relay for vagal reflexes, and its integration center for autonomic control of circulatory, immunological, gastrointestinal, and laryngeal function. The NTS facilitates normal cerebrovascular perfusion, and is the seminal point for an ascending noradrenergic system that modulates many complex behaviors. Microvascular configuration predisposes the NTS to focal hypoxia. A subregion--the "pNTS"--permits exposure to all blood-borne neurotoxins, including those that do not readily transit the blood-brain barrier. Impairment of acetylcholinesterase (mercury and cadmium cations, nitrates/nitrites, organophosphates, monosodium glutamate), competition for hemoglobin (carbon monoxide, nitrates/nitrites), and higher blood viscosity (net systemic oxidative stress) are suggested to potentiate microcirculatory insufficiency of the NTS, and thus autism.

Full Report

http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3881151/

"A subregion—the "pNTS"—permits exposure to all blood-borne neurotoxins, including those that do not readily transit the blood-brain barrier. Impairment of acetylcholinesterase (mercury and cadmium cations, nitrates/nitrites, organophosphates, monosodium glutamate), competition for hemoglobin (carbon monoxide, nitrates/nitrites), and higher blood viscosity (net systemic oxidative stress) are suggested to potentiate microcirculatory insufficiency of the NTS, and thus autism."

"... the present study provides new epidemiological evidence

supporting an association between increasing organic-mercury exposure

from Thimerosal-containing childhood vaccines and the subsequent risk of an Autistic Spectrum Disorder diagnosis."

Translational Neurodegeneration • December 2013

A two-phase study evaluating the relationship between Thimerosal-containing vaccine administration and the risk for an autism spectrum disorder diagnosis in the United States

Author information

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Abstract

BACKGROUND

Autism spectrum disorder (ASD) is defined by standardized criteria of qualitative impairments in social interaction, qualitative impairments in communication, and restricted and stereotyped patterns of behavior, interests, and activities. A significant number of children diagnosed with ASD suffer a loss of previously-acquired skills, which is suggestive of neurodegeneration or a type of progressive encephalopathy with an etiological pathogenic basis occurring after birth. To date, the etiology of ASD remains under debate, however, many studies suggest toxicity, especially from mercury (Hg), in individuals diagnosed with an ASD. The present study evaluated concerns about the toxic effects of organic-Hg exposure from Thimerosal (49.55% Hg by weight) in childhood vaccines by conducting a two-phased (hypothesis generating/hypothesis testing) study with documented exposure to varying levels of Thimerosal from vaccinations.

METHODS

A hypothesis generating cohort study was undertaken to evaluate the relationship between exposure to organic-Hg from a Thimerosal-containing Diphtheria-Tetanus-acellular-Pertussis (DTaP) vaccine in comparison to a Thimerosal-free DTaP vaccine administered, from 1998 through 2000, for the risk of ASD as reported in the Vaccine Adverse Event Reporting System (VAERS) database (phase I). A hypothesis testing case-control study was undertaken to evaluate the relationship between organic-Hg exposure from Thimerosal-containing hepatitis B vaccines administered at specific intervals in the first six months of life among cases diagnosed with an ASD and controls born between 1991 through 1999 in the Vaccine Safety Datalink (VSD) database (phase II).

RESULTS

In phase I, it was observed that there was a significantly increased risk ratio for the incidence of ASD reported following the Thimerosal-containing DTaP vaccine in comparison to the Thimerosal-free DTaP vaccine. In phase II, it was observed that cases diagnosed with an ASD were significantly more likely than controls to receive increased organic-Hg from Thimerosal-containing hepatitis B vaccine administered within the first, second, and sixth month of life.

CONCLUSIONS

Routine childhood vaccination is an important public health tool to reduce the morbidity and mortality associated with infectious diseases, but the present study provides new epidemiological evidence supporting an association between increasing organic-Hg exposure from Thimerosal-containing childhood vaccines and the subsequent risk of an ASD diagnosis.

Full Report

http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3878266/

Current Medical Chemistry • 2013

Low-dose mercury exposure in early life: relevance of thimerosal to fetuses, newborns and infants

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Abstract

This review explores the different aspects of constitutional factors in early life that modulate toxicokinetics and toxicodynamics of low-dose mercury resulting from acute ethylmercury (etHg) exposure in Thimerosal-containing vaccines (TCV). Major databases were searched for human and experimental studies that addressed issues related to early life exposure to TCV. It can be concluded that: a) mercury load in fetuses, neonates, and infants resulting from TCVs remains in blood of neonates and infants at sufficient concentration and for enough time to penetrate the brain and to exert a neurologic impact and a probable influence on neurodevelopment of susceptible infants; b) etHg metabolism related to neurodevelopmental delays has been demonstrated experimentally and observed in population studies; c) unlike chronic Hg exposure during pregnancy, neurodevelopmental effects caused by acute (repeated/cumulative) early life exposure to TCV-etHg remain unrecognized; and d) the uncertainty surrounding low-dose toxicity of etHg is challenging but recent evidence indicates that avoiding cumulative insults by alkyl-mercury forms (which include Thimerosal) is warranted. It is important to a) maintain trust in vaccines while reinforcing current public health policies to abate mercury exposure in infancy; b) generally support WHO policies that recommend vaccination to prevent and control existing and impending infectious diseases; and c) not confuse the 'need' to use a specific 'product' (TCV) by accepting as 'innocuous' (or without consequences) the presence of a proven 'toxic alkyl-mercury' (etHg) at levels that have not been proven to be toxicologically safe.

http://www.ncbi.nlm.nih.gov/pubmed/?term=23992327

"... mercury load in fetuses, neonates, and infants resulting from TCVs remains in blood of neonates and infants at sufficient concentration and for enough time to penetrate the brain and to exert a neurologic impact and a probable influence on neurodevelopment of susceptible infants ..."

Toxicology And Applied Pharmacology • February 2014

The retention time of inorganic mercury in the brain a systematic review of the evidence

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Abstract

Reports from human case studies indicate a half-life for inorganic mercury in the brain in the order of years-contradicting older radioisotope studies that estimated half-lives in the order of weeks to months in duration. This study systematically reviews available evidence on the retention time of inorganic mercury in humans and primates to better understand this conflicting evidence. A broad search strategy was used to capture 16,539 abstracts on the Pubmed database. Abstracts were screened to include only study types containing relevant information. 131 studies of interest were identified. Only 1 primate study made a numeric estimate for the half-life of inorganic mercury (227-540 days). Eighteen human mercury poisoning cases were followed up long term including autopsy. Brain inorganic mercury concentrations at death were consistent with a half-life of several years or longer. 5 radionucleotide studies were found, one of which estimated head half-life (21 days). This estimate has sometimes been misinterpreted to be equivalent to brain half-life-which ignores several confounding factors including limited radioactive half-life and radioactive decay from surrounding tissues including circulating blood. No autopsy cohort study estimated a half-life for inorganic mercury, although some noted bioaccumulation of brain mercury with age. Modelling studies provided some extreme estimates (69 days vs 22 years). Estimates from modelling studies appear sensitive to model assumptions, however predications based on a long half-life (27.4 years) are consistent with autopsy findings. In summary, shorter estimates of half-life are not supported by evidence from animal studies, human case studies, or modelling studies based on appropriate assumptions. Evidence from such studies point to a half-life of inorganic mercury in human brains of several years to several decades. This finding carries important implications for pharmcokinetic modelling of mercury and potentially for the regulatory toxicology of mercury.

http://www.ncbi.nlm.nih.gov/pubmed/24368178

“Evidence from such studies point to a half-life of inorganic mercury in human brains of several years to several decades. This finding carries important implications for pharmcokinetic modelling of mercury and potentially for the regulatory toxicology of mercury.”

“These and other studies suggest that susceptibility to mercury toxicity differs among individuals based on multiple genes, not all of which have been identified. These studies further suggest that the levels of exposure to mercury vapor from dental amalgams may be unsafe for certain subpopulations.”

Biometals • February 2014

New science challenges old notion that mercury dental amalgam is safe

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Abstract

Mercury dental amalgam has a long history of ostensibly safe use despite its continuous release of mercury vapor. Two key studies known as the Children’s Amalgam Trials are widely cited as evidence of safety. However, four recent reanalyses of one of these trials now suggest harm, particularly to boys with common genetic variants. These and other studies suggest that susceptibility to mercury toxicity differs among individuals based on multiple genes, not all of which have been identified. These studies further suggest that the levels of exposure to mercury vapor from dental amalgams may be unsafe for certain subpopulations. Moreover, a simple comparison of typical exposures versus regulatory safety standards suggests that many people receive unsafe exposures. Chronic mercury toxicity is especially insidious because symptoms are variable and nonspecific, diagnostic tests are often misunderstood, and treatments are speculative at best. Throughout the world, efforts are underway to phase down or eliminate the use of mercury dental amalgam.

Full Report

http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3905169/

Current Neuropharmacology • March 2014

Redox Regulation and the Autistic Spectrum: Role of Tryptophan Catabolites, Immuno-inflammation, Autoimmunity and the Amygdala

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Abstract

The autistic spectrum disorders (ASD) form a set of multi-faceted disorders with significant genetic, epigenetic and environmental determinants. Oxidative and nitrosative stress (O&NS), immuno-inflammatory pathways, mitochondrial dysfunction and dysregulation of the tryptophan catabolite (TRYCATs) pathway play significant interactive roles in driving the early developmental etiology and course of ASD. O&NS interactions with immuno-inflammatory pathways mediate their effects centrally via the regulation of astrocyte and microglia responses, including regional variations in TRYCATs produced. Here we review the nature of these interactions and propose an early developmental model whereby different ASD genetic susceptibilities interact with environmental and epigenetic processes, resulting in glia biasing the patterning of central interarea interactions. A role for decreased local melatonin and N-acetylserotonin production by immune and glia cells may be a significant treatment target.

Perinatal Mercury

Maternal prenatal mercury levels have sharply increased in recent decades, with foetal cord blood levels being significantly increased versus maternal levels [61,62]. This suggests that prenatal mercury, which can induce many of the changes evident in ASD, including increased O&NS and immuno-inflammation, as well as decreased endogenous anti-oxidants and mitochondrial functioning, may play a significant role in the etiology of ASD. As to whether mercury interacts with the consequences of prenatal infection in the offspring is unknown, although not unlikely given that mercury significantly modulates murine viral immune response [63,64] and viral infection increases brain mercury levels [65]. SNPs in genes involved in mercury regulation associate with ASD [66]. It also requires testing as to whether mercury has any impact on the development of foetal gamma-delta (□□) T cells and prenatal epigenetic regulation.

http://www.ncbi.nlm.nih.gov/pubmed/?term=24669209

“Maternal prenatal mercury levels have sharply increased in recent decades, with foetal cord blood levels being significantly increased versus maternal levels. This suggests that prenatal mercury, which can induce many of the changes evident in Autistic Spectrum Disorder, including increased O&NS and immuno-inflammation, as well as decreased endogenous anti-oxidants and mitochondrial functioning, may play a significant role in the etiology of Autistic Spectrum Disorder.”

PLoS One • April 2014

Suppression by Thimerosal of Ex-Vivo CD4+ T Cell Response to Influenza Vaccine and Induction of Apoptosis in Primary Memory T Cells

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Competing Interests

CrossJect provided the academic research/private research partnership to fund a CIFRE fellowship used in this study. There are no patents, products in development or marketed products to declare. This does not alter the authors' adherence to all the PLOS ONE policies on sharing data and materials.

Abstract

Thimerosal is a preservative used widely in vaccine formulations to prevent bacterial and fungal contamination in multidose vials of vaccine. Thimerosal was included in the multidose non-adjuvanted pandemic 2009 H1N1 vaccine Panenza. In the context of the analysis of the ex-vivo T cell responses directed against influenza vaccine, we discovered the in vitro toxicity Panenza, due to its content in thimerosal. Because thimerosal may skew the immune response to vaccines, we investigated in detail the ex-vivo effects of thimerosal on the fate and functions of T cells in response to TCR ligation. We report that ex-vivo exposure of quiescent or TCR-activated primary human T cells to thimerosal induced a dose-dependent apoptotic cell death associated with depolarization of mitochondrial membrane, generation of reactive oxygen species, cytochrome c release from the mitochondria and caspase-3 activation. Moreover, exposure to non-toxic concentrations of thimerosal induced cell cycle arrest in G0/G1 phase of TCR-activated T cells, and inhibition of the release of proinflammatory cytokines such as IFN gamma, IL-1 beta, TNF alpha, IL-2, as well as the chemokine MCP1. No shift towards Th2 or Th17 cells was detected. Overall these results underline the proapoptotic effect of thimerosal on primary human lymphocytes at concentrations 100 times less to those contained in the multidose vaccine, and they reveal the inhibitory effect of this preservative on T-cell proliferation and functions at nanomolar concentrations.

http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3972181/

"Overall these results underline the proapoptotic effect of thimerosal on primary human lymphocytes at concentrations 100 times less to those contained in the multidose vaccine, and they reveal the inhibitory effect of this preservative on T-cell proliferation and functions at nanomolar concentrations."

Environmental Toxicology And Chemistry • June 2014

Ecogenetics of mercury: from genetic polymorphisms and epigenetics to risk assessment and decision-making

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Abstract

The risk assessment of mercury (Hg), in both humans and wildlife, is made challenging by great variability in exposure and health effects. Although disease risk arises following complex interactions between genetic ("nature") and environmental ("nurture") factors, most Hg studies thus far have focused solely on environmental factors. In recent years, ecogenetic-based studies have emerged and have started to document genetic and epigenetic factors that may indeed influence the toxicokinetics or toxicodynamics of Hg. The present study reviews these studies and discusses their utility in terms of Hg risk assessment, management, and policy and offers perspectives on fruitful areas for future research. In brief, epidemiological studies on populations exposed to inorganic Hg (e.g., dentists and miners) or methylmercury (e.g., fish consumers) are showing that polymorphisms in a number of environmentally responsive genes can explain variations in Hg biomarker values and health outcomes. Studies on mammals (wildlife, humans, rodents) are showing Hg exposures to be related to epigenetic marks such as DNA methylation. Such findings are beginning to increase understanding of the mechanisms of action of Hg, and in doing so they may help identify candidate biomarkers and pinpoint susceptible groups or life stages. Furthermore, they may help refine uncertainty factors and thus lead to more accurate risk assessments and improved decision-making.

http://www.ncbi.nlm.nih.gov/pubmed/24038486

"In recent years, ecogenetic-based studies have emerged and have started to document genetic and epigenetic factors that may indeed influence the toxicokinetics or toxicodynamics of mercury."

Human Vaccines & Immunotherapeutics • June 2014

Thimerosal compromises human dendritic cell maturation, IL-12 production, chemokine release, and T-helper polarization

by Emily Loison & Marie-Lise Gougeon

Abstract

In conclusion, our study indicates that ex-vivo exposure of human immature dendritic cells to very low nontoxic concentrations of thimerosal alters the LPS-induced maturation process and dampens their proinflammatory response, in particular the production of the T-helper polarizing cytokine IL-12. Moreover, thimerosal exposure of DCs corrupts their interaction with naïve CD4+ T cells, leading to a decreased production of IFN-□ IP10 and GM-CSF and increased levels of IL-8, IL-9, and MIP-1□. Today, except for some flu vaccines in multi-dose vials, no recommended childhood vaccines contain thimerosal as a preservative. It must be stressed that the toxicity and immunomodulatory effects of thimerosal that we report ex-vivo on human monocyte-derived DCs may occur in vivo and induce an alteration of the immune response to the vaccine. These observations highlight the need to use this preservative with caution and avoid it if possible.

Full Report

https://app.box.com/s/0dg5ksp3f377qes3m5qsp16rl1gxws8l

“These observations highlight the need to use this preservative with caution and avoid it if possible.”

“Our results indicate that higher dose of neonatal thimerosal-mercury
is capable of inducing long-lasting substantial dysregulation of neurodevelopment,
synaptic function, and endocrine system, which could be the causal involvements of autistic-like behavior in mice.”

Toxicology Science • June 2014

Transcriptomic analyses of neurotoxic effects in mouse brain after intermittent neonatal administration of thimerosal

Author information

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Abstract

Thimerosal is a vaccine antimicrobial preservative which has long been suspected an iatrogenic factor possibly contributing to neurodevelopmental disorders including autism. The association between infant vaccine thimerosal exposure and autism remains an open question. Although thimerosal has been removed from mandatory childhood vaccines in the United States, thimerosal-preserved vaccines are still widely used outside of the United States especially in developing countries. Notably, thimerosal-containing vaccines are being given to the newborns within the first 12-24 h after birth in some countries. To examine the possible neurotoxic effects of early neonatal exposure to a higher level of thimerosal, FVB mice were subcutaneously injected with thimerosal-mercury at a dose which is 20× higher than that used for regular Chinese infant immunization during the first 4 months of life. Thimerosal-treated mice exhibited neural development delay, social interaction deficiency, and inclination of depression. Apparent neuropathological changes were also observed in adult mice neonatally treated with thimerosal. High-throughput RNA sequencing of autistic-behaved mice brains revealed the alternation of a number of canonical pathways involving neuronal development, neuronal synaptic function, and the dysregulation of endocrine system. Intriguingly, the elevation of anterior pituitary secreting hormones occurred exclusively in male but not in female thimerosal-treated mice, demonstrating for the first time the gender bias of thimerosal-mercury toxicity with regard to endocrine system. Our results indicate that higher dose of neonatal thimerosal-mercury (20× higher than that used in human) is capable of inducing long-lasting substantial dysregulation of neurodevelopment, synaptic function, and endocrine system, which could be the causal involvements of autistic-like behavior in mice.

http://www.ncbi.nlm.nih.gov/pubmed/24675092

Environmental Toxicology And Chemistry • June 2014

Ecogenetics of mercury: From genetic polymorphisms and epigenetics to risk assessment and decision-making

Author Information

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Abstract

The risk assessment of mercury (Hg), in both humans and wildlife, is made challenging by great variability in exposure and health effects. Although disease risk arises following complex interactions between genetic ("nature") and environmental ("nurture") factors, most Hg studies thus far have focused solely on environmental factors. In recent years, ecogenetic-based studies have emerged and have started to document genetic and epigenetic factors that may indeed influence the toxicokinetics or toxicodynamics of Hg. The present study reviews these studies and discusses their utility in terms of Hg risk assessment, management, and policy and offers perspectives on fruitful areas for future research. In brief, epidemiological studies on populations exposed to inorganic Hg (e.g., dentists and miners) or methylmercury (e.g., fish consumers) are showing that polymorphisms in a number of environmentally responsive genes can explain variations in Hg biomarker values and health outcomes. Studies on mammals (wildlife, humans, rodents) are showing Hg exposures to be related to epigenetic marks such as DNA methylation. Such findings are beginning to increase understanding of the mechanisms of action of Hg, and in doing so they may help identify candidate biomarkers and pinpoint susceptible groups or life stages. Furthermore, they may help refine uncertainty factors and thus lead to more accurate risk assessments and improved decision-making.

http://onlinelibrary.wiley.com/doi/10.1002/etc.2375/abstract

"In brief, epidemiological studies on populations exposed to inorganic mercury (e.g., dentists and miners) or methylmercury (e.g., fish consumers) are showing that polymorphisms in a number of environmentally responsive genes can explain variations in mercury biomarker values and health outcomes."

[polymorphosms explain why some individuals injected with an aluminum containing vaccine will become autistic and others will not. Polymorphism is the genetic variant]

Pediatric Neurology • July 2014

Effect of low-level prenatal mercury exposure on neonate neurobehavioral development in China

Author information

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Abstract

BACKGROUND:
This study aimed to assess the effects of low-level prenatal mercury exposure on neonate neurobehavioral development in China.

METHODS:
In total, 418 mother-neonate pairs were included in the study. Maternal urine, hair, and blood samples and cord blood samples were used to document prenatal exposure to mercury. The Neonatal Behavioral Neurological Assessment was used to estimate neurobehavioral development in the neonates at 3 days of age.

RESULTS:
Total mercury level was significantly higher in cord blood than that in maternal blood. A strong correlation was found between total mercury levels in maternal blood and those in cord blood ($r = 0.7431$; $P < 0.0001$). Trend analysis revealed that mothers who consumed more fish had higher blood and cord blood mercury levels (all $P < 0.0001$). Significant differences were also found between male and female cord blood mercury levels among groups with different fish consumption frequencies (all $P < 0.0001$). Cord blood mercury level was significantly associated with total Neonatal Behavioral Neurological Assessment scores (ß = 0.03; standard error = 0.01; $P = 0.0409$), passive muscle tone (odds ratio = 1.07; 95% confidence interval = 1.12-1.13; $P = 0.0071$), and active muscle tone (odds ratio = 1.06; 95% confidence interval = 1.01-1.11; $P = 0.0170$) scores after adjustment, respectively.

CONCLUSIONS:
Neonatal neurodevelopment was associated with prenatal exposure to mercury. Women with high mercury levels should avoid intake seafood excessively during pregnancy. Long-term effects of exposure to mercury on childhood development need to be further explored.

Full Report

http://www.pedneur.com/article/S0887-8994(14)00195-7/fulltext

"Neonatal neurodevelopment was associated with prenatal exposure to mercury. Women with high mercury levels should avoid intake seafood excessively during pregnancy."

International Journal Of Environmental Research And Public Health • September 2014

A Dose-Response Relationship between Organic Mercury Exposure from Thimerosal-Containing Vaccines and Neurodevelopmental Disorders

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Abstract

A hypothesis testing case-control study evaluated concerns about the toxic effects of organic-mercury (Hg) exposure from thimerosal-containing (49.55% Hg by weight) vaccines on the risk of neurodevelopmental disorders (NDs). Automated medical records were examined to identify cases and controls enrolled from their date-of-birth (1991–2000) in the Vaccine Safety Datalink (VSD) project. ND cases were diagnosed with pervasive developmental disorder (PDD), specific developmental delay, tic disorder or hyperkinetic syndrome of childhood. In addition, putative non-thimerosal-related outcomes of febrile seizure, failure to thrive and cerebral degenerations were examined. The cumulative total dose of Hg exposure from thimerosal-containing hepatitis B vaccine (T-HBV) administered within the first six months of life was calculated. On a per microgram of organic-Hg basis, PDD (odds ratio (OR) = 1.054), specific developmental delay (OR = 1.035), tic disorder (OR = 1.034) and hyperkinetic syndrome of childhood (OR = 1.05) cases were significantly more likely than controls to receive increased organic-Hg exposure. By contrast, none of the non-thimerosal related outcomes were significantly more likely than the controls to have received increased organic-Hg exposure. Routine childhood vaccination may be an important public health tool to reduce infectious disease-associated morbidity/mortality, but the present study significantly associates organic-Hg exposure from T-HBV with an increased risk of an ND diagnosis.

Full Report

http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4199012/

“Routine childhood vaccination may be an important public health tool to reduce infectious disease-associated morbidity/mortality, but the present study significantly associates organic-mercury exposure from thimerosal-containing hepatitis B vaccine with an increased risk of an neurodevelopmental disorder diagnosis.”

"... the present study supports an association between increasing organic-mercury exposure from Thimerosal-containing childhood vaccines and the subsequent risk of specific delays in development ..."

North American Journal Of Medical Science • October 2014

Thimerosal-containing hepatitis B vaccination and the risk for diagnosed specific delays in development in the United States: a case-control study in the vaccine safety datalink

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Abstract

BACKGROUND

Within the first 3 years of life, the brain develops rapidly. Its development is characterized by critical developmental periods for speech, vision, hearing, language, balance, etc.; and alteration in any of the processes occurring in those critical periods can lead to specific delays in development.

AIMS

The present study evaluated the potential toxic effects of organic-mercury exposure from Thimerosal (49.55% mercury by weight) in childhood vaccines and its hypothesized possible relationship with specific delays in development.

MATERIALS AND METHODS

A hypothesis testing case-control study was undertaken to evaluate the relationship between exposure to Thimerosal-containing hepatitis B vaccines administered at specific intervals in the first 6 months among cases diagnosed with specific delays in development and controls born between 1991-2000, utilizing data in the Vaccine Safety Datalink database.

RESULTS

Cases were significantly more likely than controls to have received increased organic-mercury from Thimerosal-containing hepatitis B vaccine administered in the first, second, and sixth month of life.

CONCLUSION

Though routine childhood vaccination may be an important public health tool to reduce the morbidity and mortality associated with infectious diseases, the present study supports an association between increasing organic-mercury exposure from Thimerosal-containing childhood vaccines and the subsequent risk of specific delays in development among males and females.

http://www.ncbi.nlm.nih.gov/pubmed/25489565

Indian Journal Of Medical Ethics • October 2014

Thimerosal as discrimination: vaccine disparity in the UN Minamata Convention on mercury

Author information

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Abstract

When addressing toxins, one unmistakable parallel exists between biology and politics: developing children and developing nations are those most vulnerable to toxic exposures. This disturbing parallel is the subject of this critical review, which examines the use and distribution of the mercury (Hg)-based compound, thimerosal, in vaccines. Developed in 1927, thimerosal is 49.55% Hg by weight and breaks down in the body into ethyl-Hg chloride, ethyl-Hg hydroxide and sodium thiosalicylate. Since the early 1930s, there has been evidence indicating that thimerosal poses a hazard to the health of human beings and is ineffective as an antimicrobial agent. While children in the developed and predominantly western nations receive doses of mostly no-thimerosal and reduced-thimerosal vaccines, children in the developing nations receive many doses of several unreduced thimerosal-containing vaccines (TCVs). Thus, thimerosal has continued to be a part of the global vaccine supply and its acceptability as a component of vaccine formulations remained unchallenged until 2010, when the United Nations (UN), through the UN Environment Programme, began negotiations to write the global, legally binding Minamata Convention on Hg. During the negotiations, TCVs were dropped from the list of Hg-containing products to be regulated. Consequently, a double standard in vaccine safety, which previously existed due to ignorance and economic reasons, has now been institutionalised as global policy. Ultimately, the Minamata Convention on Hg has sanctioned the inequitable distribution of thimerosal by specifically exempting TCVs from regulation, condoning a two-tier standard of vaccine safety: a predominantly no-thimerosal and reduced-thimerosal standard for developed nations and a predominantly thimerosal-containing one for developing nations. This disparity must now be evaluated urgently as a potential form of institutionalised discrimination.

http://www.ncbi.nlm.nih.gov/pubmed/?term=25101548

“While children in the developed and predominantly western nations receive doses of mostly no-thimerosal and reduced-thimerosal vaccines, children in the developing nations receive many doses of several unreduced thimerosal-containing vaccines (TCVs).”

"... the preponderance of evidence suggests that mercury exposure from dental amalgams may cause or contribute to many chronic conditions."

Neuro Endocrinology Letters • 2014

Evidence supporting a link between dental amalgams and chronic illness, fatigue, depression, anxiety, and suicide

Author information

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Abstract

The purpose of this review is to examine the evidence for a relationship between mercury (Hg) exposure from dental amalgams and certain idiopathic chronic illnesses--chronic fatigue syndrome (CFS), fibromyalgia (FM), depression, anxiety, and suicide. Dental amalgam is a commonly used dental restorative material that contains approximately 50% elemental mercury (Hg0) by weight and releases Hg0 vapor. Studies have shown that chronic Hg exposure from various sources including dental amalgams is associated with numerous health complaints, including fatigue, anxiety, and depression--and these are among the main symptoms that are associated with CFS and FM. In addition, several studies have shown that the removal of amalgams is associated with improvement in these symptoms. Although the issue of amalgam safety is still under debate, the preponderance of evidence suggests that Hg exposure from dental amalgams may cause or contribute to many chronic conditions. Thus, consideration of Hg toxicity may be central to the effective clinical investigation of many chronic illnesses, particularly those involving fatigue and depression.

http://www.ncbi.nlm.nih.gov/pubmed/25617876

Reviews Of Environmental Contamination And Toxicology • 2014

Mercury toxicity and neurodegenerative effects

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Abstract

Mercury is among the most toxic heavy metals and has no known physiological role in humans. Three forms of mercury exist: elemental, inorganic and organic. Mercury has been used by man since ancient times. Among the earliest were the Chinese and Romans, who employed cinnabar (mercury sulfide) as a red dye in ink (Clarkson et al. 2007). Mercury has also been used to purify gold and silver minerals by forming amalgams. This is a hazardous practice, but is still widespread in Brazil’s Amazon basin, in Laos and in Venezuela, where tens of thousands of miners are engaged in local mining activities to find and purify gold or silver. Mercury compounds were long used to treat syphilis and the element is still used as an antiseptic,as a medicinal preservative and as a fungicide. Dental amalgams, which contain about 50% mercury, have been used to repair dental caries in the U.S. since 1856.Mercury still exists in many common household products around the world.Examples are: thermometers, barometers, batteries, and light bulbs (Swain et al.2007). In small amounts, some organo mercury-compounds (e.g., ethylmercury tiosalicylate(thimerosal) and phenylmercury nitrate) are used as preservatives in some medicines and vaccines (Ballet al. 2001).Each mercury form has its own toxicity profile. Exposure to Hg0 vapor and MeHg produce symptoms in CNS, whereas, the kidney is the target organ when exposures to the mono- and di-valent salts of mercury (Hg+ and Hg++, respectively)occur. Chronic exposure to inorganic mercury produces stomatitis, erethism and tremors. Chronic MeHg exposure induced symptoms similar to those observed in ALS, such as the early onset of hind limb weakness (Johnson and Atchison 2009).Among the organic mercury compounds, MeHg is the most biologically available and toxic (Scheuhammer et al. 2007). MeHg is neurotoxic, reaching high levels of accumulation in the CNS; it can impair physiological function by disrupting endocrine glands (Tan et al. 2009).The most important mechanism by which mercury causes toxicity appears to bemitochondrial damage via depletion of GSH (Nicole et al. 1998), coupled with binding to thiol groups (-SH), which generates free radicals. Mercury has a high affinity for thiol groups (-SH) and seleno groups (-SeH) that are present in amino acids as cysteine and N-acetyl cysteine, lipoic acid, proteins, and enzymes. N-acetylcysteine and cysteine are precursors for the biosynthesis of GSH, which is among the most powerful intracellular antioxidants available to protect against oxidative stress and inflammation.Mercury and methylmercury induce mitochondrial dysfunction, which reduces ATP synthesis and increases lipid, protein and DNA peroxidation. The content of metallothioneines, GSH, selenium and fish high in omega-3 fatty acids appear to be strongly related with degree of inorganic and organic mercury toxicity, and with the protective detoxifying mechanisms in humans. In conclusion, depletion of GSH, breakage of mitochondria, increased lipid peroxidation, and oxidation of proteins and DNA in the brain, induced by mercury and his salts, appear to be important factors in conditions such as ALS and AD (Bains and Shaw 1997; Nicole et al. 1998;Spencer et al. 1998; Alberti et al. 1999).

http://www.ncbi.nlm.nih.gov/pubmed/24515807

“In conclusion,

depletion of GSH,

breakage of mitochondria,

increased lipid peroxidation,

and oxidation of proteins and DNA in the brain,

induced by mercury and his salts,

appear to be important factors in

conditions such as Amyotrophic Lateral Sclerosis

and Alzheimers Disease ...”

"These findings suggest that the epidemiological link between environmental mercury exposure and an increased risk of developing autism may be mediated through mitochondrial dysfunction ..."

Journal of Toxicology • January 2015

Increased Susceptibility to Ethylmercury-Induced Mitochondrial Dysfunction in a Subset of Autism Lymphoblastoid Cell Lines

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Abstract

The association of autism spectrum disorders with oxidative stress, redox imbalance, and mitochondrial dysfunction has become increasingly recognized. In this study, extracellular flux analysis was used to compare mitochondrial respiration in lymphoblastoid cell lines (LCLs) from individuals with autism and unaffected controls exposed to ethylmercury, an environmental toxin known to deplete glutathione and induce oxidative stress and mitochondrial dysfunction. We also tested whether pretreating the autism LCLs with N-acetyl cysteine (NAC) to increase glutathione concentrations conferred protection from ethylmercury. Examination of 16 autism/control LCL pairs revealed that a subgroup (31%) of autism LCLs exhibited a greater reduction in ATP-linked respiration, maximal respiratory capacity, and reserve capacity when exposed to ethylmercury, compared to control LCLs. These respiratory parameters were significantly elevated at baseline in the ethylmercury-sensitive autism subgroup as compared to control LCLs. NAC pretreatment of the sensitive subgroup reduced (normalized) baseline respiratory parameters and blunted the exaggerated ethylmercury-induced reserve capacity depletion. These findings suggest that the epidemiological link between environmental mercury exposure and an increased risk of developing autism may be mediated through mitochondrial dysfunction and support the notion that a subset of individuals with autism may be vulnerable to environmental influences with detrimental effects on development through mitochondrial dysfunction.

http://www.hindawi.com/journals/jt/2015/573701/

"... the present study provides new epidemiological evidence of a significant relationship between increasing organic ethyl mercury exposure from Thimerosal-containing vaccines and the subsequent risk of pervasive developmental disorder diagnosis ..."

Biological Trace Element Research • February 2015

A case-control study evaluating the relationship between thimerosal-containing haemophilus influenzae type b vaccine administration and the risk for a pervasive developmental disorder diagnosis in the United States

Author information

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Abstract

Thimerosal is an organic mercury (Hg)-containing compound (49.55 % Hg by weight) historically added to many multi-dose vials of vaccine as a preservative. A hypothesis testing case-control study evaluated automated medical records in the Vaccine Safety Datalink (VSD) for organic Hg exposure from Thimerosal in Haemophilus influenzae type b (Hib)-containing vaccines administered at specific times within the first 15 months of life among subjects diagnosed with pervasive developmental disorder (PDD) (n = 534) in comparison to controls. The generally accepted biologically non-plausible linkage between Thimerosal exposure and subsequent diagnosis of febrile seizure (n = 5886) was examined as a control outcome. Cases diagnosed with PDD received significantly more organic Hg within the first 6 months of life (odds ratio (OR) = 1.97, $p < 0.001$) and first 15 months of life (OR = 3.94, $p < 0.0001$) than controls, whereas cases diagnosed with febrile seizure were no more likely than controls to have received increased organic Hg. On a per microgram of organic Hg basis, cases diagnosed with a PDD in comparison to controls were at significantly greater odds (OR = 1.0197, $p < 0.0001$) of receiving increasing organic Hg exposure within the first 15 months of life, whereas cases diagnosed febrile seizure were no more likely than controls (OR = 0.999, $p > 0.20$) to have received increasing organic Hg exposure within the first 15 months of life. Routine childhood vaccination is an important public health tool to reduce the morbidity and mortality associated with infectious diseases, but the present study provides new epidemiological evidence of a significant relationship between increasing organic Hg exposure from Thimerosal-containing vaccines and the subsequent risk of PDD diagnosis in males and females.

http://www.ncbi.nlm.nih.gov/pubmed/25382662

Clinica Chimica Acta • April 2015

Thimerosal: clinical, epidemiologic and biochemical studies

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Abstract

INTRODUCTION

Thimerosal (or Thiomersal) is a trade name for an organomercurial compound (sodium ethyl-mercury (Hg) thiosalicylate) that is 49.55% Hg by weight, which rapidly decomposes in aqueous saline solutions into ethyl-Hg hydroxide and ethyl-Hg chloride. Developed in 1927, it has been and is still being used as a preservative in some cosmetics, topical pharmaceuticals, and biological drug products, including vaccines. Concerns have been voiced about its use because it is toxic to human cells. Although it is banned in several countries, it continues to be added to some vaccines in the United States and many vaccines in the developing world.

DISCUSSION

This critical review focuses on the clinical, epidemiological, and biochemical studies of adverse effects from Thimerosal in developing humans. This review will include research that examines fetal, infant, and childhood death; birth defects; neurodevelopmental testing deficits in children; and neurodevelopmental disorders (attention deficit/hyperactivity disorder, autism spectrum disorder, tic disorder, and specific developmental delays). The review will also look at the research that examined the outcomes of acute accidental ethyl-Hg poisoning in humans. The studies that examine the underlying biochemical insights into the neuronal cellular damage will also be explored.

CONCLUSION

The culmination of the research that examines the effects of Thimerosal in humans indicates that it is a poison at minute levels with a plethora of deleterious consequences, even at the levels currently administered in vaccines.

http://www.ncbi.nlm.nih.gov/pubmed/?term=25708367

“The culmination of the research that examines the effects of Thimerosal in humans indicates that it is a poison at minute levels with a plethora of deleterious consequences, even at the levels currently administered in vaccines.”

“During the decade in which Thimerosal-containing hepatitis B vaccines were routinely recommended and administered to US infants, an estimated 0.5-1 million additional US children were diagnosed with specific delays in development as a consequence of 25µg or 37.5µg organic mercury from Thimerosal-containing hepatitis B vaccines ... The resulting lifetime costs to the United States may exceed $1 trillion.”

Journal Of Epidemiology And Global Health • July 2015

A longitudinal cohort study of the relationship between Thimerosal-containing hepatitis B vaccination and specific delays in development in the United States: Assessment of attributable risk and lifetime care costs

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Abstract

Epidemiological evidence suggests a link between mercury (Hg) exposure from Thimerosal-containing vaccines and specific delays in development. A hypothesis-testing longitudinal cohort study (n=49,835) using medical records in the Vaccine Safety Datalink (VSD) was undertaken to evaluate the relationship between exposure to Hg from Thimerosal-containing hepatitis B vaccines (T-HBVs) administered at specific intervals in the first 6months of life and specific delays in development [International Classification of Disease, 9th revision (ICD-9): 315.xx] among children born between 1991 and 1994 and continuously enrolled from birth for at least 5.81years. Infants receiving increased Hg doses from T-HBVs administered within the first month, the first 2 months, and the first 6 months of life were significantly more likely to be diagnosed with specific delays in development than infants receiving no Hg doses from T-HBVs. During the decade in which T-HBVs were routinely recommended and administered to US infants (1991-2001), an estimated 0.5-1 million additional US children were diagnosed with specific delays in development as a consequence of 25µg or 37.5µg organic Hg from T-HBVs administered within the first 6 months of life. The resulting lifetime costs to the United States may exceed $1 trillion.

Full Report

http://www.sciencedirect.com/science/article/pii/S2210600615000647

[an epidemic with a multi-trillion-dollar cost]

Science And Engineering Ethics • October 2015

Systematic Assessment of Research on Autism Spectrum Disorder and Mercury Reveals Conflicts of Interest and the Need for Transparency in Autism Research

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Abstract

Historically, entities with a vested interest in a product that critics have suggested is harmful have consistently used research to back their claims that the product is safe. Prominent examples are: tobacco, lead, bisphenol A, and atrazine. Research literature indicates that about 80-90 % of studies with industry affiliation found no harm from the product, while only about 10-20 % of studies without industry affiliation found no harm. In parallel to other historical debates, recent studies examining a possible relationship between mercury (Hg) exposure and autism spectrum disorder (ASD) show a similar dichotomy. Studies sponsored and supported by industry or entities with an apparent conflict of interest have most often shown no evidence of harm or no “consistent” evidence of harm, while studies without such affiliations report positive evidence of a Hg/autism association. The potentially causal relationship between Hg exposure and ASD differs from other toxic products since there is a broad coalition of entities for whom a conflict of interest arises. These include influential governmental public health entities, the pharmaceutical industry, and even the coal burning industry. This review includes a systematic literature search of original studies on the potential relationship between Hg and ASD from 1999 to date, finding that of the studies with public health and/or industry affiliation, 86 % reported no relationship between Hg and ASD. However, among studies without public health and/or industry affiliation, only 19 % find no relationship between Hg and ASD. The discrepancy in these results suggests a bias indicative of a conflict of interest.

http://www.ncbi.nlm.nih.gov/pubmed/26507205

This review includes a systematic literature search of original studies on the potential relationship between Hg [ethyl mercury] and ASD [Autisitic Spectrum Disorder] from 1999 to date, finding that of the studies with public health and/or industry affiliation, 86% reported no relationship between Hg [ethyl mercury] and ASD [Autisitic Spectrum Disorder]. However, among studies without public health and/or industry affiliation, only 19% find no relationship between Hg [ethyl mercury] and ASD [Autisitic Spectrum Disorder]. The discrepancy in these results suggests a bias indicative of a conflict of interest.”

Journal of Toxicology • 2015

Increased Susceptibility to Ethylmercury-Induced Mitochondrial Dysfunction in a Subset of Autism Lymphoblastoid Cell Lines

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Abstract

The association of autism spectrum disorders with oxidative stress, redox imbalance, and mitochondrial dysfunction has become increasingly recognized. In this study, extracellular flux analysis was used to compare mitochondrial respiration in lymphoblastoid cell lines (LCLs) from individuals with autism and unaffected controls exposed to ethylmercury, an environmental toxin known to deplete glutathione and induce oxidative stress and mitochondrial dysfunction. We also tested whether pretreating the autism LCLs with N-acetyl cysteine (NAC) to increase glutathione concentrations conferred protection from ethylmercury. Examination of 16 autism/control LCL pairs revealed that a subgroup (31%) of autism LCLs exhibited a greater reduction in ATP-linked respiration, maximal respiratory capacity, and reserve capacity when exposed to ethylmercury, compared to control LCLs. These respiratory parameters were significantly elevated at baseline in the ethylmercury-sensitive autism subgroup as compared to control LCLs. NAC pretreatment of the sensitive subgroup reduced (normalized) baseline respiratory parameters and blunted the exaggerated ethylmercury-induced reserve capacity depletion. These findings suggest that the epidemiological link between environmental mercury exposure and an increased risk of developing autism may be mediated through mitochondrial dysfunction and support the notion that a subset of individuals with autism may be vulnerable to environmental influences with detrimental effects on development through mitochondrial dysfunction.

http://www.hindawi.com/journals/jt/2015/573701/

"These findings suggest that the epidemiological link between environmental mercury exposure and an increased risk of developing autism may be mediated through mitochondrial dysfunction and support the notion that a subset of individuals with autism may be vulnerable to environmental influences with detrimental effects on development through mitochondrial dysfunction."

Eli Lilly And The History of Thimerosal

The following is a summary of the history of thimerosal. It is not a complete list, as there is much more information out there but we hit the high points and we give a good frame of reference for where the discussion of the safety of this product and its relationship to autism and neurodevelopmental disorders should begin.

Invented in the 1920's by Eli Lilly, thimerosal is 49.6% ethlymercury by weight, a neurotoxin known to be more than a hundreds times more lethal to tissue than lead.

Eli Lilly's safety testing of the product consists of a 1930 study of 22 patients dieing from mengiococcal meningitis in an Indiana hospital. Patients are injected with the solutions and followed until their death, which is within days. Because the patients die of meningitis, they are declared to show no adverse reaction to thimerosal and the product is declared safe for use. Thimerosal is subsequently introduced for use in vaccines and in over the counter remedies as a preservative to kill bacteria in the product.

When the FDA is created, Thimerosal is grandfathered in and is not subjected to any additional safety testing. The 1930 study remains the only safety testing done on the substance even after being in use for over 75 years.

Through FOIA requests and documents acquired as a part of discovery process in lawsuits against Lilly, it is clear that they have been warned about, and have been aware of the dangers of the product since at least 1947.

The use of thimerosal in teething powders for infants leads to a fatal out break of Acrodynia, or "Pink's Disease", a form of mercury poisoning. This illness has many symptoms in common with Autism. The link to mercury powders was found in the 1940's and by the 1950's Pink's disease was disappearing.

In 1963 Eli Lilly was forwarded an article that read in part: "There is another point of practical significance: does the parenteral injection of thimerosal - containing fluids cause disturbances in thimerosal-sensitive patients?" "It is known that persons that are contact sensitive to a drug may tolerate the same medications internally, but it seems advisable to use a preservative other than thimerosal for injections in thimerosal-sensitive people."

On August 17, 1967 the Medical/Science department requests that the claim "non-toxic" on thimerosal labels be deleted in next printing run. Two weeks later the label is changed to "non-irritating to body tissues," and the phrase non-toxic omitted.

In 1972 The British Medical Journal reports case of skin burns resulting from the chemical interaction of thimerosal and aluminum. "Mercury is known to act as a catalyst and to cause aluminum to oxidize rapidly, with the production of heat." The manufacturers who supply us with thimerosal have been informed." [Thimerosal is being used in vaccines which also contain aluminum].

In the 1970's six newborns at one hospital die as a result of having a thimerosal containing antiseptic wiped on their wounds.

In 1982 the FDA reviews the use of thimerosal. Their statement reads in part: "At the cellular level, thimerosal has been found to be more toxic for human epithelial cells in vitro than mercuric chloride, mercuric nitrate, and merbromim (mercurichrom). "It was found to be 35.3 times more toxic for embryonic chick heart tissue than for staphylococcus areus." [a pathogen that the thimerosal is intended to kill]. A 1950 study showed that thimerosal was no better than water in protecting mice from potential fatal streptococcal infection." "The Panel concludes that thimerosal is not safe for over the counter topical use because of its potential for cell damage if applied to broken skin and its allergy potential. It is not effective as a topical antimicrobial because its bacteriastatic action can be reversed." Additional language added to some Lilly labels: "As with any drug, if you are pregnant or nursing a baby, seek the advice of a health professional before using this product." The FDA orders the withdrawal of over the counter thimerosal containing products within a 6 month period. It does not order removal from vaccines, but recommends that the issue be studied and that the incidence of neurological problems in unvaccinated populations like the Amish be compared to the vaccinated population. [22 years later no such study has yet been done. On July 19, 2005 Dr. Julie Gerberding, head of the CDC says that such a study would be difficult to undertake because of genetic confounders. This seems contrary to the scientific process because if indeed such a study is done and it is found that the Amish have a lower incidence of neurodevelopmental disorders, the next step would be to undertake genetic studies to see if their genes differ dramatically from the general population and if their differences can help us locate the genetic component of autism. In addition studies designed to see if the small number of vaccinated Amish differ in their risk for NDDs to the larger Amish population would offer information about increased risk from thimerosal.]

In the 1930's the average child only received three vaccines in their young life. Many vaccines are added to the schedule over the years, with an increase in the 1980's and with 3 vaccines added to the schedule in 1991 alone. The current vaccine schedule calls for 31 vaccines in the first 18 months of life, 48 with full flu vaccination by 72 months of life.

A Merck internal memo is obtained during discovery discloses that in 1991 a Merck researcher added up the amount of mercury that is in the new vaccine schedule and sounded an alarm at the company that children who are vaccinated according to it would receive amounts of mercury far and above that considered to be safe by the EPA. Merck takes no action in regard to the information.

During the 1990's, autism rates begin to rise dramatically. Parents complain to the health authorities that they believe that their children's developmental disorders are related to their vaccines.

In 1998, a researcher at the CDC does the same math that Merck did 7 years previously. She finds that children are getting as much as 125 times the EPA limit of mercury for their weight. The EPA limit is based on the ingestion of methlymercury in food by a healthy adult. Because 90% of ingested mercury is excreted in the digestive track and never enters the blood stream, so even the EPA limit may be drastically lacking considering that thimerosal is injected directly into the blood stream and is not subject to the bodies natural defenses against toxic poisoning.

In 1999, the CDC and the American Association of Pediatrics issue a joint statement saying that although they find no "evidence of harm" from the mercury exposure that children are getting in their vaccines, they are calling on vaccine manufacturers to remove it from vaccines on a voluntary basis as a precautionary measure because "some children may" get more than the EPA limit for mercury at their 6 month visits. Manufactures begin the process in 1999, but do not remove it from all vaccines.

No legal ban on thimerosal is issued.

No recall of the mercury laden vaccines is issued and companies continue to sell lots already manufactured. Some of these vaccines containing full doses of thimerosal have been found in doctors' offices by parents who request to read package inserts with expiration dates as late as 2007.

No independent or government testing of vaccines is done to confirm that thimerosal has been removed. FDA denies parents request that they set up a system to verify manufacturers claims of low dose or thimerosal free vaccines. No statement is issued to pediatricians to alert them to the symptoms of mercury poisoning. No recommendation is made to pediatricians to screen children who suffered the onset of neurological impairment after vaccination for mercury toxicity.

Vaccines with 25mcg of thimerosal are still shipped to developing countries. Most flu shots still contain a full dose

of thimerosal. The EPA estimates that a person must weigh 550 lbs. to safely tolerate this amount of mercury.

In November of 1999, the CDC commissions one of its new employees, a Belgian named Thomas Verstraten, to study the Vaccine Safety Datalink to find the risk of autism and other NDDs in relation to thimerosal exposure. Verstraten's first draft of the study finds a relative risk above 7 for children who receive the highest dose of thimerosal to develop autism. In simple terms, such children have more than a 600% higher chance of developing autism than children who don't receive any thimerosal. A relative risk of 2 is sufficient proof in U.S. courts to find for vaccine injury. Verstraten and other scientists at the CDC spend 4 years trying to change the study so that the relationship between the preservative and NDD's is significantly reduced or eliminated. The Center for Disease Control will later describe these changes to the study as "improvements". When the study is published in 2003, it concludes that "no consistent significant associations are found between thimerosal containing vaccines and neurodevelopmental outcomes." By this time Thomas Verstraten, who is listed as a CDC employee on the study, has been an employee of GlaxoSmithKlein (a defendant in thimerosal law suits) for more than 2 years.

In November of 2000, despite being born almost two months prematurely and despite the assurance of my pediatrician that thimerosal had been removed from vaccines, my son Webster is injected with a DTaP vaccine that was 74.5 times the EPA limit for mercury exposure for his weight, just two weeks past his due date. He will go on to develop verbal apraxia and sensory integration disorder.

In 2001 Bernard et. al. publish their hypothesis: Autism: A Novel Form of Mercury Poisoning. It reads in part: "Exposure to mercury can cause immune, sensory, neurological, motor, and behavioral dysfunctions similar to traits defining or associated with autism, and the similarities extend to neuroanatomy, neurotransmitters, and biochemistry. Thimerosal, a preservative added to many vaccines, has become a major source of mercury in children who, within their first two years, may have received a quantity of mercury that exceeds safety guidelines. A review of medical literature and US government data suggests that: (i) many cases of idiopathic autism are induced by early mercury exposure from thimerosal; (ii) this type of autism represents an unrecognized mercurial syndrome; and (iii) genetic and non-genetic factors establish a predisposition whereby thimerosal's adverse effects occur only in some children."

In 2001 the Institute of Medicine is commissioned by the CDC to undertake a comprehensive review of all research into the thimerosal/autism connection. At their first meeting, Dr Stratton, head of the commission, when discussing what the process and product of the working group would be states that, "We said this before you got here, and I think we said this yesterday, the point of no return, the line we will not cross in public policy is to pull the vaccine, change the schedule. We could say it is time to revisit this, but we would never recommend that level. Even recommending research is recommendations for policy. We wouldn't say compensate, we wouldn't say pull the vaccine, we wouldn't say stop the program". When the transcript of the meeting is made public through a FOIA request, many interpret this to mean that no matter what they find, they will not publicly say that there is any link between the thimerosal and autism. Dr. Harvey Fineberg, head of the IOM, states that this is an incorrect interpretation of the comments, but will not offer any alternate interpretation of what else they could mean.

In 2001 Verstraten presents a version of his study to the IOM. He begins his presentation by telling the panel that as of 8 am that morning, he had become an employee of Glaxo Smith Klein. Despite the conflict of interest and the drastic changes made over the course of the study, the IOM will rely heavily on the study in making their determination. Dr. Verstraten returns to Belgium and except for a letter published in Pediatrics, little is heard from him again.

In March of 2002 my son Chandler, who was born one month early, is injected with Hepatitis B vaccine containing a "trace amount" of thimerosal (currently still on the schedule), despite the fact that he has no risk factors for Hepatitis B, and he is still two weeks from reaching his due date. Within days he develops fevers and uncontrollable crying that lasts for three months and bowel problems that persist for two years until he is placed on the GFCF diet. He will go on to be diagnosed with both Autism and mercury poisoning at age 2. I later discover that the "trace amount" of thimerosal is still just over the EPA limit of mercury for his weight.

In 2003 the Verstraten Study is published in Pediatrics with no mention of the conflict of interest of the lead researcher. Later a private contractor would testify before congress that he was ordered to destroy the original data sets used in the 1999 version of the study that found the dramatic link between thimerosal and autism in the interest of "patient confidentiality". The entire Vaccine Safety Datalink is eventually moved to an offshore private company and can no longer be accessed by FOIA request.

In February of 2004, the IOM rushes to hold public hearings where researchers on both sides of the issues present their studies. The meeting is considered to be a "draw" between the two sides by many of those in attendance. A link is neither proved nor disproved, but new research in to the mechanism of how mercury can trigger autism and NDDs in a genetically vulnerable sub population is presented, along with case studies of successful treatment of autistic symptoms based on the new research.

In May of the same year, the IOM issues their final conclusion on the link between Thimerosal and NDDs. They state that, "the body of epidemiological evidence favors rejection of a causal relationship between thimerosal-containing vaccines and autism. The committee further finds that potential biological mechanisms for vaccine-induced autism that have been generated to date are theoretical only." They then go on to take the unusual step of recommending that research into a link between the two be abandoned and funds be spent on other lines of inquiry. The conclusion relies heavily on Verstraten and several other epidemiological studies that are considered to implement fatally flawed methods and to be riddled with conflict of interest by members of the autism community. Parent groups are enraged. The IOM panel disbands.

Later that year, Thomas Verstraten publishes a letter in Pediatrics in response to those who criticize his study and his conflict of interest. His letter does not address the substance of the charges made against the study and the changes that were made to it over it's 4 year evolution, but instead says that continuing to debate the validity of the 1999 study would be a "waste of scientific energy and not to the benefit of the safety of US children or of all the children world wide that have the privilege of being vaccinated." He goes on to say that any suggestion of impropriety on the part of himself, the CDC or GSK is an insult and accuses his critics of having "pitiable attitudes".

In July of 2005, in the face of continuing criticism of the IOM findings, the head of the IOM, Dr. Harvey Fineberg, issues a letter stating that Dr. Stratton's 2001 comments that they would not say "pull the vaccine" or "change the schedule" were taken out of context and did not suggest that the IOM decision was compromised. Dr. Fineberg has not, despite requests, offered an alternative interpretation of what her comments meant in context.

In March of 2005, Author David Kirby released his book, "Evidence of Harm - Mercury in Vaccines and the Autism Epidemic: A Medical Controversy" detailing the history of thimerosal in vaccines and its relationship to autism. In April of 2005 the CDC posts a notice on their web site stating that they were in the process of reviewing "Evidence of Harm" and would be responding to the book.

In June of 2005 Robert F. Kennedy Jr. echoed the information found in the book and charged the CDC and Eli Lilly of malfeasance in covering up evidence of a causal effect between thimerosal and autism in an article published in Rolling Stone and Salon.com. It is entitled "Deadly Immunity: Robert F. Kennedy Jr. investigates the government cover-up of a mercury/autism scandal".

July 19, 2005. The CDC holds a press conference to: "communicate the importance of infants and children receiving their recommended vaccinations on time, and reassure parents that vaccines are safe. The renewed attention to the potential causal link between thimerosal, a vaccine preservative, and autism will also be addressed during the press conference." Vaccine safety groups are not informed of the press conference nor invited. The conference

presents no new information and does not answer important questions raised in Evidence of Harm or Deadly Immunity about the conduct of the CDC the IOM or the reliability of the research that continues to be used to show no link between thimerosal and autism.

In June of 2007 the first vaccinated v. unvaccinated study is finally done ... by parents. Generation Rescue funded a survey using the CDC's techniques for determining incidence of a disorder and found that vaccinated children are two and a half times more likely to have a neurodevelopmental disorder. CDC spokesman Curtis Allen said, "We look forward to learning more about the survey."

On June 25, 2007 Congresswoman Carolyn Maloney (D-NY) introduced the "Comprehensive Comparative Study of Vaccinated and Unvaccinated Populations Act of 2007" (H.R. 2832), legislation that would require the National Institutes of Health (NIH) to conduct a comprehensive comparative study of vaccinated and unvaccinated populations. Her stated purpose is to resolve the controversy about the possible link between autism and mercury or other vaccine components. The study is never done.

Today, January 2016, autism, ADHD and learning disabilities are at truly epidemic levels with one in six children presenting. The government and the pharmaceutical companies will claim that mercury has not been used in the manufacture of most vaccines for some time now, is used only in influenza vaccines and appears only in trace amounts in others. In the next chapter you'll read about aluminum which is even more deadly than mercury.

Chapter Three
Aluminum • Alum
1911 - 2015

Aluminum rescued Big Pharma from the mercury-autism connection. Not only does aluminum cause the symptoms found on the autistic spectrum, it also causes nearly 100 more disorders. Big Pharma can rest easy. Vaccines no longer contain mercury and the autism epidemic continues to grow. Obviously it couldn't have been the mercury ...

JAMA • September 2, 1911

Some Objections To The Use Of Alum Baking Powder

by William J. Gies, Ph.D.

Abstract

During a period of about seven years I have occasionally conducted experiments on the effects of aluminum salts. These studies have convinced me that the use in food of alum or any other aluminum compound is a dangerous practice. That the aluminum ion is very toxic is well known. That “aluminized” food yields soluble aluminum compounds to gastric juice (and stomach contents) has been demonstrated. That such soluble aluminum is in part absorbed and carried to all parts of the body by the blood can no longer be doubted. That the organism can “tolerate” such treatment without suffering harmful consequences has not been shown. It is believed that the facts in this paper will give emphasis to my conviction that aluminum should be excluded from food.

http://jama.jamanetwork.com/article.aspx?articleid=448038

“That the aluminum ion is very toxic is well known.

That “aluminized” food yields soluble aluminum compounds to gastric juice (and stomach contents) has been demonstrated.

That such soluble aluminum is in part absorbed and carried to all parts of the body by the blood can no longer be doubted.

That the organism can “tolerate” such treatment without suffering harmful consequences has not been shown.”

“I was recently called to see a man ...”

The Lancet • June 18, 1921

Case Of Aluminum Poisoning

by Dr. John Spofforth
L.R.C.P.EDIN., Membership At The Royal College Of Surgeons, England

Abstract

I was recently called to see a man, aged 46, who was then employed at a firm of metalworkers. He was in a state of great exhaustion and suffering from very severe and persistent vomiting. The pulse was slow and irregular. I suspected metallic poisoning and later sent a specimen of his urine to …, analytical chemists, who reported that it contained a large amount of aluminium, also of phosphates. The patient said he had been dipping red-hot metal articles, contained in an aluminium holder, into concentrated nitric acid. Aluminium produces a rather slow intoxication. In this case it caused loss of memory, tremor, jerking movements and impaired co-ordination. There was also a chronic constipation and incontinence of urine.

http://www.thelancet.com/journals/lancet/article/PIIS0140-6736(01)24927-7/abstract

JAMA • February 17, 1945

Early immunization against Pertussis with Alum precipitated vaccine

by Wallace Sako, MD., Ph.D., W. L. Treuting, MD., MPH.,
David B. Witt, Samuel J. Nichamin

Abstract

According to the recent mortality records the majority of deaths from pertussis occur in infants. Between 1938 and 1940 inclusive almost 67 per cent of the 10,730 deaths from whooping cough reported in the United States occurred during the first year of life and 47 per cent of these deaths were in infants under 7 months of age (table 1 and fig. 1). The exceptionally high mortality which pertussis exacts in the first half year of life calls for thorough investigation of the possibility of increasing the resistance of young infants to the disease by immunizing them shortly after birth. This procedure has been objected to chiefly because of the belief that young infants do not possess the ability to develop active immunity. No extensive study has been carried out, however, to establish the earliest age at which immunity to pertussis can be acquired.

http://jama.jamanetwork.com/article.aspx?articleid=272944&resultClick=3

“This procedure has been objected to chiefly because of the belief that young infants do not possess the ability to develop active immunity. No extensive study has been carried out, however, to establish the earliest age at which immunity to pertussis can be acquired.”

“Aluminium intoxication ... is associated with periorbital bleeding, lethargy, anorexia, and death. It is recommended that aluminium salts should be withdrawn from use in patients with renal failure and their use restricted in normal persons pending clarification of the issue.”

The Lancet • Volume 299, No. 7750, p564–568 • March 1972

Aluminium Toxicity In Rats

G.M. Berlyne, J. Ben Ari, E. Knopf, R. Yagil, G. Weinberger, G.M. Danovitch

Department of Nephrology
Negev Central Hospital and Division of Life Sciences
Negev Arid Zone Research Institute and Faculty of Natural Science
University of Negev, Beer Sheva, Israel

Abstract

Aluminium intoxication has been demonstrated in the uræmic and non-uræmic rat after modest doses of oral and parenteral aluminium salts. The clinical syndrome is associated with periorbital bleeding, lethargy, anorexia, and death. Plasma-levels of aluminium were greatly raised, as were tissue levels in liver, heart, striated muscle, brain, and bone. Histological changes were found in the cornea. Liver oxygen consumption was reduced by giving the animals aluminium salts before death or by adding aluminium in vitro to normal liver homogenates. It is recommended that aluminium salts should be withdrawn from use in patients with renal failure and their use restricted in normal persons pending clarification of the issue.

http://www.ncbi.nlm.nih.gov/pubmed/4110051

Science • May 1973

Brain aluminum distribution in Alzheimer's disease and experimental neurofibrillary degeneration

Crapper DR, Krishnan SS, Dalton AJ.

Abstract

Neurofibrillary degeneration is an important pathological finding in senile and presenile dementia of the Alzheimer type. Experimentally, aluminum induces neurofibrillary degeneration in neurons of higher mammals. Aluminum concentrations approaching those used experimentally have been found in some regions of the brains of patients with Alzheimer's disease.

http://www.ncbi.nlm.nih.gov/pubmed/4735595

"Experimentally, aluminum induces neurofibrillary degeneration in neurons of higher mammals."

Physiology & Behavior • May 1973

Alterations in short-term retention, conditioned avoidance response acquisition and motivation following aluminum induced neurofibrillary degeneration

D.R. Crapper

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Faculty of Medicine, University of Toronto
Toronto, Canada

A.J. Dalton
Department of Psychology
Mental Retardation Centre, Toronto, Canada

Abstract

Aluminum chloride induced neurofibrillary degeneration may provide a useful model for the study of a human dementia process. This possibility was assessed in cats trained to perform on a delayed-response task, a conditioned avoidance task, visual and temporal discrimination tasks and a motivational task involving rewarding intracranial electrical stimulation. After an initial asymptomatic period short term retention and acquisition of a conditioned avoidance response were selectively impaired. The associated ultrastructural abnormalities plausibly implicate the cytoplasmic streaming mechanism in the cellular substrate for some retention and acquisition phenomena.

http://www.sciencedirect.com/science/article/pii/0031938473900632

“Aluminum chloride induced neurofibrillary degeneration may provide a useful model for the study of a human dementia process.”

“... exerted selective and differential effects on the transport systems

of neurotransmitter substances in the synaptosomal membrane.”

Journal of Inorganic Biochemistry • 1981

Selective inhibition of L-glutamate and gammaaminobutyrate transport in nerve ending particles by aluminium, manganese, and cadmium chloride

Patrick C.L. Wong, James C.K. Lai, Louis Lim, Alan N. Davison

Abstract

AlCl3, MnCl2, and CdCl2 inhibited the rates of accumulation of 14C] L-glutamate and 3H] gammaaminobutyrate (GABA) in purified rat forebrain nerve-ending particles in a dose-dependent fashion. The concentrations that would give 50% inhibition (IC50) of GABA transport were 316 µM, 7.4 mM, and 1.4 mM, respectively. Ca2+ (1 mM) enhanced the inhibitory effect of Al3+ (IC50 decreased to 149 µM) but antagonized that of Mn2+ (IC50 = 10 mM) and Cd2+ (IC50 = 2.1 mM). For glutamate transport 1 mM Ca2+ changed the IC50 values from 299 to 224 µm for Al3+, 7.1 to 10 mM for Mn2+, and 2 to 3 mM for Cd2+. In contrast, the rates of accumulation of 14C] 2-deoxy-glucose and 3H] L-phenylalanine were mostly unaffected by these metal ions. The results indicate that Al3+, Mn2+, and Cd2+ exerted selective and differential effects on the transport systems of neurotransmitter substances in the synaptosomal membrane.

http://www.sciencedirect.com/science/article/pii/S0162013400800057

Journal Of Neurochemistry • February 1984

Inhibition of brain glycolysis by aluminum

Lai JC, Blass JP.

Abstract

Aluminum inhibited both the cytosolic and mitochondrial hexokinase activities in rat brain. The IC50 values were between 4 and 9 microM. Aluminum was effective at mildly acidic (pH 6.8) or slightly alkaline (pH 7.2-7.5) pH, in the presence of a physiological level of magnesium (0.5 mM). However, saturating (8 mM) magnesium antagonized the effect of aluminum on both forms of hexokinase activity. Other enzymes examined were considerably less sensitive to inhibition by aluminum. The IC50 of aluminum for phosphofructokinase was 1.8 mM and for lactate dehydrogenase 0.4 mM. At 10-600 microM, aluminum actually stimulated pyruvate kinase. Aluminum also inhibited lactate production by rat brain extracts: this effect was much more marked with glucose as substrate than with glucose-6-phosphate. However, the IC50 for inhibiting lactate production using glucose as substrate was 280 microM, higher than that required to inhibit hexokinase. This concentration of aluminum is comparable to those reportedly found in the brains of patients who had died with dialysis dementia and in the brains of some of the patients who had died with Alzheimer disease. Inhibition of carbohydrate utilization may be one of the mechanisms by which aluminum can act as a neurotoxin.

http://www.ncbi.nlm.nih.gov/pubmed/6229606

“This concentration of aluminum is comparable to those reportedly found in the brains of patients who had died with dialysis dementia and in the brains of some of the patients who had died with Alzheimer disease. Inhibition of carbohydrate utilization may be one of the mechanisms by which aluminum can act as a neurotoxin.”

Journal Of Neurology, Neurosurgery And Psychiatry • February 1984

Experimental aluminium encephalopathy: quantitative EEG analysis of aluminium bioavailability

Cutrufo C, Caroli S, Delle Femmine P, Ortolani E,
Palazzesi S, Violante N, Zapponi GA, Loizzo A.

Abstract

Single oral doses of aluminium hydroxide (50 to 200 mg/kg) were found to induce in mice a dose-dependent diminution of the power of the 7.5 to 12 Hz frequency band, with a parallel dose-dependent increase of aluminium content in the brain, as early as 45 min after administration, and indicated that aluminium hydroxide is readily absorbed through an empty stomach or duodenum and is able to induce alterations of background EEG rhythms at doses equivalent to the ones used in human therapy. These data suggest that the EEG disturbances of the background type, (which are observed during the early stage of dialysis encephalopathy in man), may be partly due to a pharmacological and therefore reversible effect induced by an increase in aluminium level in the brain.

Full Report

http://www.ncbi.nlm.nih.gov/pmc/articles/PMC1027694/

“Single oral doses of aluminium hydroxide were found to induce in mice a dose-dependent diminution of the power of the 7.5 to 12 Hz frequency band, with a parallel dose-dependent increase of aluminium content in the brain, as early as 45 min after administration, and indicated that aluminium hydroxide is readily absorbed through an empty stomach or duodenum and is able to induce alterations of background EEG rhythms at doses equivalent to the ones used in human therapy.”

Acta Neuropathology • 1985

Histochemical localization of aluminum in the rabbit Central Nervous System

Wen GY, Wisniewski HM.

Abstract

Aluminum was observed in the nucleolus, interchromatin granules, rough endoplasmic reticulum, free ribosomes, euchromatin, and the heterochromatin of the neuron. The association of aluminum with the first four r-RNA-containing cellular components and with the last two DNA-containing chromatins suggests the association of aluminum with the nucleic acids. The aluminum may interfere with the normal mechanism of the protein synthesis of r-RNA and of the transcription or gene modulation of DNA. Aluminum was also observed in the astrocytic process and in the nuclei of endothelial cells, pericytes, and the muscle cells of the blood vessels. The detection of aluminum in the pyrimidal cells of the cerebral cortex and hippocampus and in the spinal cord neurons, was observed 1 h after i.v. injection, indicating a rapid entry of aluminum from the injection site through the blood-brain barrier (BBB) to the neurons. Using Morin stain, pyramidal neurons of the cerebral cortex and hippocampus, motoneurons of spinal cord, ganglion cells, and bipolar cells of retina and Purkinje cells of cerebellum, exhibited yellow fluorescence, with peak intensity at 560 nm. Tangles were observed in these six types of neurons. The granule cells of hippocampus and cerebellum and the photoreceptors of the retina exhibited green fluorescence with the peak intensity at 490-500 nm. Tangles were not observed in these three types of neurons.

http://www.ncbi.nlm.nih.gov/pubmed/?term=2417440

“The detection of aluminum in the pyrimidal cells of the cerebral cortex and hippocampus and in the spinal cord neurons, was observed 1-hour after i.v. injection, indicating a rapid entry of aluminum from the injection site through the blood-brain barrier (BBB) to the neurons.”

Environmental Health Perspectives • March 1986

Metabolism and possible health effects of aluminum

by P. O. Ganrot

Abstract

Literature regarding the biochemistry of aluminum and eight similar ions is reviewed. Close and hitherto unknown similarities were found. A hypothetical model is presented for the metabolism, based on documented direct observations of Al3+ and analogies from other ions. Main characteristics are low intestinal absorption, rapid urinary excretion, and slow tissue uptake, mostly in skeleton and reticuloendothelial cells. Intracellular Al3+ is probably first confined in the lysosomes but then slowly accumulates in the cell nucleus and chromatin. Large, long-lived cells, e.g., neurons, may be the most liable to this accumulation. In heterochromatin, Al3+ levels can be found comparable to those used in leather tannage. It is proposed that an accumulation may take place at a subcellular level without any significant increase in the corresponding tissue concentration. The possible effects of this accumulation are discussed. As Al3+ is neurotoxic, the brain metabolism is most interesting. The normal and the lethally toxic brain levels of Al3+ are well documented and differ only by a factor of 3-10. The normal brain uptake of Al3+ is estimated from data on intestinal uptake of Al3+ and brain uptake of radionuclides of similar ions administered intravenously. The uptake is very slow, 1 mg in 36 years, and is consistent with an assumption that Al3+ taken up by the brain cannot be eliminated and is therefore accumulated. The possibility that Al3+ may cause or contribute to some specific diseases, most of them related to aging, is discussed with the proposed metabolic picture in mind.

http://www.ncbi.nlm.nih.gov/pmc/articles/PMC1474689/

“The uptake is very slow, 1 mg in 36 years, and is consistent with an assumption that Al3+ taken up by the brain cannot be eliminated and is therefore accumulated.”

The Society of Toxicology • May 1987

Maternal and Developmental Toxicity of Chronic Aluminum Exposure in Mice

Author Information

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Abstract

The present study demonstrated aluminum-induced neurotoxicity in mouse dams and developmental retardation in their offspring following oral exposure to several dose levels during gestation and lactation. Female mice fed aluminum lactate (AL) at levels of 500 or 1000 ppm in their diet from Day 0 gestation to Day 21 postpartum were compared to mice which received a 100 ppm aluminum diet either ad libitum or pair-fed to the 1000 ppm AL group. Dams receiving the 500 and 1000 ppm AL diets showed signs of neurotoxicity beginning at Days 12–15 postpartum and showed significant weight loss. Offspring showed dose-dependent decreases in body weight ($F = 6.47$, $p < 0.001$), crown-rump length ($F = 1.11$, $p < 0.0001$), and ponderal index ($F = 6.90$, $p < 0.0002$), at birth and preweaning. Absolute and relative liver and spleen weights were lower in pups from the high AL groups compared to controls ($F = 3.34$, $p < 0.025$ and $F = 15.54$, $p < 0.001$, respectively). Neurobehavioral development was somewhat delayed in aluminum-treated pups, but not in their pair-fed controls ($F = 5.52$, $p < 0.005$). In addition to showing oral toxicity of excess AL during development dose-dependent toxic effects of parenteral aluminum exposure were demonstrated in pregnant mice which were injected subcutaneously with aluminum lactate solution at 10, 20, or 40 mg Al/kg body wt on Days 3, 5, 7, 9, 12, 13, and 15 of gestation. Maternal spleen and liver weights were significantly increased in aluminum treated animals ($p < 0.001$ and $p < 0.05$, respectively). Fetal crown-rump lengths were significantly reduced in the 20 mg/kg aluminum group ($F = 9.79$, $p < 0.001$).

http://toxsci.oxfordjournals.org/content/8/3/346

“The present study demonstrated aluminum-induced neurotoxicity in mouse dams and developmental retardation in their offspring following oral exposure to several dose levels during gestation and lactation.”

Neurotoxicology • Fall 1988

Neuropathologic, neurochemical and immunocytochemical characteristics of aluminum-induced neurofilamentous degeneration

Author information

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Abstract

Inoculation of aluminum salts or metallic aluminum into the central nervous system of rabbits produces an encephalomyelopathy accompanied by widespread neurofibrillary degeneration (NFD) affecting restricted neuronal populations. Some investigators have suggested that this preparation may serve as an animal model for human neurodegenerative disorders, such as Alzheimer's disease (AD), in which neurofibrillary tangle (NFT) formation is a prominent histopathologic finding. However, neurochemical, immunocytochemical and behavioral features of the model are largely unknown and its neuropathology only partially described. We have undertaken a series of experiments designed to further characterize these aspects of the model. We have used an intraventricular route of injection of aluminum chloride and found that the distribution of NFD in rabbit brain is similar to the distribution of NFT formation in AD. Immunocytochemical probes demonstrate that phosphorylated neurofilaments accumulate in neuronal perikarya containing NFD, and double labelling techniques suggest that NFD affects primarily projection type neurons. The neurochemical profile of aluminum intoxicated rabbits shows both similarities and discrepancies to that of AD. Finally, as reported in a companion article in this issue of Neurotoxicology (Solomon and Pendlebury, 1988), aluminum-exposed rabbits develop learning and memory deficits which are strongly correlated with the degree of whole brain NFD but not with motor, sensory or motivational factors. We conclude that aluminum-induced NFD may have relevance for understanding NFT formation in AD and other neurodegenerative disorders in which abnormalities of the neuronal cytoskeletal architecture are present.

http://www.ncbi.nlm.nih.gov/pubmed/?term=3200512

"... aluminum-induced neurofibrillary degeneration may have relevance for understanding neurofibrillary tangle formation in Alzheimer's disease and other neurodegenerative disorders ..."

Neuroscience And Biobehavioral Reviews • Spring 1989

Aluminum-induced neurotoxicity: alterations in membrane function at the blood-brain barrier

Author information

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Abstract

Aluminum is established as a neurotoxin, although the basis for its toxicity is unknown. It recently has been shown to alter the function of the blood-brain barrier (BBB), which regulates exchanges between the central nervous system (CNS) and peripheral circulation. The BBB owes its unique properties to the integrity of the cell membranes that comprise it. Aluminum affects some of the membrane-like functions of the BBB. It increases the rate of transmembrane diffusion and selectively changes saturable transport systems without disrupting the integrity of the membranes or altering CNS hemodynamics. Such alterations in the access to the brain of nutrients, hormones, toxins, and drugs could be the basis of CNS dysfunction. Aluminum is capable of altering membrane function at the BBB; many of its effects on the CNS as well as peripheral tissues can be explained by its actions as a membrane toxin.

http://www.ncbi.nlm.nih.gov/pubmed/2671833

“Aluminum is established as a neurotoxin ... Aluminum affects some of the membrane-like functions of the BBB ... many of its effects on the CNS as well as peripheral tissues can be explained by its actions as a membrane toxin.”

Kidney International • May 1989

Micromolar aluminum levels reduce 3H-thymidine incorporation by cell line UMR 106-01

Author information

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Abstract

Aluminum-induced osteomalacia is a frequent complication observed in patients on maintenance hemodialysis. However, it is not known whether there are direct effects of aluminum on osteoblasts, or alternatively, whether the observed changes are due to changes in PTH or other factors. We sought to determine the effect of micromolar levels of aluminum on osteoblasts using a well-defined cell line derived from a 32P induced osteosarcoma of rat, UMR 106-01, which is alkaline-phosphatase positive, responds to PTH, and synthesizes type I collagen. Aluminum exposure was controlled using tissue culture media with [Al] less than 1 microgram/liter (40 nM), produced by precipitation of aluminum salts at pH 8.5. The effect of defined [Al], from 20 to 800 micrograms/liter (0.7 to 30 microM), was then determined by adding back aluminum while measuring DNA and protein synthesis. We found that aluminum depressed DNA synthesis, as determined by 3H-thymidine incorporation, by 60%, with half maximal effect at 20 micrograms/liter (740 nM) in cells at a density of 20,000/cm2. Alternatively, protein synthesis, as determined by 3H-leucine incorporation, did not decline, and in some cases increased. However, qualitative analysis of matrix proteins produced with and without 800 micrograms/liter (30 mM) [Al] showed no differences. Direct measurements of cell number and protein synthesis confirmed these findings. Al does not alter the PTH-induced cAMP response of these cells. Thus, aluminum has a direct effect on cell division, and probably on protein synthesis, in this osteoblast-like cell line. These effects occur at levels of aluminum below those commonly contaminating tissue culture media, and thus are seen reproducibly only in media of defined [Al].

http://www.ncbi.nlm.nih.gov/pubmed/2549294

“... aluminum has a direct effect

on cell division, and probably on protein synthesis ...”

Clinical Science • London England • November 1989

Effect of aluminium on superoxide dismutase

Author information

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Abstract

1. The effect of Al3+ on superoxide dismutase in vitro was studied, since in uraemia there is excessive superoxide production and frequently an elevated serum Al3+ level. Thus, the protective role of superoxide dismutase is particularly important.

2. Al3+ in concentrations similar to those found in the serum of uraemic patients inhibits superoxide dismutase activity. The degree of inhibition is directly proportional to the Al3+ level.

3. The combination of excessive oxygen free radical production with an increased Al3+ level may contribute to a variety of complications, including aluminium dementia or initiation and promotion of carcinogenic processes, which are known to be more common in uraemic patients.

http://www.ncbi.nlm.nih.gov/pubmed/2582719

“The combination of excessive oxygen free radical production with an increased aluminum level may contribute to a variety of complications, including aluminium dementia or initiation and promotion of carcinogenic processes ...”

Environmental Geochemistry And Health • March 1990

Aluminum neurotoxicity in mammals

Author information

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Abstract

Although aluminum comprises a large percentage of the Earth's crust, it is excluded from body tissues, and especially from the central nervous system. When aluminum is experimentally introduced to the central nervous system, several neurotoxic effects are observed: i.e. neurofibrillary changes, behavioral and cognitive deficits and enzymatic and neurotransmitter changes, as well as certain types of epileptic seizures. The localization of relatively high levels of aluminum in Alzheimer disease, Guamanian amyotrophic lateral sclerosis and Parkinsonism-dementia has led to the implication of aluminum as a pathogenic factor in these diseases. Recent studies have shown that microtubule-associated proteins are part of the paired helical filaments which make up the intraneuronal neurofibrillary tangle. Other studies have identified the protein making the vascular and neuritic (senile) plaque amyloid and located the gene responsible for this protein to chromosome 21.Our electron microprobe analysis studies have not found the levels of aluminum or silicon in either the neurofibrillary tangles or amyloid cores reported elsewhere, nor have the levels of aluminum been elevated in approximately one half of the tangles and plaque cores examined to date.

http://www.ncbi.nlm.nih.gov/pubmed/?term=24202577

"When aluminum is experimentally introduced to the central nervous system, several neurotoxic effects are observed: i.e. neurofibrillary changes, behavioral and cognitive deficits and enzymatic and neurotransmitter changes, as well as certain types of epileptic seizures."

Biofactors • July 1990

Aluminum, a neurotoxin which affects diverse metabolic reactions

Author information

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Abstract

Experimental evidence is summarized to support the hypothesis that chronic exposure to low levels of aluminum may lead to neurological disorders. These disorders result from defective phosphorylation--dephosphorylation reactions, reduced glucose utilization and site-specific damage inflicted by free radicals produced by altered iron metabolism. The brain is a highly compartmentalized organ. Therefore, a co-localization of critical mass of metabolic errors rather than a single event may be essential to precipitate a neural disease. Aluminum appears to participate in formulating this critical mass. Patients with dialysis dementia get partial relief by desferroxamine which chelates aluminum. However, it also chelates iron and therefore limits its applicability. While the specific chelator for aluminum is yet to be made available, exercising a caution in aluminum intake appears prudent.

http://www.ncbi.nlm.nih.gov/pubmed/?term=2198876

“Experimental evidence is summarized to support the hypothesis that chronic exposure to low levels of aluminum may lead to neurological disorders.”

Journal Of Pharmacology And Experimental Therapeutics • July 1990

Mechanism of aluminum-induced inhibition of hepatic glycolysis: inactivation of phosphofructokinase

Author information

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Abstract

Aluminum, an abundant element in the earth's crust, has been implicated in various pathological disorders and low concentrations of this element have recently been shown to inhibit brain glycolysis. However, despite the fact that aluminum accumulates in high concentrations in the liver, potential effects of this metal on hepatic intermediary metabolism have not been explored. In perfused livers from untreated rats, maximal rates of production of lactate plus pyruvate (glycolysis) were 93 +/- 15 mumols/g/hr. Glycolysis was severely inhibited in livers from aluminum-treated rats (0.5 mg/kg, 6 hr before experiment) with maximal rates of only 23 +/- 4 mumols/g/hr. In contrast, glucose production (glycogenolysis) and hepatic oxygen uptake were not altered significantly by prior treatment with aluminum. In livers from fasted rats, pretreatment with aluminum did not influence gluconeogenesis or production of lactate and pyruvate from fructose (5 mM). This finding indicates that pyruvate kinase is not inhibited by aluminum and implicates phosphofructokinase, hexokinase and/or glucokinase as sites for the inhibitory effect of aluminum on glycolysis. In liver homogenates from untreated rats, increasing concentrations of aluminum did not show any appreciable effect on hexokinase or glucokinase activity but did cause progressive decreases in phosphofructokinase activity. Therefore, aluminum-induced inhibition of liver phosphofructokinase, an important control site in the glycolytic pathway, is most likely responsible for aluminum-induced inhibition of hepatic glycolysis.

http://www.ncbi.nlm.nih.gov/pubmed/2142221

"Aluminum, an abundant element in the earth's crust, has been implicated in various pathological disorders and low concentrations of this element have recently been shown to inhibit brain glycolysis."

“These studies clearly demonstrate the philosophy that chronic rather than acute experimental models of toxicity are necessary in order to enhance our understanding of human neurodegenerative disorders with long-latency and slow progression.”

Neurotoxicology • Fall 1991

Pacific paradigms of environmentally-induced neurological disorders: clinical, epidemiological and molecular perspectives

Author information

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Abstract

During the past quarter century biomedical scientists have begun to recognize the unique opportunities for studying disease etiology and mechanisms of pathogenesis in non-Western anthropological populations with focal, endemic diseases. Such natural experiments as they are called, are important paradigms for solving etiological and epidemiological problems of widespread medical significance, with an ultimate goal towards treatment and prevention. The systematic search for etiological factors and mechanisms of pathogenesis of neurodegenerative disorders is perhaps nowhere better exemplified than in the western Pacific. During the past three decades, the opportunistic and multidisciplinary study of hyperendemic foci of amyotrophic lateral sclerosis and parkinsonism-dementia which occur in different cultures, in different ecological zones and among genetically divergent populations have served as natural models that have had a major impact on our thinking and enhanced our understanding of these and other neurodegenerative disorders such as Alzheimer disease and the process of early neuronal aging. Our cross-disciplinary approach to these intriguing neurobiological problems and the accumulated epidemiological, genetic, cellular and molecular evidence strongly implicates environmental factors in their causation, specifically the role of aluminum and its interaction with calcium in neuronal degeneration. As a direct consequence of our studies in these Pacific populations, we have undertaken the long-term development of experimental models of neuronal degeneration, in an attempt to understand the cellular and molecular mechanisms by which these toxicants affect the central nervous system. Our experimental studies have resulted in the establishment of an aluminum-induced chronic myelopathy in rabbits and the development of neurofilamentous lesions after low-dose aluminum administration in cell culture. These studies clearly demonstrate the philosophy that chronic rather than acute experimental models of toxicity are necessary in order to enhance our understanding of human neurodegenerative disorders with long-latency and slow progression. Finally, the ultimate significance of these Pacific paradigms may well depend on our ability to comprehensively evaluate and synthesize the growing body of relevant scientific data from other human disorders and from widely divergent academic fields, as well as our ability to recognize emerging new models in nature.

http://www.ncbi.nlm.nih.gov/pubmed/?term=1745428

Annals Of Neurology • March 1992

Selective accumulation of aluminum and iron in the neurofibrillary tangles of Alzheimer's disease: a laser microprobe (LAMMA) study

Author information

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Abstract

We report the results of an examination of the elemental content of neurofibrillary tangle-bearing and neurofibrillary tangle-free neurons identified within the hippocampus of 10 subjects with Alzheimer's disease and 4 neuropathologically intact age-matched control subjects. The study employed laser microprobe mass analysis (LAMMA), a technique that provides extremely sensitive multielement detection in plastic-embedded, semithin-sectioned tissues. Evidence for the selective accumulation of aluminum within the neurofibrillary tangle-bearing neurons was obtained in all 10 subjects with Alzheimer's disease. The site of aluminum deposition within these cells was the neurofibrillary tangle itself, and not the "nuclear region," as we previously reported. Iron accumulation was also detected within neurofibrillary tangles. Evaluation for the accumulation of other elements within the tangle-bearing neurons failed to reveal any other metallic element as being consistently present. In addition, probe sites directed to neurons identified in snap-frozen cryostat sections from 2 subjects with Alzheimer's disease revealed similar spectra with prominent aluminum-related peaks, confirming that our findings are not related to exogenous contamination through fixation, embedding, or other procedures prior to analysis. This study further confirms the association of aluminum and neurofibrillary tangle formation in Alzheimer's disease.

http://www.ncbi.nlm.nih.gov/pubmed/1637136

"This study further confirms the association of aluminum and neurofibrillary tangle formation in Alzheimer's disease."

Pharmacology And Toxicology • April 1992

Aluminium-adjuvanted vaccines transiently increase aluminium levels in murine brain tissue

Author information

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Abstract

Aluminium is widely used as an adjuvant in human vaccines, and children can often receive up to 3.75 mg of parenteral aluminium during the first six months of life. We show that intraperitoneal injection of aluminium adsorbed vaccines into mice causes a transient rise in brain tissue aluminium levels peaking around the second and third day after injection. This rise is not seen in the saline control group of animals or with vaccine not containing aluminium. It is likely that aluminium is transported to the brain by the iron-binding protein transferrin and enters the brain via specific transferrin receptors.

http://www.ncbi.nlm.nih.gov/pubmed/1608913

“... children can often receive up to 3.75 mg of parenteral aluminium during the first six months of life We show that intraperitoneal injection of aluminium adsorbed vaccines into mice causes a transient rise in brain tissue aluminium levels peaking around the second and third day after injection.”

Life Sciences • June 1992

Long-term effects of aluminium on the fetal mouse brain

Author information

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Abstract

Potentially noxious substances may act as fetal teratogens at levels far lower than those required to produce detectable effects in adults, and behavioural teratogenicity may occur at levels lower than those which produce morphological teratogenesis. Aluminium (Al) is a potential neurotoxin in adults. Since pregnant women may be exposed to untoward levels of Al compounds under certain conditions, we have examined the long-term effects of treating the pregnant mouse with intraperitoneal or oral aluminium sulphate on brain biochemistry and behaviour of the offspring. The cholinergic system, as evaluated by the activity of choline acetyltransferase (ChAT), was affected differentially in different regions of the brain, and still showed significant effects in the adult. Differences between the intraperitoneal and oral series in the magnitude of effect seen in the regions of the brain probably reflect differences in the effective level of exposure. Growth rate and psychomotor maturation in the pre-weaning mouse were affected in the intraperitoneal series only, showing a marked post-natal maternal effect.

http://www.ncbi.nlm.nih.gov/pubmed/?term=1453876

“Potentially noxious substances may act as fetal teratogens at levels far lower than those required to produce detectable effects in adults, and behavioural teratogenicity may occur at levels lower than those which produce morphological teratogenesis.”

Neurotoxicology • Summer 1992

Aluminum inhibits glutamate release f rom transverse rat hippocampal slices: role of G proteins, Ca channels and protein kinase C

Author information

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Abstract

Aluminum (Al) has been shown to produce deficits in learning and memory. The present experiments tested the hypothesis that Al-induced inhibition of learning may be due to its effect on glutamate release secondary to changes in calcium channel function and/or intracellular events triggering glutamate release. Calcium-dependent potassium (K)-evoked [14C]-glutamate release from 400 microns transverse rat hippocampal slices was inhibited by Al in a concentration dependent manner (IC50 = 40 microM). Aluminum (30, 100 microM) noncompetitively inhibited Bay K 8644-evoked glutamate release. 4-Aminopyridine (30, 1000 microM) noncompetitively attenuated the Al inhibition of glutamate release, suggesting an Al-induced alteration of Ca channel function. Activation of the Gi protein by R(-)phenylisopropyladenosine (PIA; 1 microM) reduced K-evoked glutamate release 69%, whereas 300 microM Al produced an 84% reduction. These effects were prevented by the Gi protein inhibitor N-ethylmaleimide (NEM; 100 microM), suggesting an effect of Al on the Gi protein to inhibit glutamate release. Phorbol myristate acetate (0.16 microM)-induced glutamate release was inhibited by 300 microM Al and 80 microM polymyxin B, suggesting an Al modulation of protein kinase C (PKC)-evoked glutamate release. These results demonstrate an Al inhibition of glutamate release that may be mediated by multiple, but interconnected mechanisms (e.g., via interactions with Ca systems), providing multiple targets for an Al-induced alteration of neuronal function.

http://www.ncbi.nlm.nih.gov/pubmed/?term=1359483

“Aluminum (Al) has been shown to produce deficits in learning and memory.”

Journal Of Theoretical Biology • November 1992

The cellular toxicity of aluminium

Author information

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Abstract

Aluminium is a serious environmental toxicant and is inimical to biota. Omnipresent, it is linked with a number of disorders in man including Alzheimer's disease, Parkinson's dementia and osteomalacia. Evidence supporting aluminium as an aetiological agent in such disorders is not conclusive and suffers principally from a lack of consensus with respect to aluminium's toxic mode of action. Obligatory to the elucidation of toxic mechanisms is an understanding of the biological availability of aluminium. This describes the fate of and response to aluminium in any biological system and is thus an important influence of the toxicity of aluminium. A general theme in much aluminium toxicity is an accelerated cell death. Herein mechanisms are described to account for cell death from both acute and chronic aluminium challenges. Aluminium associations with both extracellular surfaces and intracellular ligands are implicated. The cellular response to aluminium is found to be biphasic having both stimulatory and inhibitory components. In either case the disruption of second messenger systems is observed and GTPase cycles are potential target sites. Specific ligands for aluminium at these sites are unknown though are likely to be proteins upon which oxygen-based functional groups are orientated to give exceptionally strong binding with the free aluminium ion.

http://www.ncbi.nlm.nih.gov/pubmed/?term=1291812

"A general theme in much aluminium toxicity is an accelerated cell death."

Toxicology • 1992

Role of aluminium in skin reactions after diphtheria-tetanus-pertussis-poliomyelitis vaccination: an experimental study in rabbits

Author information

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Abstract

The occurrence of subcutaneous nodules at the injection site is one of the complications of diphtheria-tetanus-pertussis-poliomyelitis vaccination, but the causes and mechanisms involved are still poorly understood. An experimental study in the New Zealand rabbit enabled us to determine the frequency of occurrence of these nodules, how long they persist and the histopathologic features of the cells involved. Aluminium (Al) assays by electrothermal atomic absorption spectrometry allowed us to study concentrations both in nodules and the organism (serum, normal skin). The results show an absence of Al diffusion outside nodules, a correlation between infiltrate intensity and Al concentration in nodules and modifications in the histological constituents of nodule cells. The histological picture indicates a foreign body reaction to Al. All these data underscore the role of Al in the formation of early postvaccinal nodules at the injection site.

http://www.ncbi.nlm.nih.gov/pubmed/?term=1589878

"All these data underscore the role of Aluminum in the formation of early postvaccinal nodules at the injection site."

[this is one of the earliest examples of "nodules at the injection site" mentioned in the medical literature. As you'll see, eventually this phenomenon leads to a new disorder, Macrophagic Myofasciitis and the coining of the term "ASIA," a wide variety of nearly 100 recognized autoimmune and inflammatory disorders induced by the Aluminum adjuvant in vaccines]

“Generally, the intake of aluminium from foods is less than 1% of that consumed by individuals using aluminium-containing pharmaceuticals. Currently the real scientific question is not the amount of aluminium in foods but the availability of the aluminium in foods and the sensitivity of some population groups to aluminium.”

Ciba Foundation Symposium • 1992

Dietary and other sources of aluminium intake

Author information

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Abstract

Aluminium in the food supply comes from natural sources including water, food additives, and contamination by aluminium utensils and containers. Most unprocessed foods, except for certain herbs and tea leaves, contain low (< 5 micrograms Al/g) levels of aluminium. Thus most adults consume 1-10 mg aluminium daily from natural sources. Cooking in aluminium containers often results in statistically significant, but not practically important, increases in the aluminium content of foods. Intake of aluminium from food additives varies greatly (0 to 95 mg Al daily) among residents in North America, with the median intake for adults being about 24 mg daily. Generally, the intake of aluminium from foods is less than 1% of that consumed by individuals using aluminium-containing pharmaceuticals. Currently the real scientific question is not the amount of aluminium in foods but the availability of the aluminium in foods and the sensitivity of some population groups to aluminium. Several dietary factors, including citrate, may affect the absorption of aluminium. Aluminium contamination of soy-based formulae when fed to premature infants with impaired kidney function and aluminium contamination of components of parenteral solutions (i.e. albumin, calcium and phosphorus salts) are of concern.

http://www.ncbi.nlm.nih.gov/pubmed/?term=1490425

Food And Chemical Toxicology • May 1993

Neurotoxic effect of enteral aluminium

Author information

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Abstract

Long Evans rats were treated for 90 days with water-soluble, insoluble or chelated aluminium compounds. The daily treatments given were as follows: controls, NaCl (100 mg/kg body weight) plus citric acid (30 mg/kg); AlCl3 (30 or 100 mg/kg); Al(OH)3 (100 mg/kg) plus citric acid (30 mg/kg); Al(OH)3 (300 mg/kg). Their learning ability was determined in the labyrinth test at day 90, and the choline-acetyltransferase, acetylcholinesterase activity and aluminium content of the brains were measured. Soluble and chelated aluminium compounds seriously worsened the learning ability, and the aluminium content of the brain was elevated. Acetylcholinesterase activity increased and choline-acetyltransferase activity decreased, resulting in a diminished cholinergic activity, which is a characteristic of Alzheimer's disease.

http://www.ncbi.nlm.nih.gov/pubmed/?term=8505021

"... resulting in a diminished cholinergic activity, which is a characteristic of Alzheimer's disease."

Vaccine • 1993

Adjuvants— a balance between toxicity and adjuvanticity

Author information

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Abstract

Adjuvants have been used to augment the immune response in experimental immunology as well as in practical vaccination for more than 60 years. The chemical nature of adjuvants, their mode of action and the profile of their side effects are highly variable. Some of the side effects can be ascribed to an unintentional stimulation of different mechanisms of the immune system whereas others may reflect general adverse pharmacological reactions. The most common adjuvants for human use today are still aluminium hydroxide, aluminium phosphate and calcium phosphate although oil emulsions, products from bacteria and their synthetic derivatives as well as liposomes have also been tested or used in humans. In recent years monophosphoryl lipid A, ISCOMs with Quil-A and Syntex adjuvant formulation (SAF) containing the threonyl derivative of muramyl dipeptide have been under consideration for use as adjuvants in humans. At present the choice of adjuvants for human vaccination reflects a compromise between a requirement for adjuvanticity and an acceptable low level of side effects.

http://www.ncbi.nlm.nih.gov/pubmed/8447157

“At present the choice of adjuvants for human vaccination reflects a compromise between a requirement for adjuvanticity and an acceptable low level of side effects.”

[today those “Side Effects” are at epidemic proportions]

“Vaccines adsorbed onto aluminium salts

are a more frequent cause of local post-vaccinal reactions than plain vaccines.”

Roczniki Panstwowego Zakladu Higieny • 1993

Aluminum as an adjuvant in vaccines and post-vaccine reactions

Author information

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Zakladu Badania Surowic
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Abstract

Aluminium compounds have been widely used as adjuvants in prophylactic and therapeutic vaccines. Adjuvants are able to stimulate the immune system in a nonspecific manner, i.e. high antibody level can be obtained with minimal dose of the antigen and with reduced number of inoculations. Adjuvants use has been mostly empirically determined by such factors as efficacy and safety. The mechanism of action of the aluminium adjuvants is not completely understood and is very complex. The basic factors of the mode of action: 1) the complex of antigen and aluminium gel is more immunogenic in structure than free antigen, 2) effect “depot”--The antigen stimulus last longer, 3) the production of local granulomas. Vaccines adsorbed onto aluminium salts are a more frequent cause of local post-vaccinal reactions than plain vaccines. 5-10% those vaccinated can develop a nodule lasting several weeks at the injection site. In some rare cases the nodules may become inflammatory and even turn into an aseptic abscess. The nodules persisting more than 6 weeks may indicate development of aluminium hypersensitivity. Finally aluminium adjuvant immunogens induce the production of IgE antibodies.

http://www.ncbi.nlm.nih.gov/pubmed/?term=8235346

Annali dell'istituto Superiore di Sanita • 1993

Behavioural effects of gestational exposure to aluminium

Author information

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Abstract

The involvement of aluminium in the aetiology of a number of human pathological diseases has altered its status from being a non-toxic, nonabsorbable, harmless element. This maybe of particular concern to the developing foetus which is more susceptible to agents and at lower levels than the adult. Little attention has been given to aluminium's potential reproductive toxicity until recently and further research is required for a full evaluation of its toxicity. Our preliminary results demonstrate behavioural and neurochemical alterations in the offspring of mice exposed to aluminium during gestation. Further, the effects of such exposure are also present in the adult animal suggesting persistent changes in behaviour following prenatal exposure.

http://www.ncbi.nlm.nih.gov/pubmed/8129261

"Our preliminary results demonstrate behavioural and neurochemical alterations in the offspring of mice exposed to aluminium during gestation. Further, the effects of such exposure are also present in the adult animal suggesting persistent changes in behaviour following prenatal exposure."

Vaccine • 1993

Studies on the toxicities of aluminium hydroxide and calcium phosphate as immunological adjuvants for vaccines

Author information

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Abstract

Aluminium hydroxide (Al) and calcium phosphate (Ca) have been used for many years as immunological adjuvants for biologicals. We investigated the toxic effects of both adjuvants with different physical properties. Al-gel elicited vascular permeability-increasing and toxic effects to macrophages (M phi), while its haemolytic effect was weak. Ca-gel elicited a significantly stronger haemolytic effect, but no other toxic effect. Incubation of M phi or polymorphonuclear leucocytes with Al-suspension resulted in the largest release of lactate dehydrogenase. Ca-suspension caused haemolysis of about 50% of that caused by Ca-gel.

http://www.ncbi.nlm.nih.gov/pubmed/8212836

“Aluminum-gel elicited vascular permeability-increasing and toxic effects to macrophages ...”

Brazilian Journal Of Medical And Biological Research • January 1994

Effects of aluminum on the mechanical and electrical activity of the Langendorff-perfused rat heart

Author information

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Abstract

The effect of aluminum (Al3+) chloride (1, 5, 10, 50 and 100 microM) on myocardial electromechanical activity was studied in 10 Langendorff-perfused hearts from adult female Wistar rats. Al3+ decreased the development of isovolumic systolic pressure from 34.3 +/- 2.95 mmHg under control conditions to 11.8 +/- 1.53 mmHg at 100 microM AlCl3 ($P < 0.01$) (diastolic pressure = 0 mmHg). The atrial and ventricular rates also decreased, but only with AlCl3 concentrations greater than 1 microM (from 180 +/- 5 to 94 +/- 11 bpm for atrial rate and from 180 +/- 5 to 78 +/- 7 bpm for ventricular rate). Reduction of coronary flow was also observed, reaching 60% at 100 microM Al3+. A delay in atrioventricular conduction occurred at 10 microM Al3+, increasing progressively up to 100 microM (62.3 +/- 4 ms in the Al(3+)-free solution to 143 +/- 34 ms in the presence of 100 microM Al3+, $P < 0.01$, ANOVA). QRS duration did not change as a function of increasing Al3+ concentrations (37.1 +/- 1.7 ms in the Al(3+)-free solution vs 32.1 +/- 1.6 ms in the presence of 100 microM Al3+). No qualitative changes in ECG were observed. These data show that the toxic effects of Al3+ on the myocardium are reflected in reduced systolic pressure development and coronary flow and increased PR interval. These effects are discussed in terms of the inhibition of nucleotide hydrolysis by Al3+.

http://www.ncbi.nlm.nih.gov/pubmed/8173535

“These data show that the toxic effects of aluminum chloride on the myocardium are reflected in reduced systolic pressure development and coronary flow and increased PR interval.”

Food Additives And Contaminants • January 1995

Estimates of dietary exposure to aluminium

Author information

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Abstract

Daily intakes of aluminium were estimated for 14 age-sex groups based on the Food and Drug Administration's (FDA) Total Diet Study dietary exposure model. The aluminium content of the core foods of the FDA Total Diet Study were determined by analyses, recipe calculation, or literature values and coupled with information on food consumption from the 1987-88 US Department of Agriculture Nationwide Food Consumption Survey. Estimates of aluminium intakes ranged from 0.7 mg/day for 6-11-month-old infants to 11.5 mg/day for 14-16-year-old males. Average intakes for adult men and women were 8-9 and 7 mg/day, respectively. The major contributors to daily intake of aluminium were foods with aluminium-containing food additives, e.g. grain products and processed cheese.

http://www.ncbi.nlm.nih.gov/pubmed/7758626

"Estimates of aluminium intakes ranged from 0.7 mg/day for 6-11-month-old infants to 11.5 mg/day for 14-16-year-old males. Average intakes for adult men and women were 8-9 and 7 mg/day, respectively."

“Although aluminum (Al) contributes to a variety of cognitive dysfunctions and mental diseases, the underlying mechanisms of Al interactions with the nervous system are still unknown.”

Experimental Neurology • July 1995

Aluminum impairs hippocampal long-term potentiation in rats in vitro and in vivo

Author information

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Abstract

Although aluminum (Al) contributes to a variety of cognitive dysfunctions and mental diseases, the underlying mechanisms of Al interactions with the nervous system are still unknown. We have studied the action of Al on synaptic transmission and long-term potentiation (LTP) by performing electrophysiological recordings both in vivo, using freely moving animals, and in vitro, using hippocampal slices. In vivo recordings of the population spikes (PSs) of dentate gyrus granule cells in response to medial perforant path stimulation were performed on both acutely and chronically (Al each day for 5 days) intraventricularly injected animals. Acute Al-infusion (calculated brain concentrations of 0.27, 0.68, and 2.7 micrograms/ml) had no influence on baseline values. Al at 0.27 microgram/ml did not alter the induction and maintenance of LTP, but 0.68 and especially 2.7 micrograms/ml Al lead to a reduction in LTP, and the potentiation declined to baseline within 2 h. In chronic animals their neuronal responsiveness was reduced and in 30% of the rats the PS was completely lost. High-frequency tetanization failed to induce LTP. In slices, field potentials were evoked stimulating Schaffer collaterals and recording pyramidal cells of the CA1 region. Bath application of 0.68 microgram/ml Al increased the baseline amplitude of the PS slightly, whereas 2.7 micrograms/ml decreased the amplitude and concentrations > 5.4 micrograms/ml blocked the PS completely. Induction of LTP in the presence of 0.68 microgram/ml Al led to a smaller increase of the PS amplitude compared to controls, but the duration of LTP was not affected. In the presence of 2.7 micrograms/ml Al LTP was further reduced and declined to baseline levels within 60 min. Given that LTP is a form of synaptic plasticity underlying some forms of learning, our data suggest that both preparations are suitable models for investigating actions of Al-induced neurotoxicity.

http://www.ncbi.nlm.nih.gov/pubmed/?term=7672040

Neurotoxicology And Teratology • July 1995

Reproductive and developmental toxicity of aluminum: a review

Author information

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Abstract

It is well known that aluminum is a developmental toxicant when administered parenterally. However, until recently, there was little concern about embryo/fetal consequences of aluminum ingestion because bioavailability was considered low. The importance of the route of exposure and the chemical form of the aluminum compound on the developmental toxicity of this element are now well established. Although no evidence of maternal and embryo/fetal toxicity was observed when high doses of aluminum hydroxide were given orally to pregnant rats and mice during organogenesis, signs of maternal and developmental toxicity were found in mice when aluminum hydroxide was given concurrently with citric or lactic acids. On the other hand, studies in rabbits have shown that aluminum-induced behavioral toxicity is greater in adult and aged animals than in young adults. However, maternal dietary exposure to excess A1 during gestation and lactation which did not produce maternal toxicity would be capable of causing permanent neurobehavioral deficits in weanling mice and rats. Adverse effects of parenteral aluminum administration on the mouse male reproductive system have also been reported. The embryo/fetal toxicity of aluminum administration, the potential reproductive toxicology of aluminum exposure, and the neurodevelopmental effects of aluminum are here reviewed.

http://www.ncbi.nlm.nih.gov/pubmed/?term=7565498

“The embryo/fetal toxicity of aluminum administration, the potential reproductive toxicology of aluminum exposure, and the neurodevelopmental effects of aluminum are here reviewed.”

Vaccine • October 1995

Adjuvants for human vaccines— current status, problems and future prospects

Author information

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Abstract

Adjuvants help antigen to elicit an early, high and long-lasting immune response with less antigen, thus saving on vaccine production costs. In recent years, adjuvants received much attention because of the development of purified, subunit and synthetic vaccines which are poor immunogens and require adjuvants to evoke the immune response. With the use of adjuvants immune response can be selectively modulated to major histocompatibility complex (MHC) class I or MHC class II and Th1 or Th2 type, which is very important for protection against diseases caused by intracellular pathogens such as viruses, parasites and bacteria (Mycobacterium). A number of problems are encountered in the development and use of adjuvants for human vaccines. The biggest issue with the use of adjuvants for human vaccines, particularly routine childhood vaccines, is the toxicity and adverse side-effects of most of the adjuvant formulations. At present the choice of adjuvants for human vaccination reflects a compromise between a requirement for adjuvanticity and an acceptable low level of side-effects. Other problems with the development of adjuvants include restricted adjuvanticity of certain formulations to a few antigens, use of aluminum adjuvants as reference adjuvant preparations under suboptimal conditions, non-availability of reliable animal models, use of non-standard assays and biological differences between animal models and humans leading to the failure of promising formulations to show adjuvanticity in clinical trials. The most common adjuvants for human use today are still aluminum hydroxide and aluminum phosphate, although calcium phosphate and oil emulsions also have some use in human vaccinations. During the last 15 years much progress has been made on development, isolation and chemical synthesis of alternative adjuvants such as derivatives of muramyl dipeptide, monophosphoryl lipid A, liposomes, QS21, MF-59 and immunostimulating complexes (ISCOMS). Other areas in adjuvant research which have received much attention are the controlled release of vaccine antigens using biodegradable polymer microspheres and reciprocal enhanced immunogenicity of protein-polysaccharide conjugates. Biodegradable polymer microspheres are being evaluated for targeting antigens on mucosal surfaces and for controlled release of vaccines with an aim to reduce the number of doses required for primary immunization. Reciprocal enhanced immunogenicity of protein-polysaccharide conjugates will be useful for the development of combination vaccines.

http://www.ncbi.nlm.nih.gov/pubmed/8585280

“Adjuvants help antigen to elicit an early, high and long-lasting immune response with less antigen, thus saving on vaccine production costs.

Journal Of Inorganic Biochemistry • November 1995

Spectroscopic study of the interaction of aluminum ions with human transferrin

Author information

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Abstract

Transferrin is the plasma protein responsible for transporting Fe3+ from the absorption to the utilization site. Interactions of apo- and holo-transferrin with Al3+ were studied by circular dichroism (CD), UV-visible, and fluorescence spectrometry. Binding of Al3+ to both metal-ion binding sites of apo-transferrin was confirmed by fluorescence studies. No interaction of Al3+ with holo-transferrin was observed, indicating that Al3+ cannot displace Fe3+ under the experimental conditions employed. An increase in tryptophan fluorescence (lambda max at 330 nm) by excitation at either 280 or 295 nm was observed after Al3+ interaction with apo-transferrin. There was no shift in wavelength of the fluorescence band of apo-transferrin after interaction with Al3+, but the intensity did increase. Since excitation at 295 nm is specific for tryptophan residues, tryptophan but not tyrosine must be responsible for the change in fluorescence intensity. Decreased fluorescence is the result of Fe3+ binding to apo-transferrin. The CD spectrum of apo-transferrin was slightly affected in the far UV by Al3+ binding, but a salient change was noted in the near UV at approximately 288 nm where tyrosine and tryptophan absorb. It is concluded that a small conformational change in the protein was induced by Al3+ binding to apo-transferrin.

http://www.ncbi.nlm.nih.gov/pubmed/8586971

“It is concluded that a small conformational change in the protein was induced by Al3+ binding to apo-transferrin.”

Biochimica et Biophysica Acta • January 1996

Altered calcium homeostasis: a possible mechanisms of aluminium-induced neurotoxicity

Author information

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Abstract

The effect of aluminium, A1(3+) (10 mg/kg body weight/day i.p.) for a period of 4 weeks was examined on the calcium homeostatic mechanisms in rat central nervous system. Incubation of synaptosomes prepared from rat brain, with aluminium in vitro had a detrimental effect on the activity of Ca2+ ATPase which could be reversed completely on exogenous addition of desferrioxamine (10 microM) and partially with glutathione (1 mM). In vivo administration also revealed a similar observation. A marked increase in the levels of intracellular calcium was observed after aluminium treatment. Concomitant to the increased levels of intracellular calcium, there was an increase in the levels of lipid peroxidation and a consequent decrease in fluidity of synaptic plasma membranes. In addition, aluminium also had an inhibitory effect on the depolarization-induced calcium uptake which was found to be of a competitive type. The biological activity of calcium regulatory proteins calmodulin and protein kinase C was considerably affected by aluminium. The results suggest that aluminium exerts its toxic effects by modification of the intracellular calcium messenger system with detrimental consequences on neuronal functioning.

http://www.ncbi.nlm.nih.gov/pubmed/8611646

“The results suggest that aluminium exerts its toxic effects by modification of the intracellular calcium messenger system with detrimental consequences on neuronal functioning.”

“Macrophages at the base of human gut associated lymphoid tissue (GALT),

become loaded early in life with dark granular pigment that is rich in aluminium ...”

Gut • March 1996

Characterisation of inorganic microparticles in pigment cells of human gut associated lymphoid tissue

Author information

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Abstract

Macrophages at the base of human gut associated lymphoid tissue (GALT), become loaded early in life with dark granular pigment that is rich in aluminium, silicon, and titanium. The molecular characteristics, intracellular distribution, and source of this pigment is described. Laser scanning and electron microscopy showed that pigmented macrophages were often closely related to collagen fibres and plasma cells in GALT of both small and large intestine and contained numerous phagolysosomes, previously described as granules, that are rich in electron dense submicron sized particles. Morphological assessment, x ray microanalysis, and image electron energy loss spectroscopy showed three distinct types of microparticle: type I - spheres of titanium dioxide, 100-200 nm diameter, characterised as the synthetic food-additive polymorph anatase; type II - aluminosilicates, < 100-400 nm in length, generally of flaky appearance, often with adsorbed surface iron, and mostly characteristic of the natural clay mineral kaolinite; and type III - mixed environmental silicates without aluminium, 100-700 nm in length and of variable morphology. Thus, this cellular pigment that is partly derived from food additives and partly from the environment is composed of inert inorganic microparticles and loaded into phagolysosomes of macrophages within the GALT of all human subjects. These observations suggest that the pathogenicity of this pigment should be further investigated since, in susceptible individuals, the same intracellular distribution of these three types of submicron particle causes chronic latent granulomatous inflammation.

Full Report

http://www.ncbi.nlm.nih.gov/pmc/articles/PMC1383068/

“... the mechanisms of Aluminum neurotoxicity are reviewed ...”

Journal Of Toxicology And Environmental Health • August 1996

Can the mechanisms of aluminum neurotoxicity be integrated into a unified scheme?

Author information

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Abstract

Regardless of the host, the route of administration, or the speciation, aluminum is a potent neurotoxicant. In the young adult or developmentally mature host, the neuronal response to Al exposure can be dichotomized on morphological grounds. In one, intraneuronal neurofilamentous aggregates are formed, whereas in the other, significant neurochemical and neurophysiological perturbations are induced without neurofilamentous aggregate formation. Evidence is presented that the induction of neurofilamentous aggregates is a consequence of alterations in the posttranslational processing of neurofilament (NF), particularly with regard to phosphorylation state. Although Al has been reported to impact on gene expression, this does not appear to be critical to the induction of cytoskeletal pathology. In hosts responding to Al exposure without the induction of cytoskeletal pathology, impairments in glucose utilization, agonist-stimulated inositol phosphate accumulation, free radical-mediated cytotoxicity, lipid peroxidation, reduced cholinergic function, and altered protein phosphorylation have been described. The extent to which these neurochemical modifications correlate with the induction of a characteristic neurobehavioral state is unknown. In addition to these paradigms, Al is toxic in the immediate postnatal interval. Whether unique mechanisms of toxicity are involved during development remains to be determined. In this article, the mechanisms of Al neurotoxicity are reviewed and recommendations are put forth with regard to future research. Primary among these is the determination of the molecular site of Al toxicity, and whether this is based on Al substitution for divalent metals in a number of biological processes. Encompassed within this is the need to further understand the genesis of host- and developmental-specific responses.

http://www.ncbi.nlm.nih.gov/pubmed/?term=8772801

Journal Of Toxicology And Environmental Health • August 1996

Speciation of aluminum in biological systems

Author information

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Abstract

As a “hard”, trivalent metal ion, Al3- binds strongly to oxygen-donor ligands such as citrate and phosphate. The aqueous coordination chemistry of Al is complicated by the tendency of many Al complexes to hydrolyze and form polynuclear species, many of which are sparingly soluble. Thus there is considerable variation among the Al stability constants reported for several important ligands. The complexity in the aqueous chemistry of Al has also affected Al toxicity studies, which have often utilized poorly characterized Al stock solutions. Serum fractionation studies show that most Al is protein bound, primarily to the serum iron transport protein transferrin. Albumin appears to play little, if any, role in serum transport. There is little agreement as to the speciation of the remaining low-molecular mass fraction of serum Al. The lability of the Al3+ion precludes the simple separation and identification of individual Al complexes. Computational methods are available for detailed computer calculations of the Al speciation in serum, but efforts in this area have been severely hampered by the uncertainties regarding the stability constants of the low molecular mass Al complexes with citrate, phosphate, and hydroxide. Specific recommendations for further research on Al speciation include: (1) Determine more accurate Al stability constants with critical low molecular mass ligands such as citrate and phosphate; (2) supplement traditional potentiometric studies on Al complexes with data from other techniques such as 27Al-NMR and accelerator mass spectrometry with 26Al; (3) develop new methods for generating reliable linear free energy relationships for Al complexation; (4) determine equilibrium and rate constants for Al binding to transferrin at 37 degrees C; (5) confirm the possible formation of low-molecular-mass Al-protein complexes following desferrioxamine therapy; (6) continue research efforts to incorporate kinetic considerations into the present equilibrium speciation calculations; (7) improve methods for preparing chemically well-defined stock solutions for toxicological studies; (8) incorporate more detailed speciation data into studies on Al toxicity and pharmacokinetics; and (9) incorporate more detailed speciation data into future epidemiological studies on the relationship between Al toxicity and various water quality parameters.

http://www.ncbi.nlm.nih.gov/pubmed/?term=8772798

[this report explains why determining the fate of aluminum in the human body is so difficult]

Journal Of Toxicology And Environmental Health • August 1996

What we know and what we need to know about developmental aluminum toxicity

Author information

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Abstract

Information concerning developmental aluminum (Al) toxicity is available from clinical studies and from animal testing. An Al toxicity syndrome including encephalopathy, osteomalacia, and anemia has been reported in uremic children receiving dialysis. In addition, some components of the syndrome, particularly osteomalacia, have been reported in non-dialyzed uremic children receiving Al-based phosphate binders, nonuremic infants receiving parenteral nutrition with Al-containing fluids, and nonuremic infants given high doses of Al antacids. The number of children in clinical populations that are at risk of Al toxicity is not known and needs to be determined. Work in animal models (rats, mice, and rabbits) demonstrates that Al is distributed transplacentally and is present in milk. Oral Al administration during pregnancy produces a syndrome including growth retardation, delayed ossification, and malformations at doses that also lead to reduced maternal weight gain. The severity of the effects is highly dependent on the form of Al administered. In the postnatal period, reduced pup weight gain and effects on neuromotor development have been described as a result of developmental exposures. The significance of these findings for human health requires better understanding of the amount and bioavailability of Al in food, drinking water, and medications and from sources unique to infants and children such as breast milk, soil ingestion, and medications used specifically by pregnant women and children. We also need a better understanding of the unique biological actions of Al that may occur during developmental periods, and unique aspects of the developing organism that make it more or less susceptible to Al toxicity.

http://www.ncbi.nlm.nih.gov/pubmed/?term=8772800

“The number of children in clinical populations that are at risk of Al toxicity is not known and needs to be determined.

Work in animal models demonstrates that Aluminum is distributed transplacentally and is present in milk.”

Journal Of Toxicology And Environmental Health • August 1996

Aluminum toxicokinetics

Author information

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Abstract

In this study of the toxicokinetics of aluminum we have examined some of the fundamental issues that currently define our understanding of the toxicology of aluminum in humans. There is a vast literature on this subject, and it was not our aim to review this literature but to use it to develop our understanding of the toxicokinetics of aluminum and to identify critical and unresolved issues related to its toxicity. In undertaking this task we have chosen to define the term toxicokinetics to encompass those factors that influence both the lability of aluminum in a body and the sites at which aluminum is known to accumulate, with or without consequent biological effect. We have approached our objective from the classical pharmacological approach of ADME: the absorption, distribution, metabolism, and excretion of aluminum. This approach was successful in identifying several key deficits in our understanding of aluminum toxicokinetics. For example, we need to determine the mechanisms by which aluminum crosses epithelia, such as those of the gastrointestinal tract and the central nervous system, and how these mechanisms influence both the subsequent transport and fate of the absorbed aluminum and the concomitant nature and severity of the biological response to the accumulation of aluminum. Our hope in highlighting these unresolved issues (summarized in Table 1) is that they will be addressed in future research.

http://www.ncbi.nlm.nih.gov/pubmed/8772799

“... we need to determine the mechanisms by which aluminum crosses epithelia, such as those of the gastrointestinal tract and the central nervous system, and how these mechanisms influence both the subsequent transport and fate of the absorbed aluminum and the concomitant nature and severity of the biological response to the accumulation of aluminum.”

“Subtle neurocognitive and psychomotor effects and electroencephalograph (EEG) abnormalities have been reported at plasma Aluminum levels as low as 50 micrograms/L. Infants could be particularly susceptible to Al accumulation and toxicity ...”

Journal Of Toxicology And Environmental Health • August 1996

Status and future concerns of clinical and environmental aluminum toxicology

Author information

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Abstract

A wide range of toxic effects of aluminum (Al) have been demonstrated in plants and aquatic animals in nature, in experimental animals by several routes of exposure, and under different clinical conditions in humans. Aluminum toxicity is a major problem in agriculture, affecting perhaps as much as 40% of arable soils in the world. In fresh waters acidified by acid rain, Al toxicity has led to fish extinction. Aluminum is a very potent neurotoxicant. In humans with chronic renal failure on dialysis, Al causes encephalopathy, osteomalacia, and anemia. There are also reports of such effects in certain patient groups without renal failure. Subtle neurocognitive and psychomotor effects and electroencephalograph (EEG) abnormalities have been reported at plasma Al levels as low as 50 micrograms/L. Infants could be particularly susceptible to Al accumulation and toxicity, reduced renal function being one contributory cause. Recent reports clearly show that Al accumulation occurs in the tissues of workers with long-term occupational exposure to Al dusts or fumes, and also indicate that such exposure may cause subtle neurological effects. Increased efforts should be directed toward defining the full range of potentially harmful effects in humans. To this end, multidisciplinary collaborative research efforts are encouraged, involving scientists from many different specialties. Emphasis should be placed on increasing our understanding of the chemistry of Al in biological systems, and on determining the cellular and molecular mechanisms of Al toxicity.

http://www.ncbi.nlm.nih.gov/pubmed/?term=8772797

New England Journal Of Medicine • May 1997

Aluminum Neurotoxicity in Preterm Infants Receiving Intravenous-Feeding Solutions

Nicholas J. Bishop, M.D., Ruth Morley,
M.B., B.Chir., J. Philip Day, Ph.D., and Alan Lucas, M.D.

BACKGROUND

Aluminum, a contaminant of commercial intravenous-feeding solutions, is potentially neurotoxic. We investigated the effect of perinatal exposure to intravenous aluminum on the neurologic development of infants born prematurely.

METHODS

We randomly assigned 227 premature infants with gestational ages of less than 34 weeks and birth weights of less than 1850 g who required intravenous feeding before they could begin enteral feeding to receive either standard or specially constituted, aluminum-depleted intravenous-feeding solutions. The neurologic development of the 182 surviving infants who could be tested was assessed by using the Bayley Scales of Infant Development at 18 months of age.

RESULTS

The 90 infants who received the standard feeding solutions had a mean (±SD) Bayley Mental Development Index of 95±22, as compared with 98±20 for the 92 infants who received the aluminum-depleted solutions (P = 0.39). In a planned subgroup analysis of infants in whom the duration of intravenous feeding exceeded the median and who did not have neuromotor impairment, the mean values for the Bayley Mental Development Index for the 39 infants who received the standard solutions and the 41 infants who received the aluminum-depleted solutions were 92±20 and 102±17, respectively (P = 0.02). The former were significantly more likely (39 percent, vs. 17 percent of the latter group; P = 0.03) to have a Mental Development Index of less than 85, increasing their risk of subsequent educational problems. For all 157 infants without neuromotor impairment, increasing aluminum exposure was associated with a reduction in the Mental Development Index (P = 0.03), with an adjusted loss of one point per day of intravenous feeding for infants receiving the standard solutions.

CONCLUSIONS

In preterm infants, prolonged intravenous feeding with solutions containing aluminum is associated with impaired neurologic development.

http://www.nejm.org/doi/full/10.1056/NEJM199705293362203

“In preterm infants, prolonged intravenous feeding with solutions containing aluminum is associated with impaired neurologic development.”

Molecular And Chemical Neuropathology • September 1997

Aluminum potentiates glutamate-induced calcium accumulation and iron-induced oxygen free radical formation in primary neuronal cultures

Author information

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Abstract

Aluminum is a neurotoxic metal that may be involved in the progression of neurodegenerative diseases, including Alzheimer disease and amyotrophic lateral sclerosis (ALS). Although the mechanism of action is not known, aluminum has been shown to alter Ca2+ flux and homeostasis, and facilitate peroxidation of membrane lipids. Since abnormal increases of intracellular Ca2+ and oxygen free radicals have both been implicated in pathways leading to neurodegeneration, we examined the effect of aluminum on these parameters in vitro using primary cultures of cerebellar granule cells. Exposure to glutamate (1-300 microM) caused a concentration-dependent uptake of 45Ca in granule cells to a maximum of 280% of basal. Pretreatment with AlCl3 (1-1000 microM) had no effect on 45Ca accumulation, but increased the uptake induced by glutamate. Similarly, AlCl3 had no effect on intracellular free Ca2+ levels measured using fluorescent probe fura-2, but potentiated the increase induced by glutamate. The production of reactive oxygen species (ROS) was examined using the fluorescent probe dichlorofluorescin. By itself, AlCl3 had little effect on ROS production. However, AlCl3 pretreatment potentiated the ROS production induced by 50 microM Fe2+. These results suggest that aluminum may facilitate increases in intracellular Ca2+ and ROS, and potentially contribute to neurotoxicity induced by other neurotoxicants.

http://www.ncbi.nlm.nih.gov/pubmed/9437657

“Aluminum is a neurotoxic metal that may be involved in the progression of neurodegenerative diseases, including Alzheimer disease and amyotrophic lateral sclerosis ... aluminum may facilitate increases in intracellular Ca2+ and ROS, and potentially contribute to neurotoxicity induced by other neurotoxicants.”

“Although the mechanisms of aluminum absorption have not been elucidated,

both passive and active transcellular processes and paracellular transport are believed to occur.”

Critical Reviews In Clinical Laboratory Science • 1997

Aluminum exposure and metabolism

Author information

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Abstract

Aluminum (Al) is a nonessential, toxic metal to which humans are frequently exposed. Oral exposure to aluminum occurs through ingestion of aluminum-containing pharmaceuticals and to a lesser extent foods and water. Parenteral exposure to aluminum can occur via contaminated total parenteral nutrition (TPN), intravenous (i.v.) solutions, or contaminated dialysates. Inhalation exposure may be important in some occupational settings. The gut is the most effective organ in preventing tissue aluminum accumulation after oral exposure. Typically gastrointestinal absorption of aluminum from diets is < 1%. Although the mechanisms of aluminum absorption have not been elucidated, both passive and active transcellular processes and paracellular transport are believed to occur. Aluminum and calcium may share some absorptive pathways. Aluminum absorption is also affected by the speciation of aluminum and a variety of other substances, including citrate, in the gut milieu. Not all absorbed or parenterally delivered aluminum is excreted in urine. Low glomerular filtration of aluminum reflects that most aluminum in plasma is nonfiltrable because of complexation to proteins, predominantly transferrin. The importance of biliary secretion of aluminum is debatable and the mechanism(s) is poorly understood and appears to be saturable by fairly low oral doses of aluminum.

http://www.ncbi.nlm.nih.gov/pubmed/?term=9405895

“Metal ions are believed to participate in many neurodegenerative conditions.”

Metal-Based Drugs • 1997

Metal Ions in Neuroscience

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Abstract

Metal ions are believed to participate in many neurodegenerative conditions. In excitotoxic cell death there is convincing evidence for the participation of Ca 2+ and Zn 2+ ions although the exact molecular mechanisms by which these metals exert their effects are unclear. Only in one instance has the metal binding site of metalloenzymes been exploited for therapeutic purposes and this is the use of Li+ in the treatment of bipolar affective disorder. Again the exact molecular target is not clear but is likely to involve a Mg2+-dependent enzyme of an intracellular signalling pathway. In Parkinson’s disease, the selective loss of dopaminergic neurones in the substantia nigra may be caused by radical-mediated damage and there is good evidence to suggest that Fe2+ or 3+ is important in promoting formation of radical species. The evidence that free radicals are important in mediating other neurodegenerative conditions is less strong but still substantial enough to suggest that removal of reactive oxygen species or preventing their formation may be a valid approach to therapy.

Full Report

http://www.hindawi.com/archive/1997/532916/abs/

Toxicology And Industrial Health • January 1998

Neurobehavioral alteration in rodents following developmental exposure to aluminum

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Abstract

Aluminum (Al) is one of the most abundant metals in the earth's crust, and humans can be exposed to it from several sources. It is present in food, water, pharmaceutical compounds, and in the environment, e.g., as a result of acid rain leaching it from the soil. Exposure to Al has recently been implicated in a number of human pathologies, but it has not yet been definitely proved that it plays a major causal role in any of them. In this paper we review the effects of developmental exposure of laboratory animals to Al salts as a model for human pathological conditions. The data presented show behavioral and neurochemical changes in the offspring of AL-exposed mouse dams during gestation, which include alterations in the pattern of ultrasonic vocalizations and a marked reduction in central nervous system (CNS) choline acetyltransferase activity. Prenatal Al also affects CNS cholinergic functions under Nerve Growth Factor (NGF) control, as shown by increased central NGF levels and impaired performances in a maze learning task in young-adult mice. The need for more detailed studies to evaluate the risks for humans associated with developmental exposure to Al, as well as the importance of using more than one strain of laboratory animal in the experimental design, is emphasized.

http://www.ncbi.nlm.nih.gov/pubmed/9460176

"The data presented show behavioral and neurochemical changes in the offspring of Aluminum-exposed mouse dams during gestation, which include alterations in the pattern of ultrasonic vocalizations and a marked reduction in central nervous system choline acetyltransferase activity. Prenatal Al also affects central nervous system cholinergic functions under Nerve Growth Factor (NGF) control, as shown by increased central NGF levels and impaired performances in a maze learning task in young-adult mice."

Journal Of Inorganic Biochemistry • July 1998

The precipitation of mucin by aluminium

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Abstract

The interactions of Al with a mucin glycopeptide have been studied. A number of specific reactions were identified the nature of which were dependent upon the Al chemistry in the hydration environment. In particular, Al was observed to precipitate mucin and it is suggested that this proceeded via the intercalation of the hydroxide within the hydrated macroreticular network of the mucin biopolymer. This precipitation of mucin was visible by eye and abolished the viscosity of native mucin. Viscometry indicated that Al was bound by mucin at low pH. At pH > 3 Al formed a low molecular weight complex with mucin which was hydrolytically stable and was not precipitated at pH up to 8. In an additional and competitive reaction Al was bound by mucin and the resultant mucin-Al complex was suggested to be the precursor to self-assembled mucin-Al spheres identified in solution, by photon correlation spectroscopy, and in precipitate using selective histochemistry. The majority of these spherical structures were of sub-micron diameter and, through their interaction with each other, were probably responsible for the observed pH-dependent peaks of mucin solution viscosity. The larger spheres, between 20 and 80 microns in diameter, were only identified in isolated mucin/Al precipitates and, being comparatively rare, were unlikely to have influenced solution viscosities. These large spheres were observed to act as possible nucleation sites for the flocculation of mucin/Al precipitate. Al at concentrations as low as 0.015 mM induced changes in the rheological properties of mucin. Considering the ubiquitous nature of mucin and the degree to which it is conserved within biota the interactions of Al with mucin may have wide ranging implications for biological systems.

http://www.ncbi.nlm.nih.gov/pubmed/9720305

“Aluminum at concentrations as low as 0.015 mM induced changes in the rheological properties of mucin. Considering the ubiquitous nature of mucin and the degree to which it is conserved within biota the interactions of Aluminum with mucin may have wide ranging implications for biological systems.”

Zhongguo Zhong Yao Za Zhi
Chinese Journal Of Chinese Materia Medica • December 1998

Influence of alum on intestinal flora in mice

Author information

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Abstract

OBJECTIVE
To observe the influence of alum on the intestinal microecological balance in normal microorganisms.

METHOD
The mice were administered orally with alum of a small dosage(0.25/kg) and a large dosage(1 g/kg) for half a month, two months and three months, and a micro flora analysis of the mice was carried out at intervals of the above mentioned administrations.

RESULT
The intestinal flora in the animals administered with alum was imbalanced. The counts of bifidobacteria and lactobacilli closely related to human physiological activities were decreased. The counts of pathogenic E. Coli significantly increased; and the longer the animals were treated with alum, the stronger the microecological balance was influenced.

CONCLUSION
Alum could induce imbalance of the normal intestinal flora in mice.

http://www.ncbi.nlm.nih.gov/pubmed/12242827

“The counts of pathogenic E. Coli significantly increased; and the longer the animals were treated with alum, the stronger the microecological balance was influenced.”

“Aluminum toxicity is well documented and contamination of milk formulas has been implicated as the source of accumulation in bone and brain tissues.”

Journal Of Pediatric Gastroenterology And Nutrition • March 1999

Aluminum contents of human milk, cow’s milk, and infant formulas

Author information

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Abstract

BACKGROUND

Aluminum toxicity is well documented and contamination of milk formulas has been implicated as the source of accumulation in bone and brain tissues. The purpose of the current study was to evaluate the aluminum contents of human milk, cow’s milk, and infant formulas.

METHODS

Aluminum contents were determined by atomic absorption spectrometry in samples of human milk in the colostrum, intermediate, and mature stages; infant formulas from eight manufacturers; and various types and brands of commercially available cow’s milk.

RESULTS

Mean aluminum concentration was lowest in human milk (23.4 +/- 9.6 microg/l), and did not differ significantly between colostrum, intermediate-stage and mature-stage milk. Mean aluminum concentration was 70 microg/l in cow’s milk, and 226 microg/l in reconstituted infant formulas. Aluminum concentrations in infant formulas differed markedly among manufacturers; concentration in milk from one of the manufacturers was particularly high (mean, 551 microg/l; range, 302-1149 microg/l). These values are for milk reconstituted with aluminum-free water under laboratory conditions; formulas prepared with tap water in the University Hospital’s infant-feeding unit had even higher aluminum content. Experiments showed that aluminum concentration in the high-aluminum milk could be reduced by more than 70% at the manufacturing stage, by using low aluminum components.

CONCLUSIONS

The results of the present study support the recommendations for infant formula manufacturers to strive to reduce aluminum concentration in their products.

http://www.ncbi.nlm.nih.gov/pubmed/?term=10067727

Zhonghua Shi Yan He Lin Chuang Bing Du Xue Za Zhi
Chinese Journal Of Experimental And Clinical Virology • June 1999

Influence of aluminum adjuvant to experimental rabies vaccine

Author information

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Abstract

OBJECTIVE
To study whether the rabies vaccine for human use should contain aluminum adjuvant.

METHODS
Testing vaccine antibodies and efficacy (ED50), comparing the effect between aluminum adjuvant contained and non-aluminum adjuvant contained vaccines in a new animal model which accords with the rabies field practice.

RESULTS
At fourth and seventh day after immunization, the neutralizing antibody titres of the rabies vaccine containing aluminium adjuvant were much lower than that of the vaccine not containing aluminum adjuvant. In the NIH efficacy test the ED50 of the vaccine containing aluminum adjuvant was 93-132 ng while the ED50 of the vaccine not containing aluminum adjuvant was 221 ng, but the NIH test does not accord with the rabies field practice. In that new animal model, aluminum adjuvant to rabies vaccine had not any promoting effect for preventing and treating rabies.

CONCLUSION
Aluminum adjuvant to rabies vaccine has no advantages, this paper suggests that the vaccines containing and not-containing aluminium adjuvant had better compare in human bodies. If the results are the same as our experiments, the aluminum adjuvant should be eliminated from rabies vaccine for human use.

http://www.ncbi.nlm.nih.gov/pubmed/?term=12569779

“Aluminum adjuvant to rabies vaccine has no advantages, this paper suggests that the vaccines containing and not-containing aluminium adjuvant had better compare in human bodies. If the results are the same as our experiments, the aluminum adjuvant should be eliminated from rabies vaccine for human use.”

Journal Of Leukocyte Biology • February 2000

Particulate adjuvants can induce macrophage survival, DNA synthesis, and a synergistic proliferative response to GM-CSF and CSF-1

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Abstract

The mode of action of immunological adjuvants is not yet completely understood. Many are particulate. Certain antigen-presenting (dendritic) cell populations belong to the monocyte/macrophage lineage and, like other members of the lineage, in some tissues appear to be short-lived. We report that many poorly degradable, particulate adjuvants, for example, aluminum hydroxide, oil-in-water emulsions, calcium phosphate, and silica, enhance murine bone marrow-derived macrophage survival; induction of DNA synthesis was even observed. No evidence could be found for a requirement for endogenous granulocyte-macrophage colony-stimulating factor (GM-CSF) or macrophage-CSF (M-CSF or CSF-1). Synergy for the proliferative effects was noted in the presence of added GM-CSF or CSF-1. It is suggested from these in vitro findings that one function of certain particulate adjuvants may be to increase by enhanced survival or even proliferation the number of cells available for subsequent antigen presentation and cytokine production.

http://www.ncbi.nlm.nih.gov/pubmed/?term=10670584

“The mode of action of immunological adjuvants is not yet completely understood.”

Presse Medicale Paris • February 2000

Macrophagic myofasciitis Study and Research Group on Acquired and Dysimmunity-related muscular diseases (GERMMAD)

Author information

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Abstract

Macrophagic Myofasciitis

A most unusual inflammatory myopathy, first described by Germmad had been reported with increasing frequency since 1993 in the leading French myopathology centers. We present our experience with this new disease: macrophagic myofasciitis.

CLINICAL FEATURES

By November 1999, 70 cases of macrophagic myofasciitis had been recorded since our first description. The first 22 patients (sex ratio M/F = 1:3) referred with the presumptive diagnosis of polymyositis (n = 11), polymyalgia rheumatica (n = 5), mitochondrial cytopathy (n = 4), and congenital myopathy or muscle dystrophy (n = 1 each). Symptoms included myalgia (91%), anthralgia (68%), marked asthenia (55%), muscle weakness (45%), and fever (32%).

LABORATORY FINDINGS

Abnormal laboratory findings included elevated CK levels (50%), markedly increased erythrocyte sedimentation rate (37%), and myopathic EMG (35%). Muscle biopsy showed a unique myopathological pattern characterized by: i) centripetal infiltration of epimysium, perimysium and perifascicular endomysium by sheets of large cells of the monocyte/macrophage lineage (CD68+, CD1a-, S100-, with a PAS-positive content; ii) absence of necrosis, of both epithelioid and giant cells, and of mitotic figures; iii) presence of occasional CD8+ T-cells; iv) inconspicuous muscle fiber damage. The picture was easily distinguishable from sarcoid myopathy and fasciitis-panniculitis syndromes. The infectious diseases know to be associated with reactive histiocytes, including Whippleís disease, Mycobacterium avium intracellulare infection and malakoplakia, could not be documented. Patients improved under corticosteroid therapy and/or immunomodulatory therapeutic.

CONCLUSION

A new inflammatory muscle disorder, characterized by a distinctive pathological pattern of macrophagic myofasciitis is emerging in France.

http://www.ncbi.nlm.nih.gov/pubmed/10705901

“A most unusual inflammatory myopathy, first described by Germmad had been reported with increasing frequency since 1993 in the leading French myopathology centers. We present our experience with this new disease: macrophagic myofasciitis.”

Pharmacology And Toxicology • March 2000

Effects of various aluminium compounds given orally to mice on Al tissue distribution and tissue concentrations of essential elements

Author information

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Abstract

To evaluate the risk of gastrointestinal long-term aluminium (Al) exposure, aluminium distribution and the levels of the following essential elements: Ca, Mg, Zn, Cu, and Fe in tissue were studied. Aluminium was administered in drinking water as aluminium chloride, dihydroxyaluminium sodium carbonate or aluminium hydroxide. Mice (strain Pzh:SFIS) were exposed to a total dose of 700 mg Al in long-term treatment (for each Al compound n = 15). Concentrations of Al, Ca, Mg, Zn, Cu, and Fe in stomach, kidneys, bone and liver were analyzed by atomic absorption spectrometry. After AlCl3 treatment, aluminium was found to accumulate in all tested tissues. A significant decrease in Fe concentration in liver and Zn in kidneys was observed in comparison to concentrations of these elements in the control group. In the Al(OH)3-treated group, accumulation of aluminium was observed in bone only and decline of Fe concentration in stomach and Cu in liver and kidney. In the NaAl(OH)2CO3-treated group the increase in Al concentration was significant in bone; there was no change in concentration of essential elements in the examined tissues. The observed aluminium accumulation was not accompanied by changes in Ca and Mg concentration except for bone. This study showed that oral administration as a route of Al exposure can result in diverging accumulation of aluminium in tissues, the concentration depending on the chemical form.

Full Report

http://onlinelibrary.wiley.com/doi/10.1034/j.1600-0773.2000.pto860308.x/epdf

“This study showed that oral administration as a route of Aluminum exposure can result in diverging accumulation of aluminium in tissues ...”

“Complaints about ... a mysterious muscle ailment

have prompted researchers to take a fresh look at the use of aluminum adjuvants ... This month,

as some 70 scientists gathered here for 2 days of often vigorous discussion of the findings about the muscle ailment,

a larger question hung over the gathering: Will aluminum be the next battleground in the vaccine wars?”

Science • May 2000

Public health: Aluminum is put on trial as a vaccine booster

Malakoff D.

SAN JUAN, PUERTO RICO—Complaints about vaccine safety and debate over a mysterious muscle ailment have prompted researchers to take a fresh look at the use of aluminum adjuvants, which are used to cause the immune system to react earlier, more potently, and more persistently to the antigen contained in the vaccine. This month, as some 70 scientists gathered here for 2 days of often vigorous discussion of the findings about the muscle ailment, a larger question hung over the gathering: Will aluminum be the next battleground in the vaccine wars?

http://www.sciencemag.org/content/288/5470/1323.summary?sid=82b7933f-c912-48c2-b2cf-40874fa78e61

Allergy • September 2000

Aluminium-induced granulomas after inaccurate intradermal hyposensitization injections of aluminium-adsorbed depot preparations

Author information

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Abstract

BACKGROUND

The development of persistent subcutaneous nodules at the injection sites of aluminium-adsorbed hyposensitization solutions is rare. These nodules have been interpreted as a delayed, granulomatous hypersensitivity reaction to aluminium. We report for the first time a case of persistent intradermal granulomas that developed at the sites of inaccurate intradermal, instead of subcutaneous, hyposensitization injections.

METHODS

An intradermal nodule was excised and processed for histopathology, scanning electron microscopy, and X-ray microanalysis. Intradermal and patch tests with aluminium hydroxide were performed.

RESULTS

Histologically, the nodule presented a pattern of granulomatous inflammatory reaction surrounding foci of necrotic tissue. Scanning electron microscopy and X-ray microanalysis revealed deposits of aluminium within the granulomas. Patch tests with aluminium hydroxide were negative, and intradermal tests caused persistent intradermal granulomas. Subsequent hyposensitization therapy in our department with the usual subcutaneous injections of aluminium-adsorbed allergen extracts was well tolerated by the patient.

CONCLUSIONS

Local toxic effects of aluminium may be crucial in the development of persistent intradermal injection-site granulomas. Such intradermal nodules may develop even if the subcutaneous route is well tolerated. We conclude that inaccurate intradermal injections of aluminium-containing solutions have to be strictly avoided.

Full Report

http://onlinelibrary.wiley.com/doi/10.1034/j.1398-9995.2000.00501.x/full

“We report for the first time a case of persistent intradermal granulomas that developed at the sites of inaccurate intradermal, instead of subcutaneous, hyposensitization injections.”

Aluminum Compounds

Prepared for Scott Masten, Ph.D., National Institute of Environmental Health Sciences P.O. Box 12233
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EXECUTIVE SUMMARY

Human Toxicity

The effects of aluminum on humans have been extensively reviewed. Overall, there is little indication that aluminum is acutely toxic for the general population; few cases of acute aluminum toxicity during alum therapy (i.e., alum bladder irrigation) have been reported. Prolonged exposure to aluminum, however, can cause systemic toxicity, mainly affecting the gastrointestinal tract and causing neurological and skeletal effects.

Aluminum is a potent neurotoxic agent in humans. The association between aluminum and characteristics of Alzheimer's disease have prompted numerous studies of all sources of intake of aluminum. Epidemiological and case control studies have examined the potential link between oral exposure to aluminum via drinking water and the disease. The causal role of aluminum, however, remains controversial. Some studies have found a significant relationship between the exposure to aluminum in water and an increased risk of Alzheimer's disease, while other studies have not. There is … convincing evidence that aluminum is the causative agent in dialysis dementia, which is seen in patients undergoing long-term hemodialysis.

Developmental effects such as encephalopathy, bone disease, microcytic anemia, and rickets have occurred in premature infants with reduced or failed renal function receiving aluminum-containing treatment (e.g., dialysate or aluminum-based phosphate binders) and in nonuremic infants receiving parenteral nutrition with aluminum-containing fluids or high doses of aluminum antacids. There are no adequate studies of the long-term effects of aluminum exposure on brain development and skeletal maturation.

No immunotoxicity studies are available. Few cases, however, report of hypersensitivity to aluminum following dermal application or parenteral administration. There have also been no reports of genetic or reproductive effects in humans.

In mice, oral administration of aluminum as aluminum ammonium sulfate decreased dopamine, dihydroxyphenylacetic acid, and homovanillic acid levels in the hypothalamus, and aluminum lactate increased the 2-thiobarbituric acid reactive substances (TBARS) in the brain but decreased brain stem weight.

In rats, oral administration of aluminum as the sulfate, nitrate, chloride, hydroxide, citrate, and lactate resulted in aluminum accumulation in bone, brain, spleen, liver, heart, gastrointestinal tract, and spleen. Significant decreases occurred in body weight, water consumption, urine volume, plasma glutamic-pyruvic transaminase, serum triglycerides, serum iron concentration, and alkaline phosphatase, ATP, ADP, and AMP, as well as in motor activity. Additional health effects include changes in the cytological and enzymatic content of the lavage fluid, inhibition of colony-forming units-erythroid (CFU-E), and neurobehavioral effects.

Subcutaneous (s.c.) injections of aluminum produced a significant decrease in iron levels in plasma and the striatum. Significant aluminum accumulation was induced in the striatum, hippocampus, and cortex, and in the hippocampus, TBARS production was increased.

Reproductive and Teratological Effects

Reproductive toxicity and teratogenicity from aluminum compounds has been reported in a number of papers. Reproductive effects observed in male mice, rats, or dogs given aluminum compounds orally or s.c. included repressed sexual behavior, decreased spermatogenesis, or other effects on the testes, sperm duct, and/or epididymis. Reproductive effects from oral administration to female rats included irregularity of the estrus cycle of female offspring or effects on the ovaries or fallopian tubes in treated adults. Maternal toxicity was observed in several studies in which pregnant mice, rats, or rabbits were administered aluminum compounds orally, i.p., or s.c. during gestation. Developmental toxicity from oral, i.p., or s.c. aluminum compound administration was also noted in some rat and mouse studies. Teratogenic effects induced by oral, i.p., or s.c. administration of aluminum compounds included skeletal or musculoskeletal variations, cleft palate or other craniofacial malformations, cardiovascular system abnormalities, and other unspecified physical effects. Injection of aluminum compounds into the yolk sac of fertilized chicken eggs induced similar developmental malformations. Neurotoxic effects were observed when aluminum compounds were given orally to mice, rats, or rabbits. A number of studies were also found that reported no reproductive, maternal, developmental toxicity or teratogenicity from oral, inhalation, i.p., or s.c. administration of aluminum compounds.

Genotoxicity

In one acellular assay, aluminum was found to bind to DNA through chelation. It was also found to reduce 3H-thymidine incorporation in a transformed cell line, indicating that aluminum compounds may impede cell cycle progression. Aluminum compounds were not mutagenic in the preponderance of Salmonella typhimurium and Escherichia coli studies. Only one study reported a positive mutagenic response, in which aluminum acetylacetonate was tested on S. typhimurium strain TA104 in the absence of metabolic activation. Effects induced in vitro by aluminum compounds included crosslinking of chromosomal proteins in rat ascites hepatoma cells, anaphasic changes in BALB/c mouse 3T3 cells, and formation of DNA-protein crosslinks, micronuclei, sister chromatic exchanges (SCEs), and chromosomal aberrations in cultured human lymphocytes. Effects induced in vivo included SCEs in mice and sheep, delayed mitosis in mice and sheep, and formation of micronucleated polychromatic lymphocytes in mice, and chromosomal aberrations in rats and mice.

Neurotoxicity

Dementia in dialysis patients and encephalopathy in infants undergoing parenteral nutrition are well known examples of aluminum intoxication in humans. Numerous in vitro studies and epidemiological studies have examined the possible role of aluminum in Alzheimer's disease, other dementias, and cognitive dysfunction.

Numerous animal studies, particularly orally studies in mice and rats, show that aluminum compounds are neurotoxic, but species variation exist. The toxicity is characterized by progressive neurological impairment leading to death associated with repeated seizures. Morphologically, the progressive encephalopathy, associated with neurofibrillary pathology in neurons mostly in the spinal cord, brain stem, and the hippocampus and cingulated gyrus of the cortex, has been induced by aluminum in susceptible animals such as the rabbit, cat, guinea pig, and ferret when given as intrathecal, intracerebral, and subcutaneous injections. For example, in cats and rabbits intracerebral injections of soluble aluminum compounds resulted in impairment in learning and memory, and in rabbits repeated subcutaneous injections affected classical conditioning, while single or repeated intracisternal injection of metallic aluminum altered motor function. Oral administration of aluminum compounds, however, produced no encephalopathy or epilepsy but resulted in behavioral impairment.

Neurotoxicology • February 2001

Differential toxicity of aluminum salts in human cell lines of neural origin: implications for neurodegeneration

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Abstract

Aluminum is highly oxophilic and its minerals are usually found surrounded by six oxygen atoms. A role for the metal has been established in dialysis encephalopathy and Al-induced osteomalacia. The metal has been implicated in Alzheimer's disease but the issue is at present controversial. Human cell lines of neural origin were utilized to study the effect of lipophilic aluminum acetylacetonate and non-lipophilic aluminum sulfate on cell proliferation and viability. Although analysis of Al species in the cell culture media demonstrated that there are positively charged Al species present in solutions prepared with both Al salts, only the aluminum acetylacetonate salt caused changes in cell proliferation and viability. Therefore, the lipophilic nature of the organic Al salt is a critical determinant of toxicity. The effect of aluminum acetylacetonate was dose-dependent and time-dependent. Neuroblastoma (SK-N-SH) cells were more susceptible to decreased cell proliferation although the lipophilic Al salt was more toxic to the glioblastoma (T98G) cells. While the toxicity of aluminum acetylacetonate was inhibited in the T98G cells by the addition of phosphate, the same treatment did not reverse cell death in the SK-N-SH cells. Thus, the mechanism of Al toxicity appears to be different in the two cell lines. It is possible that the principal neurotoxic target of the metal is glial and when these cells are in a compromised state, this may secondarily impact the neuronal population and thus eventually lead to neurodegeneration.

http://www.ncbi.nlm.nih.gov/pubmed/11307852

"It is possible that the principal neurotoxic target of the metal is glial and when these cells are in a compromised state, this may secondarily impact the neuronal population and thus eventually lead to neurodegeneration."

“Aluminum is a nonessential metal to which humans are frequently exposed.”

Regulatory Toxicology And Pharmacology • February 2001

Safety evaluation of dietary aluminum

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Abstract

Aluminum is a nonessential metal to which humans are frequently exposed. Aluminum in the food supply comes from natural sources, water used in food preparation, food ingredients, and utensils used during food preparations. The amount of aluminum in the diet is small, compared with the amount of aluminum in antacids and some buffered analgesics. The healthy human body has effective barriers (skin, lungs, gastrointestinal tract) to reduce the systemic absorption of aluminum ingested from water, foods, drugs, and air. The small amount of aluminum (<1%) that is systemically absorbed is excreted principally in the urine and, to a lesser extent, in the feces. No reports of dietary aluminum toxicity to healthy individuals exist in the literature. Aluminum can be neurotoxic, when injected directly into the brains of animals and when accidentally introduced into human brains (by dialysis or shrapnel). A study from Canada reports cognitive and other neurological deficits among groups of workers occupationally exposed to dust containing high levels of aluminum. While the precise pathogenic role of aluminum in Alzheimer’s disease (AD) remains to be defined, present data do not support a causative role for aluminum in AD. High intake of aluminum from antacid for gastrointestinal ailments has not been reported to cause any adverse effects and has not been correlated with neurotoxicity or AD. Foods and food ingredients are generally the major dietary sources of aluminum in the United States. Cooking in aluminum utensils often results in statistically significant, but relatively small, increases in aluminum content of food. Common aluminum-containing food ingredients are used mainly as preservatives, coloring agents, leavening agents, anticaking agents, etc. Safety evaluation and approval of these ingredients by the Food and Drug Administration indicate that these aluminum-containing compounds are safe for use in foods.

http://www.ncbi.nlm.nih.gov/pubmed/11259180

Pharmacology And Toxicology • April 2001

Aluminium toxicokinetics: an updated minireview

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Abstract

This MiniReview updates and expands the MiniReview of aluminium toxicokinetics by Wilhelm et al. published by this journal in 1990. The use of 26Al, analyzed by accelerator mass spectrometry, now enables determination of Al toxicokinetics under physiological conditions. There is concern about aluminium in drinking water. The common sources of aluminium for man are reviewed. Oral Al bioavailability from water appears to be about 0.3%. Food is the primary common source. Al bioavailability from food has not been adequately determined. Industrial and medicinal exposure, and perhaps antiperspirant use, can significantly increase absorbed aluminium. Inhalation bioavailability of airborne soluble Al appears to be about 1.5% in the industrial environment. Al may distribute to the brain from the nasal cavity, but the significance of this exposure route is unknown. Systemic Al bioavailability after single underarm antiperspirant application may be up to 0.012%. All intramuscularly injected Al, e.g. from vaccines, may eventually be absorbed. Al distributes unequally to all tissues. Distribution and renal excretion appear to be enhanced by citrate. Brain uptake of Al may be mediated by Al transferrin and Al citrate complexes. There appears to be carrier-mediated efflux of Al citrate from the brain. Elimination half-lives of years have been reported in man, probably reflecting release from bone. Al elimination is primarily renal with < or = 2% excreted in bile. The contribution of food to absorbed Al needs to be determined to advance our understanding of the major components of Al toxicokinetics.

http://www.ncbi.nlm.nih.gov/pubmed/11322172

“All intramuscularly injected Aluminum, e.g. from vaccines, may eventually be absorbed.”

Brain Research Bulletin • May 2001

Aluminium toxicity in the rat brain: histochemical and immunocytochemical evidence

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Abstract

Although the neurotoxic actions of aluminium (Al) have been well documented, its contribution to neurodegenerative diseases such as Alzheimer's disease remains controversial. In the present study, we applied histochemical techniques to identify changes induced by intracerebroventricular Al injections (5.4 microg in 5.5 microl, daily over a period of 5 successive days) in the adult rat brain after survival periods of either 1 or 6 weeks. For both Al- and saline-infused controls, no major signs of gross histological changes were evident in cresyl violet-stained sections. Al (as indicated by the fluorescent Morin staining) was concentrated in white matter of the medial striatum, corpus callosum, and cingulate bundle. Immunoreactivity of astrocytes and phagocytic microglia based on glial fibrillary acidic protein and ED1 markers, respectively, revealed a greater inflammatory response in Al-injected animals compared to controls. Damage of the cingulate bundle in Al-treated animals led to a severe anterograde degeneration of cholinergic terminals in cortex and hippocampus, as indicated by acetylcholinesterase labelling. Our data suggest that the enhancement of inflammation and the interference with cholinergic projections may be the modes of action through which Al may cause learning and memory deficits, and contribute to pathological processes in Alzheimer's disease.

http://www.ncbi.nlm.nih.gov/pubmed/?term=11470325

"Our data suggest that the enhancement of inflammation and the interference with cholinergic projections may be the modes of action through which Aluminum may cause learning and memory deficits, and contribute to pathological processes in Alzheimer's disease."

"... these results firmly establish that aluminium hydroxide-containing vaccines represent the direct cause of the Macrophagic myofasciitis (MMF) lesion."

Brain • September 2001

Macrophagic myofasciitis lesions assess long-term persistence of vaccine-derived aluminium hydroxide in muscle

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Abstract

Macrophagic myofasciitis (MMF) is an emerging condition of unknown cause, detected in patients with diffuse arthromyalgias and fatigue, and characterized by muscle infiltration by granular periodic acid-Schiff's reagent-positive macrophages and lymphocytes. Intracytoplasmic inclusions have been observed in macrophages of some patients. To assess their significance, electron microscopy was performed in 40 consecutive cases and chemical analysis was done by microanalysis and atomic absorption spectrometry. Inclusions were constantly detected and corresponded to aluminium hydroxide, an immunostimulatory compound frequently used as a vaccine adjuvant. A lymphocytic component was constantly observed in MMF lesions. Serological tests were compatible with exposure to aluminium hydroxide-containing vaccines. History analysis revealed that 50 out of 50 patients had received vaccines against hepatitis B virus (86%), hepatitis A virus (19%) or tetanus toxoid (58%), 3-96 months (median 36 months) before biopsy. Diffuse myalgias were more frequent in patients with than without an MMF lesion at deltoid muscle biopsy ($P < 0.0001$). Myalgia onset was subsequent to the vaccination (median 11 months) in 94% of patients. MMF lesion was experimentally reproduced in rats. We conclude that the MMF lesion is secondary to intramuscular injection of aluminium hydroxide-containing vaccines, shows both long-term persistence of aluminium hydroxide and an ongoing local immune reaction, and is detected in patients with systemic symptoms which appeared subsequently to vaccination.

Full Report

http://brain.oxfordjournals.org/content/124/9/1821

Pediatric And Developmental Pathology • March 2002

Aluminum phagocytosis in quadriceps muscle following vaccination in children: relationship to macrophagic myofasciitis

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Abstract

Macrophagic myofasciitis (MMF) is a rare, seemingly emerging entity among adult patients in France. We encountered two children with the first two cases of MMF in North America. A 5-year-old male with chronic intestinal pseudo-obstruction required nighttime parenteral nutrition. Abnormal pupillary reflexes and urinary retention suggested a diffuse dysautonomia, which prompted a neurological diagnostic work-up. A 3-year-old child had developmental delay and hypotonia. Both children received age-appropriate immunizations. Quadriceps muscle biopsy from each child showed the typical patchy, cohesive centripetal infiltration of alpha-1-antitrypsin+, alpha-1-antichymotrypsin+, CD68+, PAS+, CD1a-, S-100-, factor XIII- granular macrophages with adjacent myofiber atrophy, dilated blood vessels, and mild endomysial and perimysial fibrosis. No myonecrosis was observed and no discrete granulomas were seen. A single aluminum peak was demonstrated on energy dispersive X-ray microanalysis. The etiology of the clinical symptoms in these cases and in cases reported as MMF remains intriguing. Despite numerous stains to demonstrate organisms, most infectious causes leading to macrophage activation were ruled out. These cases are being reported to increase awareness of this condition and to encourage a systematic epidemiologic and clinicopathologic study in North America.

http://www.ncbi.nlm.nih.gov/pubmed/11910509

"Macrophagic myofasciitis (MMF) is a rare, seemingly emerging entity among adult patients in France. We encountered two children with the first two cases of MMF in North America."

Vaccine • May 2002

Mechanisms of stimulation of the immune response by aluminum adjuvants

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Abstract

Aluminum adjuvants are widely used in human and veterinary vaccines. They are appropriate adjuvants for vaccines that confer protection by inducing antibodies via the induction of a type 2 immune response, but they do not induce cytotoxic T cell and cell-mediated immunity. The mechanisms by which aluminum adjuvants selectively enhance the immune response are poorly understood. Following exposure to interstitial fluid in vitro and in vivo, most antigens are rapidly desorbed from aluminum adjuvants, suggesting that sustained release of antigen from a depot does not significantly contribute to the adjuvant effect of aluminum compounds. However, the adsorption of antigens onto aluminum salts may result in a high local concentration of antigen at the injection site and enhance the uptake by antigen-presenting cells. Aluminum compounds can further enhance the immune response by direct or indirect stimulation of dendritic cells, activation of complement and by inducing the release of chemokines. The relative importance of these mechanisms remains to be determined.

http://www.ncbi.nlm.nih.gov/pubmed/12184362

“Aluminum compounds can further enhance the immune response by direct or indirect stimulation of dendritic cells, activation of complement and by inducing the release of chemokines. The relative importance of these mechanisms remains to be determined.”

“Dr. Gherardi believes that Macrophagic Myofasciitis, a syndrome of ascending myalgias, fatigue and diffuse musculoskeletal pain, may be related to a chronic immune response to aluminum granulomas persisting at the sites of prior immunization with aluminum adjuvated vaccines.”

Vaccine • May 2002

Macrophagic myofasciitis: a summary of Dr. Gherardi’s presentations

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Abstract

Dr. R.K. Gherardi presented two papers at the symposium, detailing his researches into a proposed new clinical entity which he has entitled Macrophagic Myofasciitis (MMF). In his first paper he described the histopathologic and immunologic characteristics of the condition, and in the second, the clinical and serologic features. Dr. Gherardi believes that MMF, a syndrome of ascending myalgias, fatigue and diffuse musculoskeletal pain, may be related to a chronic immune response to aluminum granulomas persisting at the sites of prior immunization with aluminum adjuvated vaccines.

http://www.ncbi.nlm.nih.gov/pubmed/?term=12184366

“there is no known physiological role for aluminum within the body ...”

Environmental Research • June 2002

Aluminum: impacts and disease

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Abstract

Aluminum is the most widely distributed metal in the environment and is extensively used in modern daily life. Aluminum enters into the body from the environment and from diet and medication. However, there is no known physiological role for aluminum within the body and hence this metal may produce adverse physiological effects. The impact of aluminum on neural tissues is well reported but studies on extraneural tissues are not well summarized. In this review, the impacts of aluminum on humans and its impact on major physiological systems are summarized and discussed. The neuropathologies associated with high brain aluminum levels, including structural, biochemical, and neurobehavioral changes, have been summarized. In addition, the impact of aluminum on the musculoskeletal system, respiratory system, cardiovascular system, hepatobiliary system, endocrine system, urinary system, and reproductive system are discussed.

http://www.ncbi.nlm.nih.gov/pubmed/?term=12123643

“The exact mechanism of aluminum toxicity is not known
but accumulating evidence suggests that the metal can potentiate oxidative and inflammatory events,
eventually leading to tissue damage.”

Toxicology And Industrial Health • August 2002

Aluminum as a toxicant

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Abstract

Although aluminum is the most abundant metal in nature, it has no known biological function. However, it is known that there is a causal role for aluminum in dialysis encephalopathy, microcytic anemia, and osteomalacia. Aluminum has also been proposed to play a role in the pathogenesis of Alzheimer’s disease (AD) even though this issue is controversial. The exact mechanism of aluminum toxicity is not known but accumulating evidence suggests that the metal can potentiate oxidative and inflammatory events, eventually leading to tissue damage. This review encompasses the general toxicology of aluminum with emphasis on the potential mechanisms by which it may accelerate the progression of chronic age-related neurodegenerative disorders.

http://www.ncbi.nlm.nih.gov/pubmed/?term=15068131

"... even intermittent or low-dose use of aluminium-based phosphate binders adds to the total load of this toxin in the bone; thus, aluminium use is inadvisable, even for a 'rescue indication'."

Nephrology, Dialysis, Transplantation • 2002

Aluminium and bone disease in chronic renal failure

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Abstract

Aluminium is absorbed by the intestines and is rapidly transported into bone, where it disrupts mineralization and bone cell growth and activity. Its toxicities result in or exacerbate painful forms of renal osteodystrophy, most notably adynamic bone disease and osteomalacia, but also other forms of the disease. Because aluminium is sequestered in bone for long periods, its toxic effects are cumulative. As a result, even intermittent or low-dose use of aluminium-based phosphate binders adds to the total load of this toxin in the bone; thus, aluminium use is inadvisable, even for a 'rescue indication'. Aluminium blood levels are not a reliable marker of aluminium absorption or organ load in dialysis patients: only stainable aluminium at the mineralization front reflects the histopathological changes observed in bone. Therefore, bone biopsies remain the only approach for definitive diagnosis of aluminium-related bone disease. Most importantly, lack of correlation between overall organ concentrations of a toxin, such as aluminium, and pathological changes does not rule out toxicity. Thus, the specific localization of the toxin is more important than overall organ concentration. What has been observed with aluminium during 25 years of research might be reproduced with other metals that are absorbed, transported and accumulated in bone. What we have learned about the toxicity of aluminium should inform our interpretation of data from studies of other metal-based therapeutics for renal patients. This calls for careful evaluation of any newly introduced therapeutic agents for bone disease in patients lacking excretory kidney function.

http://www.ncbi.nlm.nih.gov/pubmed/?term=11904354

Vaccine • 2002

Workshop Summary Aluminum In Vaccines

Conference report

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Abstract

On May 11–12 in San Juan, Puerto Rico the National Vaccine Program Office (NVPO) sponsored a workshop on aluminum in vaccines. The meeting was attended by a diverse group of vaccinologists, immunologists, experts on metals, pathologists, rheumatologists, and other interested parties. The objectives of this meeting were to: (1) establish a better understanding of the role and need of aluminum as an adjuvant in vaccines; (2) explore the possibility of adverse events due to the use of aluminum in vaccines; and (3) develop a research agenda to expand existing knowledge of the impact of aluminum on the human body. From the Metal Ions in Biology and Medicine International Symposium held immediately prior to the aluminum workshop, we learned about "pervasive uncertainty", a phrase used in this workshop to denote missing data on pharmocokinetics and toxicities of aluminum injected into humans. Even with identification of areas needing further study, it was apparent that aluminum which has been used as a vaccine adjuvant for more than 70 years, has an established safety record with low incidence of reported adverse events.

The first session of the workshop was devoted to important background about immunologic adjuvants in general and aluminum adjuvants in particular. Dr. Robert Hunter, University of Texas, provided a broad overview of the history and development of adjuvants, and the conventional views of their mechanism of action and uses. Aluminum adjuvants have been thought to form a repository of antigen in tissue, to produce particulate antigen for presentation to immune cells, and perhaps to activate complement and other immune enhancers. The immune response to some, but not all, protein antigens is enhanced by aluminum salts, however, these salts have little effect on peptide and polysaccharide antigens. Aluminum adjuvants enhance the primary immunization series, reducing the amount of antigen needed per dose and the number of required doses. They increase the proportion of responders, however, there appears to be little effect of adjuvant in subsequent booster doses.

Dr. Norman Baylor, US Food and Drug Administra- tion, provided a detailed analysis of aluminum adjuvants, as well as regulatory perspectives. The three general types of aluminum-containing adjuvants are: (1) aluminum hydroxide, (2) aluminum phosphate, and (3) alum, or potassium aluminum sulfate. Each of these types of formulations has different isoelectric points, and properties; they are not simply interchangeable. The efficacy of each salt as an adjuvant depends also on the characteristics of the antigens in the vaccine. FDA regulations limit the aluminum content of an individual dose of a vaccine to 0.85 mg. of elemental aluminum. This is equivalent to 15 mg. of alum per dose.

The immunologic advantage conferred by these adjuvants has been well documented, although most of this documentation is found in studies published before 1970. In general, these studies showed that aluminum-adjuvanted vaccines resulted in higher and more prolonged antibody responses than did comparable aqueous vaccines. This advantage was most apparent during primary immunization; there seemed to be little advantage to incorporating adjuvant in booster doses.

The US licensed products that contain aluminum adjuvants include DTP, DTaP, some but not all HIB vaccines, hepatitis B vaccine, and all combination DTaP, HIB, or HB vaccines. Others containing aluminum include hepatitis A vaccine, lyme disease vaccine, anthrax vaccine, and rabies vaccine. Inactivated vaccines that do not contain aluminum salts include IPV and influenza vaccines. Of interest was the fact that there are substantial differences among manufacturers both in the specific aluminum adjuvant used, as well as the amount of that adjuvant, in vaccines such as DTaP and in combination vaccines made by several manufacturers. Dr. Baylor also pointed out that any alteration of a vaccine, such as removal of aluminum in booster doses, would necessitate treating the altered vaccine as a new product requiring the collection of additional clinical data.

Adverse reactions that have been reported with aluminum-containing vaccines are generally local reactions including sterile abscesses, erythema, subcutaneous (SC) nodules, granulomatous inflammation, and contact hypersensitivity. None of these reactions, however, has been sufficiently frequent to arouse concern.

http://archive.hhs.gov/nvpo/nvac/documents/Aluminumws.pdf

Journal Of Inorganic Biochemistry • September 2003

A biogeochemical cycle for aluminium?

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Abstract

The elaboration of biogeochemical cycles for elements which are known to be essential for life has enabled a broad appreciation of the homeostatic mechanisms which underlie element essentiality. In particular they can be used effectively to identify any part played by human activities in element cycling and to predict how such activities might impact upon the lithospheric and biospheric availability of an element in the future. The same criteria were the driving force behind the construction of a biogeochemical cycle for aluminium, a non-essential element which is a known ecotoxicant and a suspected health risk in humans. The purpose of this exercise was to examine the concept of a biogeochemical cycle for aluminium and not to review the biogeochemistry of this element. The cycle as presented is rudimentary and qualitative though, even in this nascent form, it is informative and predictive and, for these reasons alone, it is deserving of future quantification. A fully fledged biogeochemical cycle for aluminium should explain the biospheric abundance of this element and whether we should expect its (continued) active involvement in biochemical evolution.

http://www.ncbi.nlm.nih.gov/pubmed/14507454

“a non-essential element

which is a known ecotoxicant and a

suspected health risk in humans.”

Vaccine • December 2003

Unexpectedly high incidence of persistent itching nodules and delayed hypersensitivity to aluminium in children after the use of adsorbed vaccines from a single manufacturer

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Abstract

During trials of aluminium adsorbed diphtheria-tetanus/acellular pertussis vaccines from a single producer, persistent itching nodules at the vaccination site were observed in an unexpectedly high frequency. The afflicted children were followed in a longitudinal observational study, and the presence of aluminium sensitization was investigated in the children with itching nodules and their symptomless siblings by patch tests. Itching nodules were found in 645 children out of about 76,000 vaccinees (0.8%) after both subcutaneous (s.c.) and intramuscular (i.m.) injection. The itching was intense and long-lasting. So far, 75% still have symptoms after a median duration of 4 years. Contact hypersensitivity to aluminium was demonstrated in 77% of the children with itching nodules and in 8% of the symptomless siblings who had received the same vaccines ($P<0.001$). Children with persistent itching nodules and/or aluminium sensitization should be warned about aluminium containing products (e.g. vaccines and antiperspirants). The reason for the high incidence of itching nodules after SSI vaccines is unknown and should be further investigated.

http://www.ncbi.nlm.nih.gov/pubmed/?term=14604572

“Itching nodules were found in 645 children out of about 76,000 vaccinees after both subcutaneous and intramuscular injection. The itching was intense and long-lasting. So far, 75% still have symptoms after a median duration of 4 years.”

Journal Of Neuroscience Research • February 2004

Chronic exposure to aluminum in drinking water increases inflammatory parameters selectively in the brain

Author information

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Abstract

A link between aluminum (Al) exposure and age-related neurological disorders has long been proposed. Although the exact mechanism by which the metal may influence disease processes is unknown, there is evidence that exposure to Al causes an increase in both oxidative stress and inflammatory events. These processes have also been suggested to play a role in Alzheimer's disease (AD), and exposure to the metal may contribute to the disorder by potentiating these events. Al lactate (0.01, 0.1, and 1 mM) in drinking water for 10 weeks increased inflammatory processes in the brains of mice. The lowest of these levels is in the range found to increase the prevalence of AD in regions where the concentrations of the metal are elevated in residential drinking water (Flaten [2001] Brain Res. Bull. 55:187-196). Nuclear factor-kappaB as well as tumor necrosis factor-alpha (TNF-alpha) and interleukin 1alpha (IL-1alpha) levels were increased in the brains of treated animals. The mRNA for TNF-alpha was also up-regulated following treatment. Enhancement of glial fibrillary acidic protein levels and reactive microglia was seen in the striatum of Al-treated animals. The level of amyloid beta (Abeta40) was not significantly altered in the brains of exposed animals. Insofar as no parallel changes were observed in the serum or liver of treated animals, the proinflammatory effects of the metal may be selective to the brain. Al exposure may not be sufficient to cause abnormal production of the principal component of senile plaques directly but does exacerbate underlying events associated with brain aging and thus could contribute to progression of neurodegeneration.

http://www.ncbi.nlm.nih.gov/pubmed/14743440

"Although the exact mechanism by which the metal may influence disease processes is unknown, there is evidence that exposure to Al causes an increase in both oxidative stress and inflammatory events. Insofar as no parallel changes were observed in the serum or liver of treated animals, the proinflammatory effects of the metal may be selective to the brain."

"... the more detailed mode of action of these adjuvants is still not completely understood."

Vaccine • September 2004

Aluminium adjuvants—in retrospect and prospect

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Abstract

Aluminium compounds have been used as adjuvants in practical vaccination for more than 60 years to induce an early, an efficient and a long lasting protective immunity and are at present the most widely used adjuvants in both veterinary and human vaccines. Although the last two decades of systematic research into the nature of these adjuvants has contributed significantly to understanding their nature and their limitations as Th2 stimulators the more detailed mode of action of these adjuvants is still not completely understood. We have a comprehensive record of their behaviour and performance in practical vaccination, but an empirical approach to optimising their use in new vaccine formulations is still to some extent a necessity. The aim of the present review is to put the recent findings into a broader perspective to facilitate the application of these adjuvants in general and experimental vaccinology.

http://www.ncbi.nlm.nih.gov/pubmed/15315845

Archives Of Toxicology • October 2004

Mitochondrial viability and apoptosis induced by aluminum, mercuric mercury and methylmercury in cell lines of neural origin

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Abstract

Mercury and aluminum are considered to be neurotoxic metals, and they are often connected with the onset of neurodegenerative diseases. In this study, mercuric mercury, methylmercury and aluminum were studied in three different cell lines of neural origin. To evaluate the effects, mitochondrial cytotoxicity and apoptosis induced by the metals were measured after various incubation times. SH-SY5Y neuroblastoma, U 373MG glioblastoma, and RPE D407 retinal pigment epithelial cells were subcultured to appropriate cell culture plates and 0.01-1,000 microM concentrations of methylmercury, mercuric and aluminum chloride were added into the growth medium. In the assay measuring the mitochondrial dehydrogenase activity, WST-1, the cultures were exposed for 15 min, 24 or 48 h before measurement. Cells were allowed to recover from the exposure in part of the study. Apoptosis induced by the metals was measured after 6-, 24- and 48-h exposure times with the determination of activated caspase 3 enzyme. Mitochondrial assays showed a clear dose-response and exposure time-response to the metals. The most toxic was methylmercury (EC50 ~0.8 microM, 48 h), and the most sensitive cell line was the neuroblastoma cell line SH-SY5Y. Furthermore, there was marked mitochondrial activation, especially in connection with aluminum and methylmercury at low concentrations. This activation may be important during the initiation of cellular processes. All the metals tested induced apoptosis, but with a different time-course and cell-line specificity. In microscopic photographs, glioblastoma cells formed fibrillary tangles, and neuroblastoma cells settled along the fibrilles in cocultures of glial and neuronal cell lines during aluminum exposure. The study emphasized the toxicity of methylmercury to neural cells and showed that aluminum alters various cellular activities.

http://www.ncbi.nlm.nih.gov/pubmed/?term=15150681

“Mercury and aluminum are considered to be neurotoxic metals, and they are often connected with the onset of neurodegenerative diseases. The study emphasized the toxicity of methylmercury to neural cells and showed that aluminum alters various cellular activities.”

Journal Of Inorganic Biochemistry • September 2005

Nanomolar aluminum induces pro-inflammatory and pro-apoptotic gene expression in human brain cells in primary culture

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Abstract

Aluminum, the most abundant neurotoxic metal in our biosphere, has been implicated in the etiology of several neurodegenerative disorders including Alzheimer's disease (AD). To further understand aluminum's influence on gene expression, we examined total messenger RNA levels in untransformed human neural cells exposed to 100 nanomolar aluminum sulfate using high density DNA microarrays that interrogate the expression of every human gene. Preliminary data indicate that of the most altered gene expression levels, 17/24 (70.8%) of aluminum-affected genes, and 7/8 (87.5%) of aluminum-induced genes exhibit expression patterns similar to those observed in AD. The seven genes found to be significantly up-regulated by aluminum encode pro-inflammatory or pro-apoptotic signaling elements, including NF-kappaB subunits, interleukin-1beta precursor, cytosolic phospholipase A2, cyclooxygenase-2, beta-amyloid precursor protein and DAXX, a regulatory protein known to induce apoptosis and repress transcription. The promoters of genes up-regulated by aluminum are enriched in binding sites for the stress-inducible transcription factors HIF-1 and NF-kappaB, suggesting a role for aluminum, HIF-1 and NF-kappaB in driving atypical, pro-inflammatory and pro-apoptotic gene expression. The effect of aluminum on specific stress-related gene expression patterns in human brain cells clearly warrant further investigation.

http://www.ncbi.nlm.nih.gov/pubmed/15961160

"The effect of aluminum on specific stress-related gene expression patterns in human brain cells clearly warrant further investigation."

Journal Of Alzheimers Disease • November 2005

Synergistic effects of iron and aluminum on stress-related gene expression in primary human neural cells

Author information

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Abstract

Disturbances in metal-ion transport, homeostasis, overload and metal ion-mediated catalysis are implicated in neurodegenerative conditions such as Alzheimer's disease (AD). The mechanisms of metal-ion induced disruption of genetic function, termed genotoxicity, are not well understood. In these experiments we examined the effects of non-apoptotic concentrations of magnesium-, iron- and aluminum-sulfate on gene expression patterns in untransformed human neural (HN) cells in primary culture using high density DNA array profiling and Western immunoassay. Two week old HN cells were exposed to low micromolar magnesium, iron, or aluminum for 7 days, representing trace metal exposure over one-third of their lifespan. While total RNA yield and abundance were not significantly altered, both iron and aluminum were found to induce HSP27, COX-2, betaAPP and DAXX gene expression. Similarly up-regulated gene expression for these stress-sensing, pro-inflammatory and pro-apoptotic elements have been observed in AD brain. The combination of iron and aluminum together was found to be particularly effective in up-regulating these genes, and was preceded by the evolution of reactive oxygen intermediates as measured by 2',7'-dichlorofluorescein diacetate assay. These data indicate that physiologically relevant amounts of iron and aluminum are capable of inducing Fenton chemistry-triggered gene expression programs that may support downstream pathogenic responses and brain cell dysfunction.

http://www.ncbi.nlm.nih.gov/pubmed/16308480

"These data indicate that physiologically relevant amounts of iron and aluminum are capable of inducing Fenton chemistry-triggered gene expression programs that may support downstream pathogenic responses and brain cell dysfunction."

Food Additives And Contaminants • March 2005

Aluminium content of some foods and food products in the USA, with aluminium food additives

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Abstract

The primary objective was to determine the aluminium (Al) content of selected foods and food products in the USA which contain Al as an approved food additive. Intake of Al from the labeled serving size of each food product was calculated. The samples were acid or base digested and analysed for Al using electrothermal atomic absorption spectrometry. Quality control (QC) samples, with matrices matching the samples, were generated and used to verify the Al determinations. Food product Al content ranged from <1-27,000 mg kg(-1). Cheese in a serving of frozen pizzas had up to 14 mg of Al, from basic sodium aluminium phosphate; whereas the same amount of cheese in a ready-to-eat restaurant pizza provided 0.03-0.09 mg. Many single serving packets of non-dairy creamer had approximately 50-600 mg Al kg(-1) as sodium aluminosilicate, providing up to 1.5 mg Al per serving. Many single serving packets of salt also had sodium aluminosilicate as an additive, but the Al content was less than in single-serving non-dairy creamer packets. Acidic sodium aluminium phosphate was present in many food products, pancakes and waffles. Baking powder, some pancake/waffle mixes and frozen products, and ready-to-eat pancakes provided the most Al of the foods tested; up to 180 mg/serving. Many products provide a significant amount of Al compared to the typical intake of 3-12 mg/day reported from dietary Al studies conducted in many countries.

http://www.ncbi.nlm.nih.gov/pubmed/16019791

“The primary objective was to determine the aluminium (Al) content of selected foods and food products in the USA which contain Al as an approved food additive. Intake of Al from the labeled serving size of each food product was calculated.”

“Aluminum has been associated with several neurodegenerative diseases,
such as dialysis encephalopathy, amyotrophic lateral sclerosis and Parkinsonism dementia
in the Kii peninsula and Guam, and in particular, Alzheimer’s disease.”

Journal Of Alzheimers Disease • November 2005

Effects of aluminum on the nervous system and its possible link with neurodegenerative diseases

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Abstract

Aluminum is environmentally abundant, but not an essential element. Aluminum has been associated with several neurodegenerative diseases, such as dialysis encephalopathy, amyotrophic lateral sclerosis and Parkinsonism dementia in the Kii peninsula and Guam, and in particular, Alzheimer’s disease. Although this association remains controversial, there is increasing evidence which suggests the implication of metal homeostasis in the pathogenesis of Alzheimer’s disease. Aluminum, zinc, copper, and iron cause the conformational changes of Alzheimer’s amyloid-beta protein. Al causes the accumulation of tau protein and amyloid-beta protein in experimental animals. Aluminum induces neuronal apoptosis in vivo as well as in vitro. Furthermore, a relationship between aluminum and the iron-homeostasis or calcium-homeostasis has been suggested. Based on these findings, the characteristics of aluminum neurotoxicity are reviewed, and the potential link between aluminum and neurodegenerative diseases is reconsidered.

http://www.ncbi.nlm.nih.gov/pubmed/16308486

Immunology Letters • January 2006

(How) do aluminium adjuvants work?

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Abstract

The aluminium compounds, originally identified as adjuvants over 70 years ago, remain unique in their widespread application to human vaccines. Given this history, it is surprising that the physicochemical interactions between aluminium compounds and antigens are relatively poorly understood. This has clearly been a contributing factor to vaccine failures, for example, through inappropriate selection of aluminium species or buffers. Similarly, the mechanism(s) of action of aluminium adjuvants are relatively unstudied, although it appears that these agents fail to fit within the current principles underlying activation of the immune response. This review aims to examine recent developments in our understanding of the physicochemical and biological aspects of research into aluminium adjuvants.

http://www.ncbi.nlm.nih.gov/pubmed/16188325?dopt=Abstract

“The aluminium compounds, originally identified as adjuvants over 70 years ago, remain unique in their widespread application to human vaccines. Given this history, it is surprising that the physicochemical interactions between aluminium compounds and antigens are relatively poorly understood.”

Neuromuscular Disorders • May 2006

AlOH3-adjuvanted vaccine-induced macrophagic myofasciitis in rats is influenced by the genetic background

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Abstract

Macrophagic myofasciitis (MMF) is a specific histopathologic lesion involved in the persistence for years of aluminum hydroxide [Al(OH)(3)] at the site of previous intramuscular (i.m.) injection. In order to study mechanisms involved persistence of MMF lesions, we set up an experimental model of MMF-lesion in Sprague-Dawley and Lewis rat, by i.m. injections of 10 microL of an Al(OH)(3)-adjuvanted vaccine. An evaluation carried out over a 12-month period disclosed significant shrinkage of MMF lesions with time. A radioisotopic study did not show significant aluminium uptake by Al(OH)(3)-loaded macrophages. A morphometric approach showed that Lewis rats with Th1-biased immunity had significantly smaller lesions than Sprague-Dawley rats with balanced Th1/Th2 immunity. Concluding, our results indicate that genetic determinatives of cytotoxic T-cell responses could interfere with the clearance process and condition the persistence of vaccine-induced MMF-lesions.

http://www.ncbi.nlm.nih.gov/pubmed/?term=16616846

“Macrophagic myofasciitis (MMF) is ... involved in the persistence for years of aluminum hydroxide at the site of previous intramuscular injection. Concluding, our results indicate that genetic determinatives of cytotoxic T-cell responses could interfere with the clearance process and condition the persistence of vaccine-induced MMF-lesions.”

Journal Of Alzheimers Disease • November 2006

Blood-brain barrier flux of aluminum, manganese, iron and other metals suspected to contribute to metal-induced neurodegeneration

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Abstract

The etiology of many neurodegenerative diseases has been only partly attributed to acquired traits, suggesting environmental factors may also contribute. Metal dyshomeostasis causes or has been implicated in many neurodegenerative diseases. Metal flux across the blood-brain barrier (the primary route of brain metal uptake) and the choroid plexuses as well as sensory nerve metal uptake from the nasal cavity are reviewed. Transporters that have been described at the blood-brain barrier are listed to illustrate the extensive possibilities for moving substances into and out of the brain. The controversial role of aluminum in Alzheimer's disease, evidence suggesting brain aluminum uptake by transferrin-receptor mediated endocytosis and of aluminum citrate by system Xc;{-} and an organic anion transporter, and results suggesting transporter-mediated aluminum brain efflux are reviewed. The ability of manganese to produce a parkinsonism-like syndrome, evidence suggesting manganese uptake by transferrin- and non-transferrin-dependent mechanisms which may include store-operated calcium channels, and the lack of transporter-mediated manganese brain efflux, are discussed. The evidence for transferrin-dependent and independent mechanisms of brain iron uptake is presented. The copper transporters, ATP7A and ATP7B, and their roles in Menkes and Wilson's diseases, are summarized. Brain zinc uptake is facilitated by L- and D-histidine, but a transporter, if involved, has not been identified. Brain lead uptake may involve a non-energy-dependent process, store-operated calcium channels, and/or an ATP-dependent calcium pump. Methyl mercury can form a complex with L-cysteine that mimics methionine, enabling its transport by the L system. The putative roles of zinc transporters, ZnT and Zip, in regulating brain zinc are discussed. Although brain uptake mechanisms for some metals have been identified, metal efflux from the brain has received little attention, preventing integration of all processes that contribute to brain metal concentrations.

http://www.ncbi.nlm.nih.gov/pubmed/17119290

"Although brain uptake mechanisms for some metals have been identified, metal efflux from the brain has received little attention, preventing integration of all processes that contribute to brain metal concentrations."

Archives Of Toxicology • January 2007

The effects of low dose aluminum on hemorheological and hematological parameters in rats

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Abstract

Aluminum (Al) is a nonessential element and humans are constantly exposed to Al as a result of an increase in industrialization and improving technology practices. Al toxicity can induce several clinical disorders such as neurotoxicity, gastrointestinal toxicity, hepatotoxicity, bone diseases, and anemia. This study aimed at evaluating the possible effects of short term and low dose Al exposure on hemorheological and hematological parameters in rats. Fourteen young, male Wistar albino rats were divided into two groups: 1 mg/200 g body weight of aluminum sulfate (Al(2)(SO(4))(3) was injected intraperitoneally to the first group for two weeks, three times a week. The animals of the control group received only physiological saline solution during this period. At the end of the experimental period, anticoagulated blood samples were collected and hematological parameters were determined using an electronic hematology analyzer. Red blood cell (RBC) deformability and aggregation were measured using an ektacytometer (LORCA) and plasma and whole blood viscosities were determined with a Wells-Brookfield cone-plate rotational viscometer. Significant decreases in mean corpuscular volume (MCV), red blood cell (RBC) deformability at low shear stress levels, the aggregation half time (t1/2) and the amplitude (AMP) of aggregation and significant increments in whole blood viscosity (WBV) at native and 40% hematocrit (Hct) of Al-treated rats have been observed. In conclusion, low dose Al(2)(SO(4))(3) exposure for a short-time may be responsible for alterations in either rheological properties of blood or hemorheological properties through a remarkable effect on RBC membrane mechanical properties. These alterations may also play an important role in the development of anemia in the Al-treated animals.

http://www.ncbi.nlm.nih.gov/pubmed/16721596

“In conclusion, low dose Aluminum exposure for a short-time may be responsible for alterations in either rheological properties of blood or hemorheological properties through a remarkable effect on RBC membrane mechanical properties. ”

“It is hypothesized, in the present review, that Aluminum is a potential factor for induction or maintaining the inflammation in Crohn’s Disease ...”

Annals Of The New York Academy Of Science • June 2007

Aluminum is a potential environmental factor for Crohn’s disease induction: extended hypothesis

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Abstract

Aluminum (Al) is a common environmental compound with immune-adjuvant activity and granulomatous inflammation inducer. Al exposure in food, additives, air, pharmaceuticals, and water pollution is ubiquitous in Western culture. Crohn’s disease (CD) is a chronic relapsing intestinal inflammation in genetically susceptible individuals and is influenced by yet unidentified environmental factors. It is hypothesized, in the present review, that Al is a potential factor for induction or maintaining the inflammation in CD. Epidemiologically, CD incidence is higher in urban areas, where microparticle pollution is prevalent. Al immune activities share many characteristics with the immune pathology of CD: increased antigen presentation and APCs activation, many luminal bacterial or dietary compounds can be adsorbed to the metal and induce Th1 profile activity, promotion of humoral and cellular immune responses, proinflammatory, apoptotic, oxidative activity, and stress-related molecule expression enhancement, affecting intestinal bacterial composition and virulence, granuloma formation, colitis induction in an animal model of CD, and terminal ileum uptake. The Al-bacterial interaction, the microparticles homing the intestine together with the extensive immune activity, put Al as a potential environmental candidate for CD induction and maintenance.

http://www.ncbi.nlm.nih.gov/pubmed/?term=17804561

Human Vaccines • July 2007

Effect of alternative aluminum adjuvants on the absorption and immunogenicity of HPV16 L1 VLPs in mice

Author information

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Abstract

Aluminum adjuvants are commonly used in prophylactic vaccines to enhance antigen immunogenicity through induction of high-titer antibody responses. Three major forms of aluminum adjuvants with substantially different physical and chemical properties have been described: aluminum phosphate (AlPO(4)), aluminum hydroxide (AlOH) and amorphous aluminum hydroxyphosphate sulfate (AAHS). Here we describe the effect of these different aluminum adjuvants on the formulation and subsequent immunogenicity in mice of virus-like particles (VLPs) consisting of the L1 protein of Human Papillomavirus (HPV) Type 16. Electron microscopy demonstrated that the physical appearance of the phosphate-containing aluminum adjuvants was markedly different from that of aluminum hydroxide. All three aluminum adjuvants were found to display unique surface charge profiles over a range of pH, while AAHS demonstrated the greatest inherent capacity for adsorption of L1 VLPs. These differences were associated with differences in immunogenicity: anti-HPV L1 VLP responses from mice immunized with AAHS-formulated HPV16 vaccine were substantially greater than those produced by mice immunized with the same antigen formulated with aluminum hydroxide. In addition, HPV L1 VLPs formulated on AAHS also induced a substantial interferon-gamma secreting T cell response to L1 peptides indicating the potential for an enhanced memory response to this antigen. These results indicate that the chemical composition of aluminum adjuvants can have a profound influence on the magnitude and quality of the immune response to HPV VLP vaccines.

http://www.ncbi.nlm.nih.gov/pubmed/17581283

“These results indicate that the chemical composition of aluminum adjuvants can have a profound influence on the magnitude and quality of the immune response to HPV VLP vaccines.”

Free Radical Biology & Medicine • October 2007

Aluminum:
a potential pro-oxidant in sunscreens/sunblocks?

Nicholson S, Exley C.

Scientists at Keele University in Staffordshire have questioned
the safety of aluminium added to sunscreens and sunblocks

The researchers, Scott Nicholson, BSc, and Dr Christopher Exley, PhD, Birchall Centre for Inorganic Chemistry and Materials Science at Keele, measured the aluminium content of sunscreens/sunblocks, which either include or do not include an aluminium salt (for example, aluminium hydroxide, aluminium oxide, aluminium silicate, aluminium stearate, aluminium starch octenylsuccinate) as an ingredient.

Aluminium was present in all seven products tested and its content was of particular significance in three products, each of which listed it as an ingredient. Following numerous enquiries the manufacturers were not forthcoming as to the role of aluminium in their product, except one manufacturer, who confirmed that aluminium hydroxide was added to their product to coat the surface and thereby prevent the agglomeration of another ingredient, titanium dioxide particles.

World Health Organisation guidelines recommend a single application of at least 35mL of a sunscreen/sunblock to achieve the stated sun protection factor. For three of the sunscreens/sunblocks investigated a single application of product would result in 200 mg of aluminium being applied to the skin surface. In addition, WHO guidelines suggest re-application of product every two hours which, for example, for an average day on the beach, would result in up to 1g of aluminium being applied to the skin surface.

Skin is permeable to aluminium salts when, for example, they are topically applied as antiperspirant formulations. It will accumulate in the skin and be transported to sites throughout the body. It is highly likely that the everyday use of sunscreens/sunblocks is an hitherto unrecognised contributor of aluminium to the human body burden of this non-essential metal. Perhaps of immediate significance is the potential for aluminium in the skin to act as a pro-oxidant.

Recent research in the journal Free Radical Biology and Medicine has shown that UV filters in sunscreens promote the formation of reactive oxygen species (ROS) in the nucleated epidermis of the skin. The authors speculate upon the role which might be played by anti-oxidants, either already in the skin or included in sunscreen formulations, in counteracting the pro-oxidant activities of UV filters though they did not consider how the presence of additional pro-oxidants might exacerbate such effects.

Aluminium is one such pro-oxidant and could significantly increase the potential for oxidative damage in the skin. While the relationship between the burgeoning use of sunscreens/sunblocks and the increased incidence of skin cancers and, in particular, melanoma, is highly controversial it has not hitherto been considered that aluminium in these products could be an extremely significant contributing factor. Of course, aluminium is already in the skin surface and may not need to be a component of sunscreens/sunblocks to exacerbate oxidative damage attributed to the application of such products.

http://www.ncbi.nlm.nih.gov/pubmed/17854717

Journal Of Inorganic Biochemistry • October 2007

A systems biology approach to the blood-aluminium problem: the application and testing of a computational model

Author information

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Abstract

Transport and distribution of systemic aluminium are influenced by its interaction with blood. Current understanding is centred upon the role played by the iron transport protein transferrin which has been shown to bind up to 90% of serum total aluminium. We have coined what we have called the blood-aluminium problem which states that the proportion of serum aluminium which, at any one moment in time, is bound by transferrin is more heavily influenced by kinetic constraints than thermodynamic equilibria with the result that the role played by transferrin in the transport and distribution of aluminium is likely to have been over estimated. To begin to solve the blood-aluminium problem and therewith provide a numerical solution to the aforementioned kinetic constraints we have applied and tested a simple computational model of the time-dependency of a putative transferrin ligand (L) binding aluminium to form an Al-L complex with a probability of existence, K(E), between 0% (no complex) and 100% (complex will not dissociate). The model is based upon the principles of a lattice-gas automaton which when ran for K(E) in the range 0.1-98.0% demonstrated the emergence of complex behaviour which could be defined in the terms of a set of parameters (equilibrium value, E(V), equilibrium time, E(T), peak value, P(V), peak time, P(T), area under curve, AUC) the values of which varied in a predictable way with K(E). When K(E) was set to 98% the model predicted that ca. 90% of the total aluminium would be bound by transferrin within ca. 350 simulation timesteps. We have used a systems biology approach to develop a simple model of the time-dependency of the binding of aluminium by transferrin. To use this approach to begin to solve the blood-aluminium problem we shall need to increase the complexity of the model to better reflect the heterogeneity of a biological system such as the blood.

http://www.ncbi.nlm.nih.gov/pubmed/17629565

“Aluminum is a metal with known neurotoxic properties

which are linked to encephalopathy and neurodegenerative diseases.”

Neurotoxicology • November 2007

Occupational aluminum exposure: evidence in support of its neurobehavioral impact

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Abstract

Aluminum is a metal with known neurotoxic properties which are linked to encephalopathy and neurodegenerative diseases. The objectives of the current meta-analysis study were: (1) to summarize neurobehavioral data obtained by epidemiological studies in occupational settings and (2) to analyze confounding within these data. The meta-analysis was based on estimates of effect sizes. Overall effect sizes were obtained by application of a random effects model. The final sample consisted of nine studies examining 449 exposed and 315 control subjects. The mean urinary aluminum concentrations in the exposed groups ranged from 13 to 133 microg/l. Six neuropsychological tests, which yielded 10 performance variables, were analyzed. Nine overall effect sizes indicated an inferior performance for the exposed group. A significant overall effect size (d(RE)=-0.43) was obtained for the digit symbol test measuring speed-related components of cognitive and motor performance. Moreover, the individual effect sizes obtained for this test suggested an exposure-response relationship. Results obtained from either raw or adjusted mean scores revealed that confounding in the data could not be excluded. The results were compared to studies not included here due to a shortage of required data. Similarities were discussed in terms of sensitivity of the tests for detecting aluminum-related changes in brain function. There was concurring evidence from different studies that urinary Al concentrations below 135 microg/l have an impact on cognitive performance. The significant effect for the digit symbol might be related to its multifaceted character which requires functioning in different components of cognitive and motor performance. This feature could possibly turn the test into a screening instrument for neurobehavioral effects. However, additional studies are necessary to verify and to differentiate the effect of aluminum on cognitive performance. From a neuropsychological perspective, implicit and explicit memory, visuo-spatial and central odor processing should be examined. A measure of verbal intelligence should be included in order to address the influence of confounding. Internationally standardized exposure measures would enhance the comparability of studies.

http://www.ncbi.nlm.nih.gov/pubmed/?term=17692380

Neuromolecular Medicine • 2007

Aluminum adjuvant linked to Gulf War illness induces motor neuron death in mice

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Abstract

Gulf War illness (GWI) affects a significant percentage of veterans of the 1991 conflict, but its origin remains unknown. Associated with some cases of GWI are increased incidences of amyotrophic lateral sclerosis and other neurological disorders. Whereas many environmental factors have been linked to GWI, the role of the anthrax vaccine has come under increasing scrutiny. Among the vaccine's potentially toxic components are the adjuvants aluminum hydroxide and squalene. To examine whether these compounds might contribute to neuronal deficits associated with GWI, an animal model for examining the potential neurological impact of aluminum hydroxide, squalene, or aluminum hydroxide combined with squalene was developed. Young, male colony CD-1 mice were injected with the adjuvants at doses equivalent to those given to US military service personnel. All mice were subjected to a battery of motor and cognitive-behavioral tests over a 6-mo period postinjections. Following sacrifice, central nervous system tissues were examined using immunohistochemistry for evidence of inflammation and cell death. Behavioral testing showed motor deficits in the aluminum treatment group that expressed as a progressive decrease in strength measured by the wire-mesh hang test (final deficit at 24 wk; about 50%). Significant cognitive deficits in water-maze learning were observed in the combined aluminum and squalene group (4.3 errors per trial) compared with the controls (0.2 errors per trial) after 20 wk. Apoptotic neurons were identified in aluminum-injected animals that showed significantly increased activated caspase-3 labeling in lumbar spinal cord (255%) and primary motor cortex (192%) compared with the controls. Aluminum-treated groups also showed significant motor neuron loss (35%) and increased numbers of astrocytes (350%) in the lumbar spinal cord. The findings suggest a possible role for the aluminum adjuvant in some neurological features associated with GWI and possibly an additional role for the combination of adjuvants.

http://www.ncbi.nlm.nih.gov/pubmed/17114826

"Among the vaccine's potentially toxic components are the adjuvants aluminum hydroxide and squalene. The findings suggest a possible role for the aluminum adjuvant in some neurological features associated with Gulf War Illness and possibly an additional role for the combination of adjuvants."

Journal Of Toxicology And Environmental Health Part B Critical Reviews • 2007

Human Health Risk Assessment For Aluminum, Aluminum Oxide, And Aluminum Hydroxide

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Findings

"This report classified the weight of evidence for each exposure pathway and health effect as strong, modest, limited, or having no clear evidence (see Table 25). We concluded that there is strong evidence that aluminum can cause irritation following exposure via either inhalation or injection. Modest evidence of an effect exists for reproductive toxicity following oral exposure, for neurological toxicity following either oral or injection exposure, and for bone toxicity following injection exposure."

Full Report
http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2782734/

"Modest evidence of an effect exists for reproductive toxicity following oral exposure, for neurological toxicity following either oral or injection exposure, and for bone toxicity following injection exposure."

Journal Of Experimental Medicine • April 2008

Alum adjuvant boosts adaptive immunity by inducing uric acid and activating inflammatory dendritic cells

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Abstract

Alum (aluminum hydroxide) is the most widely used adjuvant in human vaccines, but the mechanism of its adjuvanticity remains unknown. In vitro studies showed no stimulatory effects on dendritic cells (DCs). In the absence of adjuvant, Ag was taken up by lymph node (LN)-resident DCs that acquired soluble Ag via afferent lymphatics, whereas after injection of alum, Ag was taken up, processed, and presented by inflammatory monocytes that migrated from the peritoneum, thus becoming inflammatory DCs that induced a persistent Th2 response. The enhancing effects of alum on both cellular and humoral immunity were completely abolished when CD11c(+) monocytes and DCs were conditionally depleted during immunization. Mechanistically, DC-driven responses were abolished in MyD88-deficient mice and after uricase treatment, implying the induction of uric acid. These findings suggest that alum adjuvant is immunogenic by exploiting “nature’s adjuvant,” the inflammatory DC through induction of the endogenous danger signal uric acid.

http://www.ncbi.nlm.nih.gov/pubmed/?term=18362170

“Alum (aluminum hydroxide) is the most widely used adjuvant in human vaccines, but the mechanism of its adjuvanticity remains unknown.”

Annales de Pathologie • April 2008

Late-onset vaccination-induced subcutaneous pseudolymphoma

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Abstract

Persistent subcutaneous nodules arise on rare occasions at sites of injection of aluminium hydroxide-adsorbed vaccine. We report a case following a diphtheria, tetanus and pertussis vaccination. The late onset of the lesion, four years after the injection, led to an uncertain preoperative diagnosis. Histopathologic examination showed features of a subcutaneous pseudolymphoma. The demonstration of aluminium by Morin staining and atomic absorption spectrometry on a paraffin-embedded tissue probe supported the diagnosis of a vaccination-induced pseudolymphoma.

http://www.ncbi.nlm.nih.gov/pubmed/18675172

“The late onset of the lesion,
four years after the injection,
led to an uncertain preoperative diagnosis.”

Experimental Gerontology • April 2008

Effects of aluminium sulphate in the mouse liver: similarities to the aging process

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Abstract

Aluminium (Al) is a ubiquitous metal that is potentially toxic to the brain. Its effects on other fundamental organs are not completely understood. This morphological in vivo study sought to compare sublethal hepatotoxic changes and Al deposition in adult mice that orally ingested Al sulphate daily for 10 months, in age matched control mice that drank tap water and in senescent mice (24 months old). Livers were examined for collagen deposition using Sirius red and Masson, for iron accumulation using Perls' stain. Light, electron microscopy and morphometry were used to assess fibrosis and vascular changes. Scanning transmission electron microscopy and EDX microanalysis were used to detect in situ elemental Al. Iron deposition, transferrin receptor expression were significantly altered following Al exposure and in the aged liver but were unaffected in age matched control mice. In Al treated mice as in senescent mice, endothelial thickness was increased and porosity was decreased like perisinusoidal actin. Furthermore, Al stimulated the deposition of collagen and laminin, mainly in acinar zones 1 and 3. Pseudocapillarization and periportal laminin in senescent mice were similar to Al treated adult liver. In conclusion, prolonged Al sulphate intake accelerates features of senescence in the adult mice liver.

http://www.ncbi.nlm.nih.gov/pubmed/18337038

"Aluminium (Al) is a ubiquitous metal that is potentially toxic to the brain ... prolonged Al sulphate intake accelerates features of senescence in the adult mice liver."

Actas Dermo-Sifiliograficas • April 2008

B-cell pseudolymphoma caused by aluminium hydroxide following hyposensitization therapy

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Abstract

Aluminium hydroxide is used as an adjuvant in vaccines. We describe the case of a patient who presented a persistent adverse local reaction to aluminium hydroxide due to hyposensitization therapy to dust mites. Multiple painful and pruriginous subcutaneous nodules were observed in both arms, along with hypertrichosis at the injection site. Histology revealed a pseudolymphomatous B cell reaction predominantly involving cells that were CD20 positive, did not express bcl-2, and did not display the t(14-18) translocation. The cells also exhibited polyclonal rearrangement of the immunoglobulin heavy chains. X-ray spectral microanalysis revealed deposits of inorganic aluminium in the granular histiocytes among the germinal centers. The patient was diagnosed with cutaneous B-cell pseudolymphoma due to aluminium hydroxide as a result of immunotherapy.

http://www.ncbi.nlm.nih.gov/pubmed/?term=18358197

“The patient was diagnosed with cutaneous B-cell pseudolymphoma due to aluminium hydroxide ...”

Vaccine • May 2008

Alum boosts TH2-type antibody responses to whole-inactivated virus influenza vaccine in mice but does not confer superior protection

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Abstract

Clinical trials with pandemic influenza vaccine candidates have focused on aluminium hydroxide as an adjuvant to boost humoral immune responses. In this study we investigated the effect of aluminium hydroxide on the magnitude and type of immune response induced by whole-inactivated virus (WIV) vaccine. Balb/c mice were immunized once with a range of antigen doses (0.04-5 microg) of WIV produced from A/PR/8 virus, either alone or in combination with aluminium hydroxide. The hemagglutination inhibition (HI) titers of mice receiving WIV+aluminium hydroxide were 4-16-fold higher than HI titers in mice receiving the same dose of WIV alone, indicating the boosting effect of aluminium hydroxide. WIV induced a TH1 skewed humoral and cellular immune response, characterized by strong influenza-specific IgG2a responses and a high number of IFNgamma-secreting T cells. In contrast, immunization with WIV adsorbed to aluminium hydroxide resulted in skewing of this response to a TH2 phenotype (high IgG1 levels and a low number of IFNgamma-producing T cells). To assess the effect of the observed immune response skewing on viral clearance from the lungs mice immunized once with 1 microg WIV without or with aluminium hydroxide were challenged with A/PR/8 virus 4 weeks later. The immunized mice showed a significant decrease in viral lung titers compared to control mice receiving buffer. However, despite higher antibody titers, mice immunized with WIV adsorbed to aluminium hydroxide suffered from more severe weight loss and had significantly higher virus loads in their lung tissue than mice receiving WIV alone. Major difference between these groups of mice was the type of immune response induced, TH2 instead of TH1, indicating that a TH1 response plays a major role in viral clearance.

http://www.ncbi.nlm.nih.gov/pubmed/?term=18400340

“despite higher antibody titers, mice immunized with whole-inactivated virus adsorbed to aluminium hydroxide suffered from more severe weight loss and had significantly higher virus loads in their lung tissue than mice receiving whole-inactivated virus alone.”

Food And Chemical Toxicology • June 2008

Aluminum bioavailability from basic sodium aluminum phosphate, an approved food additive emulsifying agent, incorporated in cheese

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Abstract

Oral aluminum (Al) bioavailability from drinking water has been previously estimated, but there is little information on Al bioavailability from foods. It was suggested that oral Al bioavailability from drinking water is much greater than from foods. The objective was to further test this hypothesis. Oral Al bioavailability was determined in the rat from basic [26Al]-sodium aluminum phosphate (basic SALP) in a process cheese. Consumption of approximately 1g cheese containing 1.5% or 3% basic SALP resulted in oral Al bioavailability (F) of approximately 0.1% and 0.3%, respectively, and time to maximum serum 26Al concentration (Tmax) of 8-9h. These Al bioavailability results were intermediate to previously reported results from drinking water (F approximately 0.3%) and acidic-SALP incorporated into a biscuit (F approximately 0.1%), using the same methods. Considering the similar oral bioavailability of Al from food vs. water, and their contribution to the typical human's daily Al intake (approximately 95% and 1.5%, respectively), these results suggest food contributes much more Al to systemic circulation, and potential Al body burden, than does drinking water. These results do not support the hypothesis that drinking water provides a disproportionate contribution to total Al absorbed from the gastrointestinal tract.

http://www.ncbi.nlm.nih.gov/pubmed/18436363

"these results suggest food contributes much more Al to systemic circulation, and potential Al body burden, than does drinking water."

Journal Of Child Neurology • June 2008

Macrophagic myofasciitis in children is a localized reaction to vaccination

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Abstract

Macrophagic myofasciitis is a novel, "inflammatory myopathy" described after a variety of vaccinations, almost exclusively in adults. We examined the relevance of histological findings of this myopathy to the clinical presentation in pediatric patients. Muscle biopsies from 8 children (7 months to 6 years old) with histological features of macrophagic myofasciitis were reviewed and correlated with the clinical manifestations. Patients underwent quadriceps muscle biopsy for suspected mitochondrial disease (4 patients), spinal muscular atrophy (2 patients), myoglobinuria (1 patient), and hypotonia with motor delay (1 patient). All biopsies showed identical granulomas composed of periodic acid-Schiff-positive and CD68-positive macrophages. Characteristic aluminum hydroxide crystals were identified by electron microscopy in 2 cases. The biopsy established diagnoses other than macrophagic myofasciitis in 5 patients: spinal muscular atrophy (2), Duchenne muscular dystrophy (1), phospho-glycerate kinase deficiency (1), and cytochrome c oxidase deficiency (1). Three children with manifestations and/or a family history of mitochondrial disease had otherwise morphologically normal muscle. All children had routine vaccinations between 2 months and 1 year before the biopsy, with up to 11 intramuscular injections, including the biopsy sites. There was no correlation between histological findings of macrophagic myofasciitis in biopsies and the clinical symptoms. We believe that macrophagic myofasciitis represents a localized histological hallmark of previous immunization with the aluminum hydroxide adjuvants contained in vaccines, rather than a primary or distinct inflammatory muscle disease.

http://www.ncbi.nlm.nih.gov/pubmed/18281624

"We believe that macrophagic myofasciitis represents a localized histological hallmark of previous immunization with the aluminum hydroxide adjuvants contained in vaccines, rather than a primary or distinct inflammatory muscle disease."

Brain Research • September 2008

Impairment of mitochondrial energy metabolism in different regions of rat brain following chronic exposure to aluminium

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Abstract

The present study was designed with an aim to evaluate the effects of chronic aluminium exposure (10 mg/kg b.wt, intragastrically for 12 weeks) on mitochondrial energy metabolism in different regions of rat brain in vivo. Mitochondrial preparations from aluminium treated rats revealed significant decrease in the activity of various electron transport complexes viz. cytochrome oxidase, NADH cytochrome c reductase and succinic dehydrogenase as well, in the hippocampus region. The decrease in the activity of these respiratory complexes was also seen in the other two regions viz. corpus striatum and cerebral cortex, but to a lesser extent. This decrease in the activities of electron transport complexes in turn affected the ATP synthesis and ATP levels adversely in the mitochondria isolated from aluminium treated rat brain regions. We also studied the spectral properties of the mitochondrial cytochromes viz. cyt a, cyt b, cyt c1, and cyt c in both control and treated rat brains. The various cytochrome levels were found to be decreased following 12 weeks of aluminium exposure. Further, these impairments in mitochondrial functions may also be responsible for the production of reactive oxygen species and impaired antioxidant defense system as observed in our study. The electron micrographs of neuronal cells depicted morphological changes in mitochondria as well as nucleus only from hippocampus and corpus striatum regions following 12 weeks exposure to aluminium. The present study thus highlights the significance of altered mitochondrial energy metabolism and increased ROS production as a result of chronic aluminium exposure in different regions of the rat brain.

http://www.ncbi.nlm.nih.gov/pubmed/?term=18691561

“The present study thus highlights the significance of altered mitochondrial energy metabolism and increased ROS production as a result of chronic aluminium exposure in different regions of the rat brain.”

“Select human population can be at risk of Aluminum neurotoxicity,

and Aluminum is proposed to be involved in the etiology of neurodegenerative diseases.”

Archives Of Toxicology • November 2008

Aluminium and lead: molecular mechanisms of brain toxicity

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Abstract

The fact that aluminium (Al) and lead (Pb) are both toxic metals to living organisms, including human beings, was discovered a long time ago. Even when Al and Pb can reach and accumulate in almost every organ in the human body, the central nervous system is a particular target of the deleterious effects of both metals. Select human population can be at risk of Al neurotoxicity, and Al is proposed to be involved in the etiology of neurodegenerative diseases. Pb is a widespread environmental hazard, and the neurotoxic effects of Pb are a major public health concern. In spite of the numerous efforts and the accumulating evidence in this area of research, the mechanisms of Al and Pb neurotoxicity are still not completely elucidated. This review will particularly address the involvement of oxidative stress, membrane biophysics alterations, deregulation of cell signaling, and the impairment of neurotransmission as key aspects involved Al and Pb neurotoxicity.

http://www.ncbi.nlm.nih.gov/pubmed/18668223

“Aluminium has been implicated in various neurodegenerative diseases

but exact mechanism of action is still not known.”

Toxicology • January 2009

Susceptibility of mitochondrial superoxide dismutase to aluminium induced oxidative damage

Author information

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Abstract

Aluminium has been implicated in various neurodegenerative diseases but exact mechanism of action is still not known. Mitochondria being a major site of reactive oxygen species production are considered to be target of oxidative stress and it seems that the oxidative damage to mitochondrial proteins may underlie the pathogenesis of aluminium induced neurodegeneration. Thus, the present study was undertaken to reveal the effects of chronic aluminium exposure (10mg/kg b.wt, intragastrically for 12 weeks) on the oxidative damage to mitochondrial proteins in male albino Wistar rats. Chronic aluminium exposure resulted in decrease in the activity of mitochondrial superoxide dismutase (MnSOD) and aconitase in different regions of rat brain suggesting increased oxidative stress. This decrease in MnSOD activity in turn might be responsible for the increased protein oxidation as observed in our study. All these processes taken together may cause increased oxidative damage to mitochondrial proteins in general. By taking the advantage of recent immunochemical probe for oxidatively modified proteins, we identified MnSOD to be susceptible to oxidative damage in aluminium treated animals. The quantitative RT-PCR analysis for Lon protease, a protease involved in the removal of oxidatively modified proteins from mitochondria, showed decreased mRNA expression suggesting increased oxidative damage and decreased removal of mitochondrial proteins. The identification of specific proteins as targets of oxidative damage may provide new therapeutic measures to reverse the effects of aluminium induced neurodegeneration.

http://www.ncbi.nlm.nih.gov/pubmed/19010380

Medical Hypotheses • February 2009

A role for the body burden of aluminium in vaccine-associated macrophagic myofasciitis and chronic fatigue syndrome

Author information

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Abstract

Macrophagic myofasciitis and chronic fatigue syndrome are severely disabling conditions which may be caused by adverse reactions to aluminium-containing adjuvants in vaccines. While a little is known of disease aetiology both conditions are characterised by an aberrant immune response, have a number of prominent symptoms in common and are coincident in many individuals. Herein, we have described a case of vaccine-associated chronic fatigue syndrome and macrophagic myofasciitis in an individual demonstrating aluminium overload. This is the first report linking the latter with either of these two conditions and the possibility is considered that the coincident aluminium overload contributed significantly to the severity of these conditions in this individual. This case has highlighted potential dangers associated with aluminium-containing adjuvants and we have elucidated a possible mechanism whereby vaccination involving aluminium-containing adjuvants could trigger the cascade of immunological events which are associated with autoimmune conditions including chronic fatigue syndrome and macrophagic myofasciitis.

http://www.ncbi.nlm.nih.gov/pubmed/19004564

“This case has highlighted potential dangers associated with aluminium-containing adjuvants and we have elucidated a possible mechanism whereby vaccination involving aluminium-containing adjuvants could trigger the cascade of immunological events which are associated with autoimmune conditions including chronic fatigue syndrome and macrophagic myofasciitis.”

Journal Of Inorganic Biochemistry • August 2009

Guest editorial
'The natural history of aluminium: from non-selection to natural selection'.

Author Information

Christopher Exley

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Abstract

"Al accumulates in the body with age and particularly so when exposure is high and/or protective gastrointestinal mechanisms are bypassed or renal function is impaired (Kisters et al., 1999). Al toxicity in humans, even at low levels of exposure (Exley, 2009b), is a well-established fact and the brain is a target organ for Al to exert its deleterious effects (Exley et al., 1996; Exley, 1999; Yokel et al., 1999). The molecular mechanisms of Al neurotoxicity are not completely understood: Al has been reported to alter the blood-brain barrier (Zatta et al., 2003) and is deposited in the human brain (Exley and House, 2011). "

"Aluminum toxicity in humans, even at low levels of exposure, is a well-established fact and the brain is a target organ for Aluminum to exert its deleterious effects. The molecular mechanisms of Al neurotoxicity are not completely understood: Aluminum has been reported to alter the blood-brain barrier and is deposited in the human brain ..."

https://www.researchgate.net/publication/26763878_Guest_editorial_%27The_natural_history_of_aluminium_from_non-selection_to_natural_selection%27

"... our findings indicate that fatty acids common in food

increase the paracellular intestinal absorption of Aluminum."

Chemical-Biological Interactions • October 2009

Fatty acids increase paracellular absorption of aluminium across Caco-2 cell monolayers

Author information

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Abstract

Passive paracellular absorption, regulated by tight junctions (TJs), is the main route for absorption of poorly absorbed hydrophilic substances. Surface active substances, such as fatty acids, may enhance absorption of these substances by affecting the integrity of TJ and increasing the permeability. It has been suggested that aluminium (Al) absorption occurs mainly by the paracellular route. Herein, we investigated if physiologically relevant exposures of fully differentiated Caco-2 cell monolayers to oleic acid and docosahexaenoic acid (DHA), which are fatty acids common in food, increase absorption of Al and the paracellular marker mannitol. In an Al toxicity test, mannitol and Al absorption through Caco-2 cell monolayers were similarly modulated by Al concentrations between 1 and 30mM, suggesting that absorption of the two compounds occurred via the same pathways. Exposure of Caco-2 cell monolayers to non-toxic concentrations of Al (2mM) and (14)C-mannitol in fatty acid emulsions (15 and 30mM oleic acid, 5 and 10mM DHA) caused a decreased transepithelial electrical resistance (TEER). Concomitantly, fractional absorption of Al and mannitol, expressed as percentage of apical Al and mannitol retrieved at the basolateral side, increased with increasing dose of fatty acids. Transmission electron microscopy was applied to assess the effect of oleic acid on the morphology of TJ. It was shown that oleic acid caused a less structured morphology of TJ in Caco-2 cell monolayers. Taken together our findings indicate that fatty acids common in food increase the paracellular intestinal absorption of Al. These findings may influence future risk assessment of human Al exposure.

http://www.ncbi.nlm.nih.gov/pubmed/?term=19576870

Archives Of Toxicology • November 2009

Aluminium neurotoxicity: neurobehavioural and oxidative aspects

Author information

Kumar V1, Gill KD.

Abstract

Aluminium is the most widely distributed metal in the environment and is extensively used in daily life that provides easy exposure to human beings. The exposure to this toxic metal occurs through air, food and water. However, there is no known physiological role for aluminium within the body and hence this metal may produce adverse physiological effects. Chronic exposure of animals to aluminium is associated with behavioural, neuropathological and neurochemical changes. Among them, deficits of learning and behavioural functions are most evident. Some epidemiological studies have shown poor performance in cognitive tests and a higher abundance of neurological symptoms for workers occupationally exposed to aluminium. However, in contrast to well established neurotoxic effects, neurobehavioural studies of aluminium in rodents have generally not produced consistent results. Current researches show that any impairment in mitochondrial functions may play a major role in many human disorders including neurodegenerative disorders. Being involved in the production of reactive oxygen species, aluminium may cause impairments in mitochondrial bioenergetics and may lead to the generation of oxidative stress which may lead to a gradual accumulation of oxidatively modified cellular proteins. In this review, the neuropathologies associated with aluminium exposure in terms of neurobehavioural changes have been discussed. In addition, the impact of aluminium on the mitochondrial functions has also been highlighted.

http://www.ncbi.nlm.nih.gov/pubmed/?term=19568732

“Aluminium is the most widely distributed metal in the environment and is extensively used in daily life that provides easy exposure to human beings. The exposure to this toxic metal occurs through air, food and water. However, there is no known physiological role for aluminium within the body and hence this metal may produce adverse physiological effects. Chronic exposure of animals to aluminium is associated with behavioural, neuropathological and neurochemical changes. Among them, deficits of learning and behavioural functions are most evident.”

Journal Of Inorganic Biochemistry • November 2009

Long-term persistence of vaccine-derived aluminum hydroxide is associated with chronic cognitive dysfunction

Author information

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Abstract

Macrophagic myofasciitis (MMF) is an emerging condition, characterized by specific muscle lesions assessing long-term persistence of aluminum hydroxide within macrophages at the site of previous immunization. Affected patients mainly complain of arthromyalgias, chronic fatigue, and cognitive difficulties. We designed a comprehensive battery of neuropsychological tests to prospectively delineate MMF-associated cognitive dysfunction (MACD). Compared to control patients with arthritis and chronic pain, MMF patients had pronounced and specific cognitive impairment. MACD mainly affected (i) both visual and verbal memory; (ii) executive functions, including attention, working memory, and planning; and (iii) left ear extinction at dichotic listening test. Cognitive deficits did not correlate with pain, fatigue, depression, or disease duration. Pathophysiological mechanisms underlying MACD remain to be determined. In conclusion, long-term persistence of vaccine-derived aluminum hydroxide within the body assessed by MMF is associated with cognitive dysfunction, not solely due to chronic pain, fatigue and depression.

http://www.ncbi.nlm.nih.gov/pubmed/19748679

“In conclusion, long-term persistence of vaccine-derived aluminum hydroxide within the body assessed by MMF is associated with cognitive dysfunction, not solely due to chronic pain, fatigue and depression.”

Journal Of Inorganic Biochemistry • November 2009

Aluminum hydroxide injections ‘ lead to motor deficits and motor neuron degeneration

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Abstract

Gulf War Syndrome is a multi-system disorder afflicting many veterans of Western armies in the 1990-1991 Gulf War. A number of those afflicted may show neurological deficits including various cognitive dysfunctions and motor neuron disease, the latter expression virtually indistinguishable from classical amyotrophic lateral sclerosis (ALS) except for the age of onset. This ALS “cluster” represents the second such ALS cluster described in the literature to date. Possible causes of GWS include several of the adjuvants in the anthrax vaccine and others. The most likely culprit appears to be aluminum hydroxide. In an initial series of experiments, we examined the potential toxicity of aluminum hydroxide in male, outbred CD-1 mice injected subcutaneously in two equivalent-to-human doses. After sacrifice, spinal cord and motor cortex samples were examined by immunohistochemistry. Aluminum-treated mice showed significantly increased apoptosis of motor neurons and increases in reactive astrocytes and microglial proliferation within the spinal cord and cortex. Morin stain detected the presence of aluminum in the cytoplasm of motor neurons with some neurons also testing positive for the presence of hyper-phosphorylated tau protein, a pathological hallmark of various neurological diseases, including Alzheimer’s disease and frontotemporal dementia. A second series of experiments was conducted on mice injected with six doses of aluminum hydroxide. Behavioural analyses in these mice revealed significant impairments in a number of motor functions as well as diminished spatial memory capacity. The demonstrated neurotoxicity of aluminum hydroxide and its relative ubiquity as an adjuvant suggest that greater scrutiny by the scientific community is warranted.

http://www.ncbi.nlm.nih.gov/pubmed/19740540

“Possible causes of Gulf War Syndrome include several of the adjuvants in the anthrax vaccine and others. The most likely culprit appears to be aluminum hydroxide.”

Nanomedicine • December 2009

Glia activation induced by peripheral administration of aluminum oxide nanoparticles in rat brains

Author information

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Abstract

With the wide application of nanoscaled particles, the risk of human exposure to these particles has been markedly increased. However, knowledge about their safety falls far behind the utility of these nanoparticles. Here we have analyzed the activation of brain microglia and astrocytes, which are sensitive to changes of brain environment after peripheral exposure to nanoscaled aluminum oxide suspension. Sprague-Dawley rats (six rats per treatment) were intraperitoneally injected once every second day for 30 or 60 days with nanoscaled aluminum oxide (NSAO; 1 mg/kg or 50 mg/kg), non-nanoscaled aluminum oxide (nNSAO, 1 mg/kg), or vehicle (saline). After 60 days' exposure the numbers of ED1+, GFAP+, and nestin+ cells in cortex and hippocampus were significantly higher in NSAO-treated rats than nNSAO- or vehicle-treated rats; thus, compared with nNSAO, NSAO has potential effects on the innate immune system of rat brain. This should be considered when evaluating the toxicological effects of nanosized particles.

From The Clinical Editor

Sprague-Dawley rats were intraperitoneally injected with nanosized aluminum oxide, (NSAO); non-nanoscaled aluminum oxide, or vehicle (saline). The numbers of ED1+, GFAP+, and nestin+ cells in cortex and hippocampus were significantly higher in NSAO-treated rats than nNSAO- or vehicle-treated rats; thus, NSAO has potential effects on the innate immune system of rat brain.

http://www.ncbi.nlm.nih.gov/pubmed/19523415

"With the wide application of nanoscaled particles, the risk of human exposure to these particles has been markedly increased. However, knowledge about their safety falls far behind the utility of these nanoparticles ... [aluminum] has potential effects on the innate immune system of rat brain."

CellPress Nucleus
Mitochondria & Metabolism
Volume 34, Issue 12, p589–593, December 2009

Darwin, natural selection and the biological essentiality of aluminium and silicon

by Christopher Exley
The Birchall Centre, Lennard-Jones Laboratories, Keele University, Staffordshire, ST5 5BG, UK

Absract

If one was asked to produce a set of 'Trump Cards™' based upon 'Forces of Nature Defining Life on Earth' then which card would be 'Top Trump'? I was recently chastised on the Darwin Today website for suggesting Darwin and 'natural selection' rather than, for example, Newton and 'gravity'. Although there is no denying the significance of gravity, my argument in favour of natural selection is simply that gravity is just one factor that contributes towards an outcome which ultimately is defined by natural selection. Both the beauty and the brilliance of natural selection are reflected in its omnipotence to explain the myriad observations of life and, as I will affirm herein, its explanation of the biological essentiality of aluminium and silicon is no exception.

Together they constitute a form of homeostasis with aluminium being retained both physically and chemically in myriad forms and each form being capable of acting as a sink or source of labile and potentially biologically reactive aluminium. It is always important to emphasise that there is no evolutionarily directed or conserved biology to enable aluminium homeostasis and so this non-essential but highly biologically reactive metal cation is at the whim of the predominant or pre-eminent chemistry of any particular environment [8] [9]. This unpredictability makes biologically available aluminium a concern for all forms of life on Earth [2].

In this year, 200th anniversary of the birth of Charles Darwin and the 150th anniversary of the publication of On the Origin of Species, a UK scientist has used Darwin's seminal work on Natural Selection in helping to define the biological essentiality of the second (silicon) and third (aluminium) most abundant elements of the Earth's crust.

The lack of any clear or significant biological essentiality for both of these elements is a mystery as all other abundant elements of the Earth's crust are known to be biologically essential.

Dr Chris Exley, Reader in Bioinorganic Chemistry at Keele University and a world authority on the ways in which aluminium impacts upon life on Earth, says natural selection is often interpreted as 'survival of the fittest' but what is often not appreciated is that the selection processes themselves are niche driven, which means that those characteristics which convey fitness in one environment may not convey fitness in another, perhaps adjacent, environment or niche. This is both the strength and the beauty of natural selection and it can be applied to cellular biochemistry as it is applied to speciation of organisms.

Aluminium is biologically reactive, while silicon is biologically inert. Natural selection informs us that the non-essentiality of aluminium is explained by its non-participation in biochemical evolution due to a complete lack of its biologically reactive forms.

On the other hand the biologically available form of silicon (silicic acid) has been extremely abundant throughout biochemical evolution and its biological essentiality has been dictated by its extremely limited biological reactivity.

It is no coincidence that one of the very few reactions of silicic acid is that with aluminium and that this reaction protects against the toxicity of aluminium.

An essential role of silicon throughout biochemical evolution has been to keep aluminium out of life! However, the activities of humans in learning how to extract aluminium from its ores and using it in myriad ways in what is now the Aluminium Age means that Earth's inherent protection against the toxicity of aluminium is being compromised and that biologically reactive aluminium is now an active participant in biochemical (and hence human) evolution.

Some of the early results of the arrival of biochemically reactive aluminium have been worryingly obvious, including the death of fish and trees in geographical regions impacted by acid deposition, whereas others, and perhaps those which in particular are linked with the human condition, might yet be too subtle to be directly attributable to the participation of biologically-reactive aluminium in the natural selection of the elements of biological essentiality.

Link: I can't provide a link for this report and I'm certain that this is not the complete report. The text above consists of excerpts found in other reports that reference this one using a variety of internet search terms. The complete document requires purchase:

"This unpredictability makes biologically available aluminium a concern for all forms of life on Earth."

http://www.cell.com/trends/biochemical-sciences/abstract/S0968-0004(09)00167-4?_returnURL=http%3A%2F%2Flinkinghub.elsevier.com%2Fretrieve%2Fpii%2FS0968000409001674%3Fshowall%3Dtrue

Trends In Immunology • March 2010

The immunobiology of aluminium adjuvants: how do they really work?

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Abstract

Aluminium adjuvants potentiate the immune response, thereby ensuring the potency and efficacy of typically sparingly available antigen. Their concomitant critical importance in mass vaccination programmes may have prompted recent intense interest in understanding how they work and their safety. Progress in these areas is stymied, however, by a lack of accessible knowledge pertaining to the bioinorganic chemistry of aluminium adjuvants, and, consequently, the inappropriate application and interpretation of experimental models of their mode of action. The objective herein is, therefore, to identify the many ways that aluminium chemistry contributes to the wide and versatile armoury of its adjuvants, such that future research might be guided towards a fuller understanding of their role in human vaccinations.

http://www.ncbi.nlm.nih.gov/pubmed/20153253

“Progress in these areas [aluminum research] is stymied, however, by a lack of accessible knowledge pertaining to the bioinorganic chemistry of aluminium adjuvants, and, consequently, the inappropriate application and interpretation of experimental models of their mode of action.”

“Preterm neonates receiving parenteral nutrition are at risk of aluminum overload because of the presence of aluminum as a contaminant in parenteral formulations. Despite US Food and Drug Administration regulation, commercial products continue to present Al contamination. Moreover, premature neonates were receiving, on average, 3 times the amount considered by the Food and Drug Administration as a safe limit.”

Journal Of Pediatric Gastroenterology And Nutrition • August 2010

Aluminum loading in preterm neonates revisited

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Abstract

Preterm neonates receiving parenteral nutrition are at risk of aluminum (Al) overload because of the presence of Al as a contaminant in parenteral formulations. Despite US Food and Drug Administration regulation, commercial products continue to present Al contamination. To reassess Al exposure in the premature neonatal population, the present study evaluated the Al balance (intake vs urinary excretion) in a group of preterm neonates during the period in which they stayed in the intensive care unit (NICU) under total parenteral nutrition. For the 10 patients selected, daily infusion solutions (nutrition and medication) were collected and the level of Al contamination was measured. From the urine collected daily, an aliquot was taken for Al determination. Blood was also collected for Al determination on the first and last day in the NICU. The measurements were carried out by atomic absorption spectrometry. The difference between Al administered and excreted revealed that 56.2% +/- 22.7% of the Al intake was not eliminated. The mean serum Al levels from the first to the last day decreased from 41.2 +/- 23.3 to 23.5 +/- 11.2 microg/L. The resulting mean Al daily intake of the 10 patients was 15.2 +/- 8.0 microg x kg(-1) x day(-1). Because Al intake was higher than that excreted and Al in serum decreased to practically half during the period in the NICU (+/-7.3 days), some amount of Al deposition occurred. Moreover, premature neonates were receiving, on average, 3 times the amount of 5 microg x kg(-1) x day(-1), considered by the Food and Drug Administration as a safe limit.

http://www.ncbi.nlm.nih.gov/pubmed/?term=20479688

"... the vulnerability of infants to early exposure to aluminium serves to highlight an urgent need to reduce the aluminium content of infant formulas ..."

BMC Pediatrics • August 2010

There is (still) too much aluminium in infant formulas

Author information

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Abstract

BACKGROUND
Infant formulas are sophisticated milk-based feeds for infants which are used as a substitute for breast milk. Historically they are known to be contaminated by aluminium and in the past this has raised health concerns for exposed infants. We have measured the aluminium content of a number of widely used infant formulas to determine if their contamination by aluminium and consequent issues of child health persists.

METHODS
Samples of ready-made milks and powders used to make milks were prepared by microwave digestion of acid/peroxide mixtures and their aluminium content determined by THGA.

RESULTS
The concentration of aluminium in ready-made milks varied from ca 176 to 700 μg/L. The latter concentration was for a milk for preterm infants. The aluminium content of powders used to make milks varied from ca 2.4 to 4.3 μg/g. The latter content was for a soya-based formula and equated to a ready-to-drink milk concentration of 629 μg/L. Using the manufacturer's own guidelines of formula consumption the average daily ingestion of aluminium from infant formulas for a child of 6 months varied from ca 200 to 600 μg of aluminium. Generally ingestion was higher from powdered as compared to ready-made formulas.

CONCLUSIONS
The aluminium content of a range of well known brands of infant formulas remains high and particularly so for a product designed for preterm infants and a soya-based product designed for infants with cow's milk intolerances and allergies. Recent research demonstrating the vulnerability of infants to early exposure to aluminium serves to highlight an urgent need to reduce the aluminium content of infant formulas to as low a level as is practically possible.

Full Report

http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2939626/

Neurotoxicology • September 2010

The neurotoxicity of environmental aluminum is still an issue

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Abstract

Evidence for the neurotoxicity of extended exposure to low levels of aluminum salts is described using an animal model treated with aluminum at low levels reflecting those found in some water supplies. Emphasis is given to the potential role of aluminum in acceleration and promotion of some indices characteristic of brain aging. These hallmarks include the appearance of excess levels of inflammation in specific brain areas. Aluminum salts can increase levels of glial activation, inflammatory cytokines and amyloid precursor protein within the brain. Both normal brain aging and to a greater extent, Alzheimer's disease are associated with elevated basal levels of markers for inflammation. These are not attributable to obvious exogenous stimuli and may reflect the lifespan history of the organism's immune responses. It is possible that aluminum salts can act as a subtle promoter of such apparently unprovoked responses.

http://www.ncbi.nlm.nih.gov/pubmed/?term=20553758

"Emphasis is given to the potential role of aluminum in acceleration and promotion of some indices characteristic of brain aging. These hallmarks include the appearance of excess levels of inflammation in specific brain areas."

Journal Of Exposure Science & Environmental Epidemiology • November 2010

Infants' exposure to aluminum from vaccines and breast milk during the first 6 months

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Abstract

The success of vaccination programs in reducing and eliminating infectious diseases has contributed to an ever-increasing number of vaccines given at earlier ages (newborns and infants). Exposure to low levels of environmental toxic substances (including metals) at an early age raises plausible concerns over increasingly lower neuro-cognitive rates. Current immunization schedules with vaccines containing aluminum (as adjuvant) are given to infants, but thimerosal (as preservative) is found mostly in vaccines used in non-industrialized countries. Exclusively, breastfed infants (in Brazil) receiving a full recommended schedule of immunizations showed an exceedingly high exposure of Al (225 to 1750 µg per dose) when compared with estimated levels absorbed from breast milk (2.0 µg). This study does not dispute the safety of vaccines but reinforces the need to study long-term effects of early exposure to neuro-toxic substances on the developing brain. Pragmatic vaccine safety needs to embrace conventional toxicology, addressing especial characteristics of unborn fetuses, neonates and infants exposed to low levels of aluminum, and ethylmercury traditionally considered innocuous to the central nervous system.

http://www.ncbi.nlm.nih.gov/pubmed/20010978

"Exclusively, breastfed infants (in Brazil) receiving a full recommended schedule of immunizations showed an exceedingly high exposure of Aluminum (225 to 1750 µg per dose) when compared with estimated levels absorbed from breast milk (2.0 µg)."

Pharmacological Reports • November 2010

Effects of ethylene glycol ethers on cell viability in the human neuroblastoma SH-SY5Y cell line

Author information

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Abstract

Ethylene glycol ethers (EGEs) are a class of chemicals used extensively in the manufacture of a wide range of domestic and industrial products, which may result in human exposure and toxicity. Hematologic and reproductive toxicity of EGEs are well known whereas their action on neuronal cell viability has not been studied so far. In the present study, we investigated the effects of some EGEs on cell viability and on the hydrogen peroxide-induced damage in the human neuroblastoma (SH-SY5Y) cells. It has been found that 2-phenoxyethanol in a concentration-dependent manner (5-25 mM, 24 h) increased the basal and H(2)O(2)-induced lactate dehydrogenase (LDH) release and 3-[4,5-dimethylthiazol-2-yl]2,5-diphenyl tetrazolium bromide (MTT) reduction. 2-Butoxyethanol given alone did not affect LDH release and MTT reduction but concentration-dependently enhanced the cytotoxic effect of H(2)O(2). 2-Isopropoxyethanol significantly and concentration-dependently (1-25 mM) increased the basal LDH release and attenuated MTT reduction, but did not potentiate the cytotoxic effect of H(2)O(2). Contrary to this, 2-methoxyethanol did not show a cytotoxic effect while 2-ethoxyethanol at high concentrations intensified the hydrogen peroxide action. This study demonstrated that among the EGEs studied, 2-phenoxyethanol showed the most consistent cytotoxic effect on neurons in in vitro conditions and enhanced the hydrogen peroxide action. 2-Isopropoxyethanol had also a potent cytotoxic effect, but it did not enhance the hydrogen peroxide action, whereas 2-butoxyethanol only potentiated cytotoxic effect of H(2)O(2). It is concluded that the results of the present study should be confirmed in in vivo conditions and that some EGEs, especially 2-phenoxyethanol, 2-butoxyethanol and 2-isopropoxyethanol, may be responsible for initiation or exacerbation of neuronal cell damage.

http://www.ncbi.nlm.nih.gov/pubmed/?term=21273685

“2-phenoxyethanol showed the most consistent cytotoxic effect on neurons in in vitro conditions and enhanced the hydrogen peroxide action.”

Environmental Health And Preventative Medicine • January 2011

Gene expression in primary cultured astrocytes affected by aluminum: alteration of chaperons involved in protein folding

Author information

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Abstract

OBJECTIVES

Aluminum is notorious as a neurotoxic metal. The aim of our study was to determine whether endoplasmic reticulum (ER) stress is involved in aluminum-induced apoptosis in astrocytes.

METHODS

Mitochondrial RNA (mRNA) was analyzed by reverse transcription (RT)-PCR following pulse exposure of aluminum glycinate to primary cultured astrocytes. Tunicamycin was used as a positive control.

RESULTS

Gene expression analysis revealed that Ire1□ was up-regulated in astrocytes exposed to aluminum while Ire1 was up-regulated by tunicamycin. Exposure to aluminum glycinate, in contrast to tunicamycin, seemed to down-regulate mRNA expression of many genes, including the ER resident molecular chaperone BiP/Grp78 and Ca(2+)-binding chaperones (calnexin and calreticulin), as well as stanniocalcin 2 and OASIS. The down-regulation or non-activation of the molecular chaperons, whose expressions are known to be protective by increasing protein folding, may spell doom for the adaptive response. Exposure to aluminum did not have any significant effects on the expression of Bax and Bcl2 in astrocytes.

CONCLUSIONS

The results of this study demonstrate that aluminum may induce apoptosis in astrocytes via ER stress by impairing the protein-folding machinery.

http://www.ncbi.nlm.nih.gov/pubmed/21432213

“The results of this study demonstrate that aluminum may induce apoptosis in astrocytes via ER stress by impairing the protein-folding machinery.”

“aluminum (Al), plays a relevant role in affecting Aß aggregation and neurotoxicity.”

PLoS One • January 2011

Microarray Analysis on Human Neuroblastoma Cells Exposed to Aluminum, ß1–42-Amyloid or the ß1–42-Amyloid Aluminum Complex

Valentina Gatta, Denise Drago, Karina Fincati, Maria Teresa Valenti,
Luca Dalle Carbonare, Stefano L. Sensi, Paolo Zatta

Abstract

Background

A typical pathological feature of Alzheimer’s disease (AD) is the appearance in the brain of senile plaques made up of ß-amyloid (Aß) and neurofibrillary tangles. AD is also associated with an abnormal accumulation of some metal ions, and we have recently shown that one of these, aluminum (Al), plays a relevant role in affecting Aß aggregation and neurotoxicity.

Methodology

In this study, employing a microarray analysis of 35,129 genes, we investigated the effects induced by the exposure to the Aß1–42-Al (Aß-Al) complex on the gene expression profile of the neuronal-like cell line, SH-SY5Y.

Principal Findings

The microarray assay indicated that, compared to Aß or Al alone, exposure to Aß-Al complex produced selective changes in gene expression. Some of the genes selectively over or underexpressed are directly related to AD. A further evaluation performed with Ingenuity Pathway analysis revealed that these genes are nodes of networks and pathways that are involved in the modulation of Ca2+ homeostasis as well as in the regulation of glutamatergic transmission and synaptic plasticity.

Conclusions and Significance

Aß-Al appears to be largely involved in the molecular machinery that regulates neuronal as well as synaptic dysfunction and loss. Aß-Al seems critical in modulating key AD-related pathways such as glutamatergic transmission, Ca2+ homeostasis, oxidative stress, inflammation, and neuronal apoptosis.

http://journals.plos.org/plosone/article?id=10.1371/journal.pone.0015965#authcontrib

Monatshefte für Chemie - Chemical Monthly • April 2011

Aluminium in the human brain

Christopher Exley , Emily R. House

Abstract

An inevitable consequence of humans living in the Aluminium Age is the presence of aluminium in the brain. This non-essential, neurotoxic metal gains entry to the brain throughout all stages of human development, from the foetus through to old age. Human exposure to myriad forms of this ubiquitous and omnipresent metal makes its presence in the brain inevitable, while the structure and physiology of the brain makes it particularly susceptible to the accumulation of aluminium with age. In spite of aluminium's complete lack of biological essentiality, it actually participates avidly in brain biochemistry and substitutes for essential metals in critical biochemical processes. The degree to which such substitutions are disruptive and are manifested as biological effects will depend upon the biological availability of aluminium in any particular physical or chemical compartment, and will under all circumstances be exerting an energy load on the brain. In short, the brain must expend energy in its 'unconscious' response to an exposure to biologically available aluminium. There are many examples where 'biological effect' has resulted in aluminium-induced neurotoxicity and most potently in conditions that have resulted in an aluminium-associated encephalopathy. However, since aluminium is non-essential and not required by the brain, its biological availability will only rarely achieve such levels of acuity, and it is more pertinent to consider and investigate the brain's response to much lower though sustained levels of biologically reactive aluminium. This is the level of exposure that defines the putative role of aluminium in chronic neurodegenerative disease and, though thoroughly investigated in numerous animal models, the chronic toxicity of aluminium has yet to be addressed experimentally in humans. A feasible test of the 'aluminium hypothesis', whereby aluminium in the human brain is implicated in chronic neurodegenerative disease, would be to reduce the brain's aluminium load to the lowest possible level by non-invasive means. The simplest way that this aim can be fulfilled in a significant and relevant population is by facilitating the urinary excretion of aluminium through the regular drinking of a silicic acid-rich mineral water over an extended time period. This will lower the body and brain burden of aluminium, and by doing so will test whether brain aluminium contributes significantly to chronic neurodegenerative diseases such as Alzheimer's and Parkinson's.

http://link.springer.com/article/10.1007%2Fs00706-010-0417-y

Vaccine • August 2011
Letter to the Editor

Aluminium-based adjuvants should not be used as placebos in clinical trials

by Christopher Exley
The Birchall Centre, Lennard-Jones Laboratories, Keele University, Staffordshire, UK

August 2011

Report available for purchase $39.95

http://www.ncbi.nlm.nih.gov/pubmed/?term=21871940

[Vaccine manufacturers use aluminum-based adjuvants with controls in clinical trials meaning adverse affects of aluminum will go unnoticed]

“Aluminium ... has no known biological role.

It accumulates in the body when protective gastrointestinal mechanisms are bypassed ...”

[for example, when it’s injected]

Proceedings Of The Nutrition Society • August 2011

Aluminium exposure from parenteral nutrition in preterm infants and later health outcomes during childhood and adolescence

Author information

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Abstract

Aluminium is the most common metallic element, but has no known biological role. It accumulates in the body when protective gastrointestinal mechanisms are bypassed, renal function is impaired, or exposure is high - all of which apply frequently to preterm infants. Recognised clinical manifestations of aluminium toxicity include dementia, anaemia and bone disease. Parenteral nutrition (PN) solutions are liable to contamination with aluminium, particularly from acidic solutions in glass vials, notably calcium gluconate. When fed parenterally, infants retain >75% of the aluminium, with high serum, urine and tissue levels. Later health effects of neonatal intravenous aluminium exposure were investigated in a randomised trial comparing standard PN solutions with solutions specially sourced for low aluminium content. Preterm infants exposed for >10 d to standard solutions had impaired neurologic development at 18 months. At 13-15 years, subjects randomised to standard PN had lower lumbar spine bone mass; and, in non-randomised analyses, those with neonatal aluminium intake above the median had lower hip bone mass. Given the sizeable number of infants undergoing intensive care and still exposed to aluminium via PN, these findings have contemporary relevance. Until recently, little progress had been made on reducing aluminium exposure, and meeting Food and Drug Administration recommendations (<5 µg/kg per d) has been impossible in patients <50 kg using available products. Recent advice from the UK Medicines and Healthcare regulatory Authority that calcium gluconate in small volume glass containers should not be used for repeated treatment in children <18 years, including preparation of PN, is an important step towards addressing this problem.

http://www.ncbi.nlm.nih.gov/pubmed/?term=21781356

Journal Of Inorganic Biochemistry • November 2011

Do aluminum vaccine adjuvants contribute to the rising prevalence of autism?

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Abstract

Autism spectrum disorders (ASD) are serious multisystem developmental disorders and an urgent global public health concern. Dysfunctional immunity and impaired brain function are core deficits in ASD. Aluminum (Al), the most commonly used vaccine adjuvant, is a demonstrated neurotoxin and a strong immune stimulator. Hence, adjuvant Al has the potential to induce neuroimmune disorders. When assessing adjuvant toxicity in children, two key points ought to be considered: (i) children should not be viewed as "small adults" as their unique physiology makes them much more vulnerable to toxic insults; and (ii) if exposure to Al from only few vaccines can lead to cognitive impairment and autoimmunity in adults, is it unreasonable to question whether the current pediatric schedules, often containing 18 Al adjuvanted vaccines, are safe for children? By applying Hill's criteria for establishing causality between exposure and outcome we investigated whether exposure to Al from vaccines could be contributing to the rise in ASD prevalence in the Western world. Our results show that: (i) children from countries with the highest ASD prevalence appear to have the highest exposure to Al from vaccines; (ii) the increase in exposure to Al adjuvants significantly correlates with the increase in ASD prevalence in the United States observed over the last two decades (Pearson $r=0.92$, $p<0.0001$); and (iii) a significant correlation exists between the amounts of Al administered to preschool children and the current prevalence of ASD in seven Western countries, particularly at 3-4 months of age (Pearson $r=0.89$-0.94, $p=0.0018$-0.0248). The application of the Hill's criteria to these data indicates that the correlation between Al in vaccines and ASD may be causal. Because children represent a fraction of the population most at risk for complications following exposure to Al, a more rigorous evaluation of Al adjuvant safety seems warranted.

http://www.ncbi.nlm.nih.gov/pubmed/22099159

"Our results show that:

(i) children from countries with the highest Autistic Spectrum Disorder prevalence appear to have the highest exposure to Aluminum from vaccines;

(ii) the increase in exposure to Al adjuvants significantly correlates with the increase in Autistic Spectrum Disorder prevalence in the United States observed over the last two decades and

(iii) a significant correlation exists between the amounts of Aluminum administered to preschool children and the current prevalence of Autistic Spectrum Disorder in seven Western countries, particularly at 3-4 months of age."

Journal Of Inorganic Biochemistry • November 2011

Aluminium and human breast diseases

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Abstract

The human breast is exposed to aluminium from many sources including diet and personal care products, but dermal application of aluminium-based antiperspirant salts provides a local long-term source of exposure. Recent measurements have shown that aluminium is present in both tissue and fat of the human breast but at levels which vary both between breasts and between tissue samples from the same breast. We have recently found increased levels of aluminium in non-invasively collected nipple aspirate fluids taken from breast cancer patients (mean 268 ± 28 μg/l) compared with control healthy subjects (mean 131 ± 10 μg/l) providing evidence of raised aluminium levels in the breast microenvironment when cancer is present. The measurement of higher levels of aluminium in type I human breast cyst fluids (median 150 μg/l) compared with human serum (median 6 μg/l) or human milk (median 25 μg/l) warrants further investigation into any possible role of aluminium in development of this benign breast disease. Emerging evidence for aluminium in several breast structures now requires biomarkers of aluminium action in order to ascertain whether the presence of aluminium has any biological impact. To this end, we report raised levels of proteins that modulate iron homeostasis (ferritin, transferrin) in parallel with raised aluminium in nipple aspirate fluids in vivo, and we report overexpression of mRNA for several S100 calcium binding proteins following long-term exposure of MCF-7 human breast cancer cells in vitro to aluminium chlorhydrate.

http://www.ncbi.nlm.nih.gov/pubmed/?term=22099158

“Recent measurements have shown that aluminium is present in both tissue and fat of the human breast but at levels which vary both between breasts and between tissue samples from the same breast. We have recently found increased levels of aluminium in noninvasively collected nipple aspirate fluids taken from breast cancer patients (mean 268 ± 28 μg/l) compared with control healthy subjects (mean 131 ± 10 μg/l) providing evidence of raised aluminium levels in the breast microenvironment when cancer is present.”

Journal Of Inorganic Biochemistry • November 2011

Long-term follow-up of cognitive dysfunction in patients with aluminum hydroxide-induced macrophagic myofasciitis (MMF)

Author information

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Abstract

Macrophagic myofasciitis (MMF) is characterized by specific muscle lesions assessing long-term persistence of aluminum hydroxide within macrophages at the site of previous immunization. Affected patients are middle-aged adults, mainly presenting with diffuse arthromyalgias, chronic fatigue, and cognitive dysfunction. Representative features of MMF-associated cognitive dysfunction (MACD) include (i) dysexecutive syndrome; (i) visual memory; (iii) left ear extinction at dichotic listening test. In present study we retrospectively evaluated the progression of MACD in 30 MMF patients. Most patients fulfilled criteria for non-amnestic/dysexecutive mild cognitive impairment, even if some cognitive deficits seemed unusually severe. MACD remained stable over time, although dysexecutive syndrome tended to worsen. Long-term follow-up of a subset of patients with 3 or 4 consecutive neuropsychological evaluations confirmed the stability of MACD with time, despite marked fluctuations.

http://www.ncbi.nlm.nih.gov/pubmed/22099155

“Macrophagic myofasciitis (MMF) is characterized by specific muscle lesions assessing long-term persistence of aluminum hydroxide within macrophages at the site of previous immunization.”

Journal Of Inorganic Biochemistry • November 2011

Towards the prevention of potential aluminum toxic effects and an effective treatment for Alzheimer's disease

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Abstract

In 1991, treatment with low dose intramuscular desferrioxamine (DFO), a trivalent chelator that can remove excessive iron and/or aluminum from the body, was reported to slow the progression of Alzheimer's disease (AD) by a factor of two. Twenty years later this promising trial has not been followed up and why this treatment worked still is not clear. In this critical interdisciplinary review, we provide an overview of the complexities of AD and involvement of metal ions, and revisit the neglected DFO trial. We discuss research done by us and others that is helping to explain involvement of metal ion catalyzed production of reactive oxygen species in the pathogenesis of AD, and emerging strategies for inhibition of metal-ion toxicity. Highlighted are insights to be considered in the quests to prevent potentially toxic effects of aluminum toxicity and prevention and intervention in AD.

http://www.ncbi.nlm.nih.gov/pubmed/?term=22099160

"Highlighted are insights to be considered in the quests to prevent potentially toxic effects of aluminum toxicity and prevention and intervention in AD."

Journal Of Inorganic Biochemistry • November 2011

Aluminum toxicity and astrocyte dysfunction: a metabolic link to neurological disorders

Author information

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Abstract

Aluminum (Al) has been implicated in a variety of neurological diseases. However, the molecular mechanisms that enable Al to be involved in these disorders have yet to be fully delineated. Using astrocytes as a model of the cerebral cellular system, we have uncovered the biochemical networks that are affected by Al toxicity. In this review, we reveal how the inhibitory influence of Al on ATP production and on mitochondrial functions help generate globular astrocytes that are fat producing machines. These biological events may be the contributing factors to Al-triggered brain disorders.

http://www.ncbi.nlm.nih.gov/pubmed/?term=22099161

“Aluminum (Al) has been implicated in a variety of neurological diseases. However, the molecular mechanisms that enable Al to be involved in these disorders have yet to be fully delineated. These biological events may be the contributing factors to Al-triggered brain disorders.”

IOS Press Library • November 2011

Aluminum and Alzheimer's Disease: After a Century of Controversy, Is there a Plausible Link?

Author Information

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Abstract

The brain is a highly compartmentalized organ exceptionally susceptible to accumulation of metabolic errors. Alzheimer's disease (AD) is the most prevalent neurodegenerative disease of the elderly and is characterized by regional specificity of neural aberrations associated with higher cognitive functions. Aluminum (Al) is the most abundant neurotoxic metal on earth, widely bioavailable to humans and repeatedly shown to accumulate in AD-susceptible neuronal foci. In spite of this, the role of Al in AD has been heavily disputed based on the following claims: 1) bioavailable Al cannot enter the brain in sufficient amounts to cause damage, 2) excess Al is efficiently excreted from the body, and 3) Al accumulation in neurons is a consequence rather than a cause of neuronal loss. Research, however, reveals that: 1) very small amounts of Al are needed to produce neurotoxicity and this criterion is satisfied through dietary Al intake, 2) Al sequesters different transport mechanisms to actively traverse brain barriers, 3) incremental acquisition of small amounts of Al over a lifetime favors its selective accumulation in brain tissues, and 4) since 1911, experimental evidence has repeatedly demonstrated that chronic Al intoxication reproduces neuropathological hallmarks of AD. Misconceptions about Al bioavailability may have mislead scientists regarding the significance of Al in the pathogenesis of AD. The hypothesis that Al significantly contributes to AD is built upon very solid experimental evidence and should not be dismissed. Immediate steps should be taken to lessen human exposure to Al, which may be the single most aggravating and avoidable factor related to AD.

http://content.iospress.com/articles/journal-of-alzheimers-disease/jad101494

"Research, however, reveals that:

1) very small amounts of Al are needed to produce neurotoxicity and this criterion is satisfied through dietary Al intake

2) Al sequesters different transport mechanisms to actively traverse brain barriers

3) incremental acquisition of small amounts of Al over a lifetime favors its selective accumulation in brain tissues

4) since 1911, experimental evidence has repeatedly demonstrated that chronic Al intoxication reproduces neuropathological hallmarks of AD."

Biomedical And Environmental Science • December 2011

Effect of aluminum hydroxide adjuvant on the immunogenicity of the 2009 pandemic influenza A/H1N1 vaccine: multi-level modeling of data with repeated measures

Author information

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Abstract

OBJECTIVE
To evaluate the effect of the aluminum hydroxide (Al-OH) adjuvant on the 2009 pandemic influenza A/H1N1 (pH1N1) vaccine.

METHODS
In a multicenter, double-blind, randomized, placebo-controlled trial, participants received two doses of split-virion formulation containing 15 μg hemagglutinin antigen, with or without aluminum hydroxide (Al-OH). We classified the participants into six age categories (>61 years, 41-60 years, 19-40 years, 13-18 years, 8-12 years, and 3-7 years) and obtained four blood samples from each participant on days 0, 21, 35, and 42 following the first dose of immunization. We assessed vaccine immunogenicity by measuring the geometric mean titer (GMT) of hemagglutination inhibiting antibody. We used a two-level model to evaluate the fixed effect of aluminum Al-OH and other factors, accounting for repeated measures.

RESULTS
The predictions of repeated measurement on GMTs of formulations with or without Al-OH, were 80.35 and 112.72, respectively. Al-OH significantly reduced immunogenicity after controlling for time post immunization, age-group and gender.

CONCLUSION
The Al-OH adjuvant does not increase but actually reduces the immunogenicity of the split-virion pH1N1 vaccine.

http://www.ncbi.nlm.nih.gov/pubmed/?term=22365398

“The aluminum hydroxide adjuvant does not increase but actually reduces the immunogenicity of the split-virion pH1N1 vaccine.”

Current Medicinal Chemistry • 2011

Aluminum Vaccine Adjuvants: Are they Safe?

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Abstract
Aluminum is an experimentally demonstrated neurotoxin and the most commonly used vaccine adjuvant. Despite almost 90 years of widespread use of aluminum adjuvants, medical science's understanding about their mechanisms of action is still remarkably poor. There is also a concerning scarcity of data on toxicology and pharmacokinetics of these compounds. In spite of this, the notion that aluminum in vaccines is safe appears to be widely accepted. Experimental research, however, clearly shows that aluminum adjuvants have a potential to induce serious immunological disorders in humans. In particular, aluminum in adjuvant form carries a risk for autoimmunity, long-term brain inflammation and associated neurological complications and may thus have profound and widespread adverse health consequences. In our opinion, the possibility that vaccine benefits may have been overrated and the risk of potential adverse effects underestimated, has not been rigorously evaluated in the medical and scientific community. We hope that the present paper will provide a framework for a much needed and long overdue assessment of this highly contentious medical issue.

http://www.meerwetenoverfreek.nl/images/stories/Tomljenovic_Shaw-CMC-published.pdf

"Experimental research, however, clearly shows that aluminum adjuvants have a potential to induce serious immunological disorders in humans. In particular, aluminum in adjuvant form carries a risk for autoimmunity, long-term brain inflammation and associated neurological complications and may thus have profound and widespread adverse health consequences. In our opinion, the possibility that vaccine benefits may have been overrated and the risk of potential adverse effects underestimated, has not been rigorously evaluated in the medical and scientific community."

Entropy • 2012

Special Issue
Biosemiotic Entropy: Disorder, Disease, and Mortality

Empirical Data Confirm Autism Symptoms Related to Aluminum and Acetaminophen Exposure

Author Information

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Abstract

Autism is a condition characterized by impaired cognitive and social skills, associated with compromised immune function. The incidence is alarmingly on the rise, and environmental factors are increasingly suspected to play a role. This paper investigates word frequency patterns in the U.S. CDC Vaccine Adverse Events Reporting System (VAERS) database. Our results provide strong evidence supporting a link between autism and the aluminum in vaccines. A literature review showing toxicity of aluminum in human physiology offers further support. Mentions of autism in VAERS increased steadily at the end of the last century, during a period when mercury was being phased out, while aluminum adjuvant burden was being increased. Using standard log-likelihood ratio techniques, we identify several signs and symptoms that are significantly more prevalent in vaccine reports after 2000, including cellulitis, seizure, depression, fatigue, pain and death, which are also significantly associated with aluminum-containing vaccines. We propose that children with the autism diagnosis are especially vulnerable to toxic metals such as aluminum and mercury due to insufficient serum sulfate and glutathione. A strong correlation between autism and the MMR (Measles, Mumps, Rubella) vaccine is also observed, which may be partially explained via an increased sensitivity to acetaminophen administered to control fever.

http://www.mdpi.com/1099-4300/14/11/2227

“Using standard log-likelihood ratio techniques, we identify several signs and symptoms that are significantly more prevalent in vaccine reports after 2000, including cellulitis, seizure, depression, fatigue, pain and death, which are also significantly associated with aluminum-containing vaccines. We propose that children with the autism diagnosis are especially vulnerable to toxic metals such as aluminum and mercury due to insufficient serum sulfate and glutathione. A strong correlation between autism and the MMR (Measles, Mumps, Rubella) vaccine is also observed, which may be partially explained via an increased sensitivity to acetaminophen administered to control fever.”

Neurotoxicology And Teratology • January 2012

Multiple toxic heavy metals and neonatal neurobehavior in China require considering co-exposure to Thimerosal-ethylmercury and adjuvant-aluminum

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https://www.infona.pl/resource/bwmeta1.element.elsevier-5ea9d498-e159-3496-99a1-2b3c4a568a20

Lupus • February 2012

Mechanisms of aluminum adjuvant toxicity and autoimmunity in pediatric populations

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Abstract

Immune challenges during early development, including those vaccine-induced, can lead to permanent detrimental alterations of the brain and immune function. Experimental evidence also shows that simultaneous administration of as little as two to three immune adjuvants can overcome genetic resistance to autoimmunity. In some developed countries, by the time children are 4 to 6 years old, they will have received a total of 126 antigenic compounds along with high amounts of aluminum (Al) adjuvants through routine vaccinations. According to the US Food and Drug Administration, safety assessments for vaccines have often not included appropriate toxicity studies because vaccines have not been viewed as inherently toxic. Taken together, these observations raise plausible concerns about the overall safety of current childhood vaccination programs. When assessing adjuvant toxicity in children, several key points ought to be considered: (i) infants and children should not be viewed as "small adults" with regard to toxicological risk as their unique physiology makes them much more vulnerable to toxic insults; (ii) in adult humans Al vaccine adjuvants have been linked to a variety of serious autoimmune and inflammatory conditions (i.e., "ASIA"), yet children are regularly exposed to much higher amounts of Al from vaccines than adults; (iii) it is often assumed that peripheral immune responses do not affect brain function. However, it is now clearly established that there is a bidirectional neuro-immune cross-talk that plays crucial roles in immunoregulation as well as brain function. In turn, perturbations of the neuro-immune axis have been demonstrated in many autoimmune diseases encompassed in "ASIA" and are thought to be driven by a hyperactive immune response; and (iv) the same components of the neuro-immune axis that play key roles in brain development and immune function are heavily targeted by Al adjuvants. In summary, research evidence shows that increasing concerns about current vaccination practices may indeed be warranted. Because children may be most at risk of vaccine-induced complications, a rigorous evaluation of the vaccine-related adverse health impacts in the pediatric population is urgently needed.

http://www.ncbi.nlm.nih.gov/pubmed/22235057

"Immune challenges during early development, including those vaccine-induced, can lead to permanent detrimental alterations of the brain and immune function.

Experimental evidence also shows that simultaneous administration of as little as two to three immune adjuvants can overcome genetic resistance to autoimmunity. In some developed countries, by the time children are 4 to 6 years old, they will have received a total of 126 antigenic compounds along with high amounts of aluminum (Al) adjuvants through routine vaccinations.

According to the US Food and Drug Administration, safety assessments for vaccines have often not included appropriate toxicity studies because vaccines have not been viewed as inherently toxic. Taken together, these observations raise plausible concerns about the overall safety of current childhood vaccination programs."

Immunology Letters • September 2012

Alum increases antigen uptake reduces antigen degradation and sustains antigen presentation by DCs in vitro

Author information

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Abstract

Aluminium adjuvants (alum) have been the only widely approved adjuvants for use in human vaccines since the 1920s, however, the mechanism of action of these adjuvants remains elusive. Due to increasing demand for novel adjuvants, a clearer understanding of the mechanisms that allow these important agents to affect adaptive immune responses will make a significant contribution to the rational design of future vaccines. Using a novel approach to tracking antigen and antigen presentation, we demonstrate that alum induces higher antigen accumulation and increased antigen presentation by dendritic cells (DCs) in vitro. Antigen accumulation was 100-fold higher and antigen presentation 10-fold higher following alum treatment when compared with soluble protein alone. We also observed that alum causes an initial reduction in presentation compared with soluble antigen, but eventually increases the magnitude and duration of antigen presentation. This was associated with reduced protein degradation in DCs following alum treatment. These studies demonstrate the dynamic alterations in antigen processing and presentation induced by alum that underlie enhanced DC function in response to this adjuvant.

http://www.ncbi.nlm.nih.gov/pubmed/?term=22732235

“Aluminium adjuvants (alum) have been the only widely approved adjuvants for use in human vaccines since the 1920s, however, the mechanism of action of these adjuvants remains elusive.”

Coordination Chemistry Reviews • October 2012

Metal Ions in Neurodegenerative Diseases
The coordination chemistry of aluminium in neurodegenerative disease

by Christopher Exley

Abstract

The coordination chemistry of a metal ion defines its optimal association with a biomolecule such that its binding by specific ligands on that molecule confers function and biological purpose. Aluminium is a non-essential metal with no known biological role which means that its coordination neurochemistry defines aluminium's putative role in a number of neurodegenerative diseases. In examining this chemistry it is found that very little is known about the complexes formed and ligands involved in aluminium's interactions with neurochemically-relevant ligands. Aluminium's action as a pro-oxidant as well as an excitotoxin are highlighted while the evidence for its interactions with amyloid beta, tau and DNA are discussed and it is concluded that it is too early to discount these ligands as targets for the neurotoxicity of aluminium.

Highlights

• There are few quantitaive data describing the coordination chemistry of aluminium in neurodegenerative disease.

• One compelling line of evidence relates to the putative aluminium superoxide semi-reduced radical ion AlO22+ and its powerful action as a pro-oxidant.

• Another important candidate is aluminium's complex with ATP and its potential to disrupt neuronal signalling and induce excitotoxicity.

• Though there are no quantitative data to describe aluminium's interactions with amyloid beta this does not preclude their association in the brain.

• The biological reactivity of aluminium supports myriad as yet unidentified interactions with biomolecules associated with brain function in health and disease.

http://www.sciencedirect.com/science/article/pii/S0010854512000392

"In examining this chemistry it is found that very little is known about the complexes formed and ligands involved in aluminium's interactions with neurochemically-relevant ligands. Aluminium's action as a pro-oxidant as well as an excitotoxin are highlighted while the evidence for its interactions with amyloid beta, tau and DNA are discussed and it is concluded that it is too early to discount these ligands as targets for the neurotoxicity of aluminium."

Journal Of Trace Elements In Medicine And Biology • October 2012

Aluminium overload after 5 years in skin biopsy following post-vaccination with subcutaneous pseudolymphoma

Author information

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Abstract

Aluminium hydroxide is used as an effective adjuvant in a wide range of vaccines for enhancing immune response to the antigen. The pathogenic role of aluminium hydroxide is now recognized by the presence of chronic fatigue syndrome, macrophagic myofasciitis and subcutaneous pseudolymphoma, linked to intramuscular injection of aluminium hydroxide-containing vaccines. The aim of this study is to verify if the subcutaneous pseudolymphoma observed in this patient in the site of vaccine injection is linked to an aluminium overload. Many years after vaccination, a subcutaneous nodule was discovered in a 45-year-old woman with subcutaneous pseudolymphoma. In skin biopsy at the injection site for vaccines, aluminium (Al) deposits are assessed by Morin stain and quantification of Al is performed by Zeeman Electrothermal Atomic Absorption Spectrophotometry. Morin stain shows Al deposits in the macrophages, and Al assays (in µg/g, dry weight) were 768.10±18 for the patient compared with the two control patients, 5.61±0.59 and 9.13±0.057. Given the pathology of this patient and the high Al concentration in skin biopsy, the authors wish to draw attention when using the Al salts known to be particularly effective as adjuvants in single or repeated vaccinations. The possible release of Al may induce other pathologies ascribed to the well-known toxicity of this metal.

http://www.ncbi.nlm.nih.gov/pubmed/22425036

“The pathogenic role of aluminium hydroxide is now recognized by the presence of chronic fatigue syndrome, macrophagic myofasciitis and subcutaneous pseudolymphoma, linked to intramuscular injection of aluminium hydroxide-containing vaccines.”

Current Aging Science • December 2012

Aluminum excytotoxicity and neuroautotoimmunity: the role of the brain expression of CD32+ (FcyRIIa), ICAM-1+ and CD3E in aging

Author information

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Abstract

In the central nervous system (CNS) microglia are crucial for the defense of the brain against invading microorganisms, formation of tumors, and damage following trauma. However, uncontrolled activation of these cells may have deleterious outcomes through activation of Fcy and the complement 3 receptors and the induction of an adaptive immune reaction. Proteins contributing to this reaction are the intercellular adhesion molecule-1 (ICAM-1) and CD3 molecules, among others. Both can be expressed on the glia cells before cytokine release and may facilitate an autoimmune inflammatory reaction in the brain. Round microglial cells among the pyramidal cells of the hippocampus with increased expression of CD32+ (FcyIIa) and near the site of injection of aluminum were detected immunohistochemically and indicate microglial activation at the site of aluminum injury. ICAM-1+ immunoreactivity significantly increased in the hippocampus and in the choroids plexus, indicating increased inflammation in the brain as well as increased CD3E+ expression in the hippocampus and non-MHC-restricted T cytotoxicity after aluminum injection. The pattern of expression of CD32+ (FcyIIa receptor) near the site of aluminum injection indicates that microglia may play a phagocytic role at the site of aluminum-induced excitotoxicity in the brain. Significant expression of ICAM-1+ and CD3E+ immunoreactive cells with the clusters of ICAM-1+ in the choroid plexus suggests a consequently neurotoxic autoimmune reaction induced by microglial hyperactivation in the injured brain.

http://www.ncbi.nlm.nih.gov/pubmed/23387884

“In the central nervous system (CNS) microglia are crucial for the defense of the brain against invading microorganisms, formation of tumors, and damage following trauma. However, uncontrolled activation of these cells may have deleterious outcomes ...”

“alum has high neurotoxic potential and planning administration of continuously escalating doses of this poorly biodegradable adjuvant in the population should be carefully evaluated by regulatory agencies since the compound may be insidiously unsafe.”

BMC Medicine • April 2013

Slow CCL2-dependent translocation of biopersistent particles from muscle to brain

Author information

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Abstract

BACKGROUND

Long-term biodistribution of nanomaterials used in medicine is largely unknown. This is the case for alum, the most widely used vaccine adjuvant, which is a nanocrystalline compound spontaneously forming micron/submicron-sized agglomerates. Although generally well tolerated, alum is occasionally detected within monocyte-lineage cells long after immunization in presumably susceptible individuals with systemic/neurologic manifestations or autoimmune (inflammatory) syndrome induced by adjuvants (ASIA).

METHODS

On the grounds of preliminary investigations in 252 patients with alum-associated ASIA showing both a selective increase of circulating CCL2, the major monocyte chemoattractant, and a variation in the CCL2 gene, we designed mouse experiments to assess biodistribution of vaccine-derived aluminum and of alum-particle fluorescent surrogates injected in muscle. Aluminum was detected in tissues by Morin stain and particle induced X-ray emission) (PIXE) Both 500 nm fluorescent latex beads and vaccine alum agglomerates-sized nanohybrids (Al-Rho) were used.

RESULTS

Intramuscular injection of alum-containing vaccine was associated with the appearance of aluminum deposits in distant organs, such as spleen and brain where they were still detected one year after injection. Both fluorescent materials injected into muscle translocated to draining lymph nodes (DLNs) and thereafter were detected associated with phagocytes in blood and spleen. Particles linearly accumulated in the brain up to the six-month endpoint; they were first found in perivascular CD11b+ cells and then in microglia and other neural cells. DLN ablation dramatically reduced the biodistribution. Cerebral translocation was not observed after direct intravenous injection, but significantly increased in mice with chronically altered blood-brain-barrier. Loss/gain-of-function experiments consistently implicated CCL2 in systemic diffusion of Al-Rho particles captured by monocyte-lineage cells and in their subsequent neurodelivery. Stereotactic particle injection pointed out brain retention as a factor of progressive particle accumulation.

CONCLUSION

Nanomaterials can be transported by monocyte-lineage cells to DLNs, blood and spleen, and, similarly to HIV, may use CCL2-dependent mechanisms to penetrate the brain. This occurs at a very low rate in normal conditions explaining good overall tolerance of alum despite its strong neurotoxic potential. However, continuously escalating doses of this poorly biodegradable adjuvant in the population may become insidiously unsafe, especially in the case of overimmunization or immature/altered blood brain barrier or high constitutive CCL-2 production.

Full Report:
http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3616851/

"... a form of the autoimmune/autoinflammatory syndrome induced by adjuvants (ASIA syndrome)

in commercial sheep, linked to the repetitive inoculation of aluminum-containing adjuvants through vaccination.

The syndrome shows an acute phase that affects less than 0.5% of animals in a given herd ..."

[a syndrome that affects 5,000 individuals per each 1 million]

Immunology Research • July 2013

Autoimmune/autoinflammatory syndrome induced by adjuvants (ASIA syndrome) in commercial sheep

Author information

Luján L1, Pérez M, Salazar E, Álvarez N, Gimeno M, Pinczowski P, Irusta S, Santamaría J, Insausti N, Cortés Y, Figueras L, Cuartielles I, Vila M, Fantova E, Chapullé JL.

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Abstract

We describe a form of the autoimmune/autoinflammatory syndrome induced by adjuvants (ASIA syndrome) in commercial sheep, linked to the repetitive inoculation of aluminum-containing adjuvants through vaccination. The syndrome shows an acute phase that affects less than 0.5% of animals in a given herd, it appears 2-6 days after an adjuvant-containing inoculation and it is characterized by an acute neurological episode with low response to external stimuli and acute meningoencephalitis, most animals apparently recovering afterward. The chronic phase is seen in a higher proportion of flocks, it can follow the acute phase, and it is triggered by external stimuli, mostly low temperatures. The chronic phase begins with an excitatory phase, followed by weakness, extreme cachexia, tetraplegia and death. Gross lesions are related to a cachectic process with muscular atrophy, and microscopic lesions are mostly linked to a neurodegenerative process in both dorsal and ventral column of the gray matter of the spinal cord. Experimental reproduction of ovine ASIA in a small group of repeatedly vaccinated animals was successful. Detection of Al(III) in tissues indicated the presence of aluminum in the nervous tissue of experimental animals. The present report is the first description of a new sheep syndrome (ovine ASIA syndrome) linked to multiple, repetitive vaccination and that can have devastating consequences as it happened after the compulsory vaccination against bluetongue in 2008. The ovine ASIA syndrome can be used as a model of other similar diseases affecting both human and animals. A major research effort is needed in order to understand its complex pathogenesis.

http://www.ncbi.nlm.nih.gov/pubmed/?term=23579772

Immunology Research • July 2013

Aluminum in the central nervous system (CNS): toxicity in humans and animals, vaccine adjuvants, and autoimmunity

Author information

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Abstract

We have examined the neurotoxicity of aluminum in humans and animals under various conditions, following different routes of administration, and provide an overview of the various associated disease states. The literature demonstrates clearly negative impacts of aluminum on the nervous system across the age span. In adults, aluminum exposure can lead to apparently age-related neurological deficits resembling Alzheimer's and has been linked to this disease and to the Guamanian variant, ALS-PDC. Similar outcomes have been found in animal models. In addition, injection of aluminum adjuvants in an attempt to model Gulf War syndrome and associated neurological deficits leads to an ALS phenotype in young male mice. In young children, a highly significant correlation exists between the number of pediatric aluminum-adjuvanted vaccines administered and the rate of autism spectrum disorders. Many of the features of aluminum-induced neurotoxicity may arise, in part, from autoimmune reactions, as part of the ASIA syndrome.

http://www.ncbi.nlm.nih.gov/pubmed/23609067

"In young children, a highly significant correlation exists between the number of pediatric aluminum-adjuvanted vaccines administered and the rate of autism spectrum disorders. Many of the features of aluminum-induced neurotoxicity may arise, in part, from autoimmune reactions, as part of the ASIA syndrome."

Journal Of Inorganic Biochemistry • September 2013

Selective accumulation of aluminum in cerebral arteries in Alzheimer's disease (AD)

Author information

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Abstract

Once biologically available aluminum bypasses gastrointestinal and blood-brain barriers, this environmentally-abundant neurotoxin has an exceedingly high affinity for the large pyramidal neurons of the human brain hippocampus. This same anatomical region of the brain is also targeted by the earliest evidence of Alzheimer's disease (AD) neuropathology. The mechanism for the selective targeting and transport of aluminum into the hippocampus of the human brain is not well understood. In an effort to improve our understanding of a pathological aluminum entry system into the brain, this study examined the aluminum content of 8 arteries that supply blood to the hippocampus, including the aorta and several cerebral arteries. In contrast to age-matched controls, in AD patients we found a gradient of increasing aluminum concentration from the aorta to the posterior cerebral artery that supplies blood to the hippocampus. Primary cultures of human brain endothelial cells were found to have an extremely high affinity for aluminum when compared to other types of brain cells. Together, these results suggest for the first time that endothelial cells that line the cerebral vasculature may have biochemical attributes conducive to binding and targeting aluminum to selective anatomical regions of the brain, such as the hippocampus, with potential downstream pro-inflammatory and pathogenic consequences.

http://www.ncbi.nlm.nih.gov/pubmed/23764827

"Once biologically available aluminum bypasses gastrointestinal and blood-brain barriers, this environmentally-abundant neurotoxin has an exceedingly high affinity for the large pyramidal neurons of the human brain hippocampus. This same anatomical region of the brain is also targeted by the earliest evidence of Alzheimer's disease (AD) neuropathology. The mechanism for the selective targeting and transport of aluminum into the hippocampus of the human brain is not well understood."

“All 30 infant formulas were contaminated with aluminium.”

BMC Pediatrics • October 2013

The aluminium content of infant formulas remains too high

Author information

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Abstract

BACKGROUND
Recent research published in this journal highlighted the issue of the high content of aluminium in infant formulas. The expectation was that the findings would serve as a catalyst for manufacturers to address a significant problem of these, often necessary, components of infant nutrition. It is critically important that parents and other users have confidence in the safety of infant formulas and that they have reliable information to use in choosing a product with a lower content of aluminium. Herein, we have significantly extended the scope of the previous research and the aluminium content of 30 of the most widely available and often used infant formulas has been measured.

METHODS
Both ready-to-drink milks and milk powders were subjected to microwave digestion in the presence of 15.8 M HNO3 and 30% w/v H2O2 and the aluminium content of the digests was measured by TH GFAAS.

RESULTS
Both ready-to-drink milks and milk powders were contaminated with aluminium. The concentration of aluminium across all milk products ranged from ca 100 to 430 μg/L. The concentration of aluminium in two soya-based milk products was 656 and 756 μg/L. The intake of aluminium from non-soya-based infant formulas varied from ca 100 to 300 μg per day. For soya-based milks it could be as high as 700 μg per day.

CONCLUSIONS
All 30 infant formulas were contaminated with aluminium. There was no clear evidence that subsequent to the problem of aluminium being highlighted in a previous publication in this journal that contamination had been addressed and reduced. It is the opinion of the authors that regulatory and other non-voluntary methods are now required to reduce the aluminium content of infant formulas and thereby protect infants from chronic exposure to dietary aluminium.

Full Report

http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3851493/

"... aluminum has the potential to induce damage at a range of levels in the Central Nervous System leading to neuronal death, circuit malfunction, and ultimately system failure."

Immunome Research • October 2013

Aluminums Role in CNS-immune System Interactions leading to Neurological Disorders

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Abstract

Multisystem interactions are well established in neurological disorders, in spite of conventional views that only the central nervous system (CNS) is impacted. We review evidence for mutual interactions between the immune and nervous systems and show how these seem to be implicated in the origin and progression of nervous system disorders. Well-established immune system triggers leading to autoimmune reactions are considered. Of these, aluminum, a known neurotoxicant, may be of particular importance. We have demonstrated elsewhere that aluminum has the potential to induce damage at a range of levels in the CNS leading to neuronal death, circuit malfunction, and ultimately system failure. Aluminum is widely used as an adjuvant in various vaccine formulations and has been implicated in a multisystem disorder termed autoimmune/inflammatory syndrome induced by adjuvants (ASIA). The implications of aluminum-induced ASIA in some disorders of the CNS are considered. We propose a unified theory capturing a progression from a local response to a systemic response initiated by disruption of water-based interfaces of exposed cells.

http://www.omicsonline.com/open-access/aluminums-role-in-cnsimmune-system-interactions-leading-to-neurological-disorders-14822-1745-7580-9-069.php?aid=20403

Environmental Science • Processes And Impacts • October 2013

Human exposure to aluminium

Author information

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Abstract

Human activities have circumvented the efficient geochemical cycling of aluminium within the lithosphere and therewith opened a door, which was previously only ajar, onto the biotic cycle to instigate and promote the accumulation of aluminium in biota and especially humans. Neither these relatively recent activities nor the entry of aluminium into the living cycle are showing any signs of abating and it is thus now imperative that we understand as fully as possible how humans are exposed to aluminium and the future consequences of a burgeoning exposure and body burden. The aluminium age is upon us and there is now an urgent need to understand how to live safely and effectively with aluminium.

http://www.ncbi.nlm.nih.gov/pubmed/23982047

“The aluminium age is upon us and there is now an urgent need to understand how to live safely and effectively with aluminium.”

Communications In Integrated Biology • November 2013

Aluminum and the human diet revisited

Christopher A Shaw and Thomas E Marler

Abstract

Concerns about aluminum (Al) exposure in the human diet have persisted for one century. We suggest that continued research would benefit from better reporting of environmental factors that are known to influence Al accumulation in plant organs that are consumed, focusing on subsets of the general public that exhibit the highest risk for neuropathological responses, increased evaluation of commercial processing procedures that may concentrate Al or other toxic substances, and designing studies with low dose, chronic exposure rather than further study of acute, brief exposure.

Neurological Disorders

Cognitive decline and central nervous system (CNS) pathologies that resemble those of Alzheimer are induced by Al in older rats.20 Soil and water sources of Al were implicated in the ALS-parkinsonism dementia complex on Guam.21 Additionally, the acute effects of higher doses of Al-induced dialysis associated encephalopathy in humans are well documented.22

The route of administration of Al plays a key role in the type of neurotoxicity exhibited. While most dietary Al is removed by the kidneys, those lacking mature or patent kidney function such as pediatric and geriatric subjects may be more likely to accumulate Al in different organs, including the CNS. Injected Al from Al adjuvants in vaccines have a very different fate and appear to be picked up from the draining lymph nodes by circulating macrophages and transported into the CNS.23 Motor neuron loss following Al hydroxide injections in mice and sheep24-26 and macrophagic myofasciitis in humans involving cognitive dysfunction in humans.27 Al adjuvants have also been linked to a series of autoimmune disorders in humans.28

Developmental neurological disorders such as autism spectrum disorder (ASD) also have a potential Al link through the accumulative weight of pediatric vaccines, many of which contain Al as adjuvants.29 Indeed, there is a highly significant correlation between ASD rates and cumulative Al adjuvant amount,30 a correlation that satisfies eight of nine Hill criteria for causality. Similar outcomes are found in new born mice injected with Al adjuvants.31 A recent review also links Al to ASD.32

http://www.ncbi.nlm.nih.gov/pubmed/24505503

“Developmental neurological disorders such as autism spectrum disorder (ASD) also have a potential Aluminum link through the accumulative weight of pediatric vaccines, many of which contain Aluminum as adjuvants.”

Journal Of Inorganic Biochemistry • November 2013

Administration of aluminium to neonatal mice in vaccine-relevant amounts is associated with adverse long term neurological outcomes

Author information

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Abstract

Our previous ecological studies of autism spectrum disorder (ASD) has demonstrated a correlation between increasing ASD rates and aluminium (Al) adjuvants in common use in paediatric vaccines in several Western countries. The correlation between ASD rate and Al adjuvant amounts appears to be dose-dependent and satisfies 8 of 9 Hill criteria for causality. We have now sought to provide an animal model to explore potential behavioural phenotypes and central nervous system (CNS) alterations using s.c. injections of Al hydroxide in early postnatal CD-1 mice of both sexes. Injections of a “high” and “low” Al adjuvant levels were designed to correlate to either the U.S. or Scandinavian paediatric vaccine schedules vs. control saline-injected mice. Both male and female mice in the “high Al” group showed significant weight gains following treatment up to sacrifice at 6 months of age. Male mice in the “high Al” group showed significant changes in light-dark box tests and in various measures of behaviour in an open field. Female mice showed significant changes in the light-dark box at both doses, but no significant changes in open field behaviours. These current data implicate Al injected in early postnatal life in some CNS alterations that may be relevant for a better understanding of the aetiology of ASD.

http://www.ncbi.nlm.nih.gov/pubmed/23932735

“Our previous ecological studies of autism spectrum disorder (ASD) has demonstrated a correlation between increasing Autism Spectrum Disorder rates and aluminium (Al) adjuvants in common use in paediatric vaccines in several Western countries.”

Journal Of Inorganic Biochemistry • November 2013

Aluminium based adjuvants and their effects on mitochondria and lysosomes of phagocytosing cells

Author information

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Abstract

Aluminium oxyhydroxide, Al(OH)3 is one of few compounds approved as an adjuvant in human vaccines. However, the mechanism behind its immune stimulating properties is still poorly understood. In vitro co-culture of an aluminium adjuvant and the human monocytic cell line THP-1 resulted in reduced cell proliferation. Inhibition occurred at concentrations of adjuvant several times lower than would be found at the injection site using a vaccine formulation containing an aluminium adjuvant. Based on evaluation of the mitochondrial membrane potential, THP-1 cells showed no mitochondrial rupture after co-culture with the aluminium adjuvant, instead an increase in mitochondrial activity was seen. The THP-1 cells are phagocytosing cells and after co-culture with the aluminium adjuvant the phagosomal pathway was obstructed. Primary or early phagosomes mature into phagolysosomes with an internal pH of 4.5 - 5 and carry a wide variety of hydrolysing enzymes. Co-culture with the aluminium adjuvant yielded a reduced level of acidic vesicles and cathepsin L activity, a proteolytic enzyme of the phagolysosomes, was almost completely inhibited. THP-1 cells are an appropriate in vitro model in order to investigate the mechanism behind the induction of a phagocytosing antigen presenting cell into an inflammatory cell by aluminium adjuvants. Much information will be gained by investigating the phagosomal pathway and what occurs inside the phagosomes and to elucidate the ultimate fate of phagocytosed aluminium particles.

http://www.ncbi.nlm.nih.gov/pubmed/23992993

“Much information will be gained by investigating the phagosomal pathway and what occurs inside the phagosomes and to elucidate the ultimate fate of phagocytosed aluminium particles.”

Journal Of Inorganic Biochemistry • November 2013

Aluminium and breast cancer: Sources of exposure, tissue measurements and mechanisms of toxicological actions on breast biology

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Abstract

This review examines recent evidence linking exposure to aluminium with the aetiology of breast cancer. The human population is exposed to aluminium throughout daily life including through diet, application of antiperspirants, use of antacids and vaccination. Aluminium has now been measured in a range of human breast structures at higher levels than in blood serum and experimental evidence suggests that the tissue concentrations measured have the potential to adversely influence breast epithelial cells including generation of genomic instability, induction of anchorage-independent proliferation and interference in oestrogen action. The presence of aluminium in the human breast may also alter the breast microenvironment causing disruption to iron metabolism, oxidative damage to cellular components, inflammatory responses and alterations to the motility of cells. The main research need is now to investigate whether the concentrations of aluminium measured in the human breast can lead in vivo to any of the effects observed in cells in vitro and this would be aided by the identification of biomarkers specific for aluminium action.

http://www.ncbi.nlm.nih.gov/pubmed/23899626

“Aluminium has now been measured in a range of human breast structures at higher levels than in blood serum and experimental evidence suggests that the tissue concentrations measured have the potential to adversely influence breast epithelial cells including generation of genomic instability, induction of anchorage-independent proliferation and interference in oestrogen action.”

Immunome Research • 2013

Aluminum's Role in CNS-immune System Interactions leading to Neurological Disorders

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Abstract

Multisystem interactions are well established in neurological disorders, in spite of conventional views that only the central nervous system (CNS) is impacted. We review evidence for mutual interactions between the immune and nervous systems and show how these seem to be implicated in the origin and progression of nervous system disorders. Well-established immune system triggers leading to autoimmune reactions are considered. Of these, aluminum, a known neurotoxicant, may be of particular importance. We have demonstrated elsewhere that aluminum has the potential to induce damage at a range of levels in the CNS leading to neuronal death, circuit malfunction and ultimately, system failure. Aluminum is widely used as an adjuvant in various vaccine formulations and has been implicated in a multisystem disorder termed "autoimmune/inflammatory syndrome induced by adjuvants" (ASIA). The implications of aluminum-induced ASIA in some disorders of the CNS are considered. We propose a unified theory capturing a progression from a local response to a systemic response initiated by disruption of water-based interfaces of exposed cells.

https://people.csail.mit.edu/seneff/Shaw_et_al_Immunome_Res_2013.pdf

"The implications of aluminum-induced ASIA in some disorders of the Central Nervous System are considered."

“Unfortunately, despite its favorable safety profile, aluminum hydroxide
can only weakly or moderately potentiate antigen-specific antibody responses.
Simply reducing the particle size of the traditional aluminum hydroxide adjuvant into nanometers
represents a novel and effective approach to improve its adjuvanticity.”

Journal Of Controlled Release • January 2014

Aluminum hydroxide nanoparticles show a stronger vaccine adjuvant activity than traditional aluminum hydroxide microparticles

Author information

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Abstract

Aluminum hydroxide is used as a vaccine adjuvant in various human vaccines. Unfortunately, despite its favorable safety profile, aluminum hydroxide can only weakly or moderately potentiate antigen-specific antibody responses. When dispersed in an aqueous solution, aluminum hydroxide forms particulates of 1-20μm. There is increasing evidence that nanoparticles around or less than 200nm as vaccine or antigen carriers have a more potent adjuvant activity than large microparticles. In the present study, we synthesized aluminum hydroxide nanoparticles of 112nm. Using ovalbumin and Bacillus anthracis protective antigen protein as model antigens, we showed that protein antigens adsorbed on the aluminum hydroxide nanoparticles induced a stronger antigen-specific antibody response than the same protein antigens adsorbed on the traditional aluminum hydroxide microparticles of around 9.3μm. The potent adjuvant activity of the aluminum hydroxide nanoparticles was likely related to their ability to more effectively facilitate the uptake of the antigens adsorbed on them by antigen-presenting cells. Finally, the local inflammation induced by aluminum hydroxide nanoparticles in the injection sites was milder than that induced by microparticles. Simply reducing the particle size of the traditional aluminum hydroxide adjuvant into nanometers represents a novel and effective approach to improve its adjuvanticity.

Full Report

http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3918952/

Bulletin de l'Academie Nationale de Medecine • January 2014

Biopersistence and systemic distribution of intramuscularly injected particles: what impact on long-term tolerability of alum adjuvants?

Gherardi RK, Cadusseau J, Authier FJ.

Abstract

Aluminium oxyhydroxide (alum), a nanocrystalline compound that forms agglomerates, has been widely used as a vaccine adjuvant since 1927, but the mechanisms by which it stimulates immune responses remain poorly understood. Although generally well tolerated, alum may occasionally cause chronic health problems in presumably susceptible individuals. Some individuals may rarely develop delayed-onset diffuse myalgia, chronic exhaustion and cognitive dysfunction, associated with long-term persistence (up to 12 years) of alum-loaded macrophages at site of i.m. immunization, defining so-called macrophagic myofasciitis (MMF). Symptoms are consistent with the chronic fatigue/myalgic encephalomyelitis (CFS/ME) syndrome, and have been used as a paradigm of the "autoimmune/inflammatory syndrome induced by adjuvants" (ASIA). Cognitive dysfunction is reminiscent of that described in workers exposed to inhaled Al particles. Individual susceptibility may influence both alum biopersistence and difusion away from injection sites. Biopersistent particles such as fluorescent alum-coated nanohybrids, when injected into mouse muscle, are captured by monocyte-lineage cells and then carried to distant organs, draining lymph nodes and blood, probably via the thoracic duct, with delayed and accumulative translocation to the brain (microglial cells). Brain penetration occurs at extremely low levels in normal conditions, possibly explaining the good tolerance of alum despite its high neurotoxic potential. However, systemic diffusion is considerably enhanced by the potentiating effect of MCP-1, the main monocyte chemoattractant factor, the production of which is subject to marked variations linked to age and to genetic and environmental factors. Selective MCP-1 elevation is the only known circulating biomarker of MMF.

http://www.ncbi.nlm.nih.gov/pubmed/26259285

"Biopersistent particles such as fluorescent alum-coated nanohybrids, when injected into mouse muscle, are captured by monocyte-lineage cells and then carried to distant organs, draining lymph nodes and blood, probably via the thoracic duct, with delayed and accumulative translocation to the brain (microglial cells). Brain penetration occurs at extremely low levels in normal conditions, possibly explaining the good tolerance of alum despite its high neurotoxic potential."

Clinical And Experimental Immunology • January 2014

Effects of adjuvants for human use in systemic lupus erythematosus (SLE)-prone (New Zealand black/New Zealand white) F1 mice

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Abstract

The safety of four different adjuvants was assessed in lupus-prone New Zealand black/New Zealand white (BW)F1 mice. Four groups of mice were injected intraperitoneally with incomplete Freund's adjuvant (IFA), complete Freund's adjuvant (CFA), squalene (SQU) or aluminium hydroxide (ALU). An additional group received plain phosphate-buffered saline (PBS) (UNT group). Mice were primed at week 9 and boosted every other week up to week 15. Proteinuria became detectable at weeks 17 (IFA group), 24 (CFA group), 28 (SQU and ALU groups) and 32 (UNT group). Different mean values were obtained among the groups from weeks 17 to 21 [week 17: one-way analysis of variance (anova) P = 0·016; weeks 18 and 19: P = 0·048; weeks 20 and 21: P = 0·013] being higher in the IFA group than the others [Tukey's honestly significant difference (HSD) post-test P < 0·05]. No differences in anti-DNA antibody levels were observed among groups. Anti-RNP/Sm antibody developed at week 19 in only one CFA-treated mouse. Mean mouse weight at week 18 was lower in the ALU group than the IFA (Tukey's HSD post-test P = 0·04), CFA (P = 0·01) and SQU (P < 0·0001) groups, while the mean weight in the SQU group was higher than in the IFA (P = 0·009), CFA (P = 0·013) and UNT (P = 0·005) groups. The ALU group weight decreased by almost half between weeks 29 and 31, indicating some toxic effect of ALU in the late post-immunization period. Thus, SQU was the least toxic adjuvant as it did not (i) accelerate proteinuria onset compared to IFA; (ii) induce toxicity compared to ALU or (iii) elicit anti-RNP/Sm autoantibody, as occurred in the CFA group.

http://www.ncbi.nlm.nih.gov/pubmed/24112107

"The aluminum group weight decreased by almost half between weeks 29 and 31, indicating some toxic effect of aluminum in the late post-immunization period."

Allergy, Asthma & Clinical Immunology • January 2014

Aluminium adjuvants and adverse events in sub-cutaneous allergy immunotherapy

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Abstract

Sub-cutaneous immunotherapy is an effective treatment for allergy. It works by helping to modify or re-balance an individual's immune response to allergens and its efficacy is greatly improved by the use of adjuvants, most commonly, aluminium hydroxide. Aluminium salts have been used in allergy therapy for many decades and are assumed to be safe with few established side-effects. This assumption belies their potency as adjuvants and their potential for biological reactivity both at injection sites and elsewhere in the body. There are very few data purporting to the safety of aluminium adjuvants in allergy immunotherapy and particularly so in relation to longer term health effects. There are, if only few, published reports of adverse events following allergy immunotherapy and aluminium adjuvants are the prime suspects in the majority of such incidents. Aluminium adjuvants are clearly capable of initiating unwanted side effects in recipients of immunotherapy and while there is as yet no evidence that such are commonplace it is complacent to consider aluminium salts as harmless constituents of allergy therapies. Future research should establish the safety of the use of aluminium adjuvants in sub-cutaneous allergy immunotherapy.

http://www.aacijournal.com/content/10/1/4

"Aluminium salts have been used in allergy therapy for many decades and are assumed to be safe with few established side-effects. This assumption belies their potency as adjuvants and their potential for biological reactivity both at injection sites and elsewhere in the body."

Computational and Structural Biotechnology Journal • March 2014

Aluminium in Biological Environments: A Computational Approach

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Abstract

The increased availability of aluminium in biological environments, due to human intervention in the last century, raises concerns on the effects that this so far “excluded from biology” metal might have on living organisms. Consequently, the bioinorganic chemistry of aluminium has emerged as a very active field of research. This review will focus on our contributions to this field, based on computational studies that can yield an understanding of the aluminum biochemistry at a molecular level. Aluminium can interact and be stabilized in biological environments by complexing with both low molecular mass chelants and high molecular mass peptides. The speciation of the metal is, nonetheless, dictated by the hydrolytic species dominant in each case and which vary according to the pH condition of the medium. In blood, citrate and serum transferrin are identified as the main low molecular mass and high molecular mass molecules interacting with aluminium. The complexation of aluminium to citrate and the subsequent changes exerted on the deprotonation pathways of its tritable groups will be discussed along with the mechanisms for the intake and release of aluminium in serum transferrin at two pH conditions, physiological neutral and endosomatic acidic. Aluminium can substitute other metals, in particular magnesium, in protein buried sites and trigger conformational disorder and alteration of the protonation states of the protein’s sidechains. A detailed account of the interaction of aluminium with proteic sidechains will be given. Finally, it will be described how alumnium can exert oxidative stress by stabilizing superoxide radicals either as mononuclear aluminium or clustered in boehmite. The possibility of promotion of Fenton reaction, and production of hydroxyl radicals will also be discussed.

http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3995234/

“The increased availability of aluminium in biological environments, due to human intervention in the last century, raises concerns on the effects that this so far “excluded from biology” metal might have on living organisms.”

“There is prolonged retention of a fraction of aluminium that enters the brain ...”

Neurotoxicology • March 2014

Oxidative stress and mitochondrial dysfunction in aluminium neurotoxicity and its amelioration: a review

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Abstract

Aluminium is light weight and toxic metal present ubiquitously on earth which has gained considerable attention due to its neurotoxic effects. The widespread use of products made from or containing aluminium is ensuring its presence in our body. There is prolonged retention of a fraction of aluminium that enters the brain, suggesting its potential for accumulation with repeated exposures. There is no known biological role for aluminium within the body but adverse physiological effects of this metal have been observed in mammals. The generation of oxidative stress may be attributed to its toxic consequences in animals and humans. The oxidative stress has been implicated in pathogenesis of various neurodegenerative conditions including Alzheimer’s disease and Parkinson’s disease. Though it remains unclear whether oxidative stress is a major cause or merely a consequence of cellular dysfunction associated with neurodegenerative diseases, an accumulating body of evidence implicates that impaired mitochondrial energy production and increased mitochondrial oxidative damage is associated with the pathogenesis of neurodegenerative disorders. Being involved in the production of reactive oxygen species, aluminium may impair mitochondrial bioenergetics and may lead to the generation of oxidative stress. In this review, we have discussed the oxidative stress and mitochondrial dysfunctions occurring in Al neurotoxicity. In addition, the ameliorative measures undertaken in aluminium induced oxidative stress and mitochondrial dysfunctions have also been highlighted.

http://www.ncbi.nlm.nih.gov/pubmed/24560992

Journal Of Trace Elements In Medical Biology • April 2014

If exposure to aluminium in antiperspirants presents health risks, its content should be reduced

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Abstract

Since aluminium (Al) pervades our environment, the scientific community has for many years raised concerns regarding its safety in humans. Al is present in numerous cosmetics such as antiperspirants, lipsticks and sunscreens. Al chlorohydrate is the active antiperspirant agent in underarm cosmetics and may constitute for Al a key exposure route to the human body and a potential source of damage. An in vitro study has demonstrated that Al from antiperspirant can be absorbed through viable human stripped skin. The potential toxicity of Al has been clearly shown and recent works convincingly argue that Al could be involved in cancerogenic processes. Nowadays, for example, Al is suspected of being involved in breast cancer. Recent work in cells in culture has lent credence to the hypothesis that this metal could accumulate in the mammary gland and selectively interfere with the biological properties of breast epithelial cells, thereby promoting a cascade of alterations reminiscent of the early phases of malignant transformation. In addition, several studies suggest that the presence of Al in human breast could influence metastatic process. As a consequence, given that the toxicity of Al has been widely recognized and that it is not a physiological component in human tissues, reducing the concentration of this metal in antiperspirants is a matter of urgency.

http://www.ncbi.nlm.nih.gov/pubmed/?term=24418462

“Al chlorohydrate is the active antiperspirant agent in underarm cosmetics and may constitute for Aluminum a key exposure route to the human body and a potential source of damage. An in vitro study has demonstrated that Aluminum from antiperspirant can be absorbed through viable human stripped skin. The potential toxicity of Aluminum has been clearly shown and recent works convincingly argue that Aluminum could be involved in cancerogenic processes.”

World Journal Of Pediatrics • May 2014

Aluminum exposure and toxicity in neonates: a practical guide to halt aluminum overload in the prenatal and perinatal periods

Author information

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Abstract

BACKGROUND

During the last years, human newborns have been overexposed to biologically reactive aluminum, with possible relevant consequences on their future health and on their susceptibility to a variety of diseases. Children, newborns and particularly preterm neonates are at an increased risk of aluminum toxicity because of their relative immaturity.

DATA SOURCES

Based on recent original publications and classical data of the literatures, we reviewed the aluminum content in mother's food during the intrauterine life as well as in breast milk and infant formula during lactation. We also determined the possible role of aluminum in parenteral nutrition solutions, in adjuvants of vaccines and in pharmaceutical products. A special focus is placed on the relationship between aluminum overexposure and the insurgence of bone diseases.

RESULTS

Practical points of management and prevention are suggested. Aluminum sources that infants may receive during the first 6 months of life are presented. In the context of prevention of possible adverse effects of aluminum overload in fetal tissues during development, simple suggestions to pregnant women are described. Finally, practical points of management and prevention are suggested.

CONCLUSIONS

Pediatricians and neonatologists must be more concerned about aluminum content in all products our newborns are exposed to, starting from monitoring aluminum concentrations in milk- and soy-based formulas in which, on the basis of recent studies, there is still too much aluminum.

http://www.ncbi.nlm.nih.gov/pubmed/24801228

"Pediatricians and neonatologists must be more concerned about aluminum content in all products our newborns are exposed to, starting from monitoring aluminum concentrations in milk and soy based formulas in which, on the basis of recent studies, there is still too much aluminum."

Mucosal Immunology • May 2014

Aluminum enhances inflammation and decreases mucosal healing in experimental colitis in mice

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"Deleterious effects of aluminum on intestinal inflammation and mucosal repair strongly suggest that aluminum might be an environmental Inflammatory Bowel Disease risk factor."

Abstract

The increasing incidence of inflammatory bowel diseases (IBDs) in developing countries has highlighted the critical role of environmental pollutants as causative factors in their pathophysiology. Despite its ubiquity and immune toxicity, the impact of aluminum in the gut is not known. This study aimed to evaluate the effects of environmentally relevant intoxication with aluminum in murine models of colitis and to explore the underlying mechanisms. Oral administration of aluminum worsened intestinal inflammation in mice with 2,4,6-trinitrobenzene sulfonic acid- and dextran sodium sulfate-induced colitis and chronic colitis in interleukin 10-negative (IL10(-/-)) mice. Aluminum increased the intensity and duration of macroscopic and histologic inflammation, colonic myeloperoxidase activity, inflammatory cytokines expression, and decreased the epithelial cell renewal compared with control animals. Under basal conditions, aluminum impaired intestinal barrier function. In vitro, aluminum induced granuloma formation and synergized with lipopolysaccharide to stimulate inflammatory cytokines expression by epithelial cells. Deleterious effects of aluminum on intestinal inflammation and mucosal repair strongly suggest that aluminum might be an environmental IBD risk factor.

http://www.ncbi.nlm.nih.gov/pubmed/24129165

Expert Reviews In Neurotherapy • June 2014

What is the risk of aluminium as a neurotoxin?

by Christopher Exley

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The body burden of aluminium:

To understand or even appreciate the risk that aluminium poses as a neurotoxin, we will need to further our understanding of the body burden of aluminium and we will need to implement measures to reduce the body burden to a lowest practical limit. I have recently reformulated the definition of aluminium's body burden placing it into the context of what I have called aluminium's exposome [13]. We have also been investigating non-invasive ways to reduce the uptake of aluminium into the body and, importantly, to facilitate the excretion of aluminium from the body. We were successful in lowering the body burden of aluminium in individuals with moderate-to-severe AD and concomitantly we were able to demonstrate clinically significant improvements in cognitive performance in some individuals [14]. These experiments offer some hope that the aluminium hypothesis of AD, and indeed other neurodegenerative diseases, might be tested by lowering the body burden of aluminium in affected individuals. Then we might be able to ascertain if AD, for example, is the human manifestation of the risk of aluminium as a known neurotoxin.

"Then we might be able to ascertain if AD, for example, is the human manifestation of the risk of aluminium as a known neurotoxin."

https://www.futsci.com/uploads/project/file/da0e1cb2dbea30e405db672eea4290b35a0d6a90.pdf

“There is now sufficient evidence from both human and animal studies

showing that cumulative exposure to aluminium adjuvants is not as benign as previously assumed.”

Autism • Causes & Prevalence • June 2014

Etiology of autism spectrum disorders: Genes, environment, or both?

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Abstract

Thus far, most of the research on both neurodevelopmental and neurodegenerative disorders has been focused on finding the presumed underlying genetic causes, while much less emphasis has been put on potential environmental factors. While some forms of autism are clearly genetic, the fact remains that heritability factors cannot adequately explain all reported cases nor their drastic increase over the last few decades. In particular, studies on twins have now shown that common environmental factors account for 55% of their risk for developing autism while genetic susceptibility explains only 37% of cases. Because the prenatal environment and early postnatal environment are shared between twins and because overt symptoms of autism emerge around the end of the first year of life, it is likely that at least some of the environmental factors contributing to the risk of autism exert their deleterious neurodevelopmental effect during this early period of life. Indeed, evidence has now emerged showing that autism may in part result from early-life immune insults induced by environmental xenobiotics. One of the most common xenobiotic with immuno-stimulating as well as neurotoxic properties to which infants under two years of age are routinely exposed worldwide is the aluminum (Al) vaccine adjuvant. In this review we discuss the mechanisms by which Al can induce adverse neurological and immunological effects and how these may provide important clues of Al’s putative role in autism. Because of the tight connection between the development of the immune and the central nervous system, the possibility that immune-overstimulation in early infancy via vaccinations may play a role in neurobehavioural disorders needs to be carefully considered.

Conclusion

There is now sufficient evidence from both human and animal studies showing that cumulative exposure to aluminium adjuvants is not as benign as previously assumed. Given that vaccines are the only medical intervention that we attempt to deliver to every living human on earth and that by far the largest target population for vaccination are healthy children, a better appreciation and understanding of vaccine adjuvant risks appears warranted.

http://www.oapublishinglondon.com/article/1368

Vaccine • July 2014

Aluminium in allergen-specific subcutaneous immunotherapy— a German perspective

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Abstract

We are living in an “aluminium age” with increasing bioavailability of the metal for approximately 125 years, contributing significantly to the aluminium body burden of humans. Over the course of life, aluminium accumulates and is stored predominantly in the lungs, bones, liver, kidneys and brain. The toxicity of aluminium in humans is briefly summarised, highlighting links and possible causal relationships between a high aluminium body burden and a number of neurological disorders and disease states. Aluminium salts have been used as depot-adjuvants successfully in essential prophylactic vaccinations for almost 100 years, with a convincing positive benefit-risk assessment which remains unchanged. However, allergen-specific immunotherapy commonly consists of administering a long-course programme of subcutaneous injections using preparations of relevant allergens. Regulatory authorities currently set aluminium limits for vaccines per dose, rather than per treatment course. Unlike prophylactic vaccinations, numerous injections with higher proportions of aluminium-adjuvant per injection are applied in subcutaneous immunotherapy (SCIT) and will significantly contribute to a higher cumulative life dose of aluminium. While the human body may cope robustly with a daily aluminium overload from the environment, regulatory cumulative threshold values in immunotherapy need further addressing. Based on the current literature, predisposing an individual to an unusually high level of aluminium, such as through subcutaneous immunotherapy, has the potential to form focal accumulations in the body with the propensity to exert forms of toxicity. Particularly in relation to longer-term health effects, the safety of aluminium adjuvants in immunotherapy remains unchallenged by health authorities - evoking the need for more consideration, guidance, and transparency on what is known and not known about its safety in long-course therapy and what measures can be taken to prevent or minimise its risks. The possibility of providing an effective means of measuring aluminium accumulation in patients undergoing long-term SCIT treatment as well as reducing their aluminium body burden is discussed.

Full Report

http://www.sciencedirect.com/science/article/pii/S0264410X14007397

“... the safety of aluminium adjuvants in immunotherapy remains unchallenged by health authorities - evoking the need for more consideration ...”

"... there is only a limited understanding of the response of regulatory T cells to aluminum adjuvants and the vaccines that contain them."

Vaccine • September 2014

A role for impaired regulatory T cell function in adverse responses to aluminum adjuvant-containing vaccines in genetically susceptible individuals

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Abstract

Regulatory T cells play a critical role in the immune response to vaccination, but there is only a limited understanding of the response of regulatory T cells to aluminum adjuvants and the vaccines that contain them. Available studies in animal models show that although induced T regulatory cells may be induced concomitantly with effector T cells following aluminum-adjuvanted vaccination, they are unable to protect against sensitization, suggesting that under the Th2 immune-stimulating effects of aluminum adjuvants, Treg cells may be functionally compromised. Allergic diseases are characterized by immune dysregulation, with increases in IL-4 and IL-6, both of which exert negative effects on Treg function. For individuals with a genetic predisposition, the beneficial influence of adjuvants on immune responsiveness may be accompanied by immune dysregulation, leading to allergic diseases. This review examines aspects of the regulatory T cell response to aluminum-adjuvanted immunization and possible genetic susceptibility factors related to that response.

http://www.ncbi.nlm.nih.gov/pubmed/?term=25066736

Journal Of Toxicology • October 2014

Aluminum-induced entropy in biological systems: implications for neurological disease

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Abstract

Over the last 200 years, mining, smelting, and refining of aluminum (Al) in various forms have increasingly exposed living species to this naturally abundant metal. Because of its prevalence in the earth's crust, prior to its recent uses it was regarded as inert and therefore harmless. However, Al is invariably toxic to living systems and has no known beneficial role in any biological systems. Humans are increasingly exposed to Al from food, water, medicinals, vaccines, and cosmetics, as well as from industrial occupational exposure. Al disrupts biological self-ordering, energy transduction, and signaling systems, thus increasing biosemiotic entropy. Beginning with the biophysics of water, disruption progresses through the macromolecules that are crucial to living processes (DNAs, RNAs, proteoglycans, and proteins). It injures cells, circuits, and subsystems and can cause catastrophic failures ending in death. Al forms toxic complexes with other elements, such as fluorine, and interacts negatively with mercury, lead, and glyphosate. Al negatively impacts the central nervous system in all species that have been studied, including humans. Because of the global impacts of Al on water dynamics and biosemiotic systems, CNS disorders in humans are sensitive indicators of the Al toxicants to which we are being exposed.

Full Report

http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4202242/

"Beginning with the biophysics of water, disruption progresses through the macromolecules that are crucial to living processes (DNAs, RNAs, proteoglycans, and proteins). It injures cells, circuits, and subsystems and can cause catastrophic failures ending in death. Aluminum forms toxic complexes with other elements, such as fluorine, and interacts negatively with mercury, lead, and glyphosate.

Aluminum negatively impacts the central nervous system in all species that have been studied, including humans. Because of the global impacts of Aluminum on water dynamics and biosemiotic systems, Central Nervous System disorders in humans are sensitive indicators of the Aluminum toxicants to which we are being exposed.

... vaccine trials often treat an Aluminum adjuvant-containing injection as a harmless " placebo " (a comparison benchmark or control treatment) or they use another Al-containing vaccine to treat a " control group, " despite evidence that Aluminum in vaccine-relevant exposures is universally toxic to humans and animals. Its use in a supposed " placebo " or in any " control " treatment in vaccine trials is indefensible."

Critical Reviews In Toxicology • October 2014

Systematic review of potential health risks posed by pharmaceutical, occupational and consumer exposures to metallic and nanoscale aluminum, aluminum oxides, aluminum hydroxide and its soluble salts

Author information

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Abstract

Abstract Aluminum (Al) is a ubiquitous substance encountered both naturally (as the third most abundant element) and intentionally (used in water, foods, pharmaceuticals, and vaccines); it is also present in ambient and occupational airborne particulates. Existing data underscore the importance of Al physical and chemical forms in relation to its uptake, accumulation, and systemic bioavailability. The present review represents a systematic examination of the peer-reviewed literature on the adverse health effects of Al materials published since a previous critical evaluation compiled by Krewski et al. (2007) . Challenges encountered in carrying out the present review reflected the experimental use of different physical and chemical Al forms, different routes of administration, and different target organs in relation to the magnitude, frequency, and duration of exposure. Wide variations in diet can result in Al intakes that are often higher than the World Health Organization provisional tolerable weekly intake (PTWI), which is based on studies with Al citrate. Comparing daily dietary Al exposures on the basis of "total Al"assumes that gastrointestinal bioavailability for all dietary Al forms is equivalent to that for Al citrate, an approach that requires validation. Current occupational exposure limits (OELs) for identical Al substances vary as much as 15-fold. The toxicity of different Al forms depends in large measure on their physical behavior and relative solubility in water. The toxicity of soluble Al forms depends upon the delivered dose of Al(+3) to target tissues. Trivalent Al reacts with water to produce bidentate superoxide coordination spheres [Al(O2)(H2O4)(+2) and Al(H2O)6 (+3)] that after complexation with O2(•-), generate Al superoxides [Al(O2(•))](H2O5)](+2). Semireduced AlO2(•) radicals deplete mitochondrial Fe and promote generation of H2O2, O2 (•-) and OH(•). Thus, it is the Al(+3)-induced formation of oxygen radicals that accounts for the oxidative damage that leads to intrinsic apoptosis. In contrast, the toxicity of the insoluble Al oxides depends primarily on their behavior as particulates. Aluminum has been held responsible for human morbidity and mortality, but there is no consistent and convincing evidence to associate the Al found in food and drinking water at the doses and chemical forms presently consumed by people living in North America and Western Europe with increased risk for Alzheimer's disease (AD). Neither is there clear evidence to show use of Al-containing underarm antiperspirants or cosmetics increases the risk of AD or breast cancer. Metallic Al, its oxides, and common Al salts have not been shown to be either genotoxic or carcinogenic. Aluminum exposures during neonatal and pediatric parenteral nutrition (PN) can impair bone mineralization and delay neurological development. Adverse effects to vaccines with Al adjuvants have occurred; however, recent controlled trials found that the immunologic response to certain vaccines with Al adjuvants was no greater, and in some cases less than, that after identical vaccination without Al adjuvants. The scientific literature on the adverse health effects of Al is extensive. Health risk assessments for Al must take into account individual co-factors (e.g., age, renal function, diet, gastric pH). Conclusions from the current review point to the need for refinement of the PTWI, reduction of Al contamination in PN solutions, justification for routine addition of Al to vaccines, and harmonization of OELs for Al substances.

http://www.ncbi.nlm.nih.gov/pubmed/25233067

"The scientific literature on the adverse health effects of Al is extensive. Conclusions from the current review point to the need for refinement of the provisional tolerable weekly intake (PTWI), reduction of Aluminum contamination in parenteral nutrition (PN) solutions, justification for routine addition of Aluminum to vaccines ..."

Frontiers In Neurology • October 2014

Why industry propaganda and political interference cannot disguise the inevitable role played by human exposure to aluminum in neurodegenerative diseases, including Alzheimer's disease

Author Information

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Abstract

In the aluminum age, it is clearly unpalatable for aluminum, the globe's most successful metal, to be implicated in human disease. It is unpalatable because for approximately 100 years human beings have reaped the rewards of the most abundant metal of the Earth's crust without seriously considering the potential consequences for human health. The aluminum industry is a pillar of the developed and developing world and irrespective of the tyranny of human exposure to aluminum it cannot be challenged without significant consequences for businesses, economies, and governments. However, no matter how deep the dependency or unthinkable the withdrawal, science continues to document, if not too slowly, a burgeoning body burden of aluminum in human beings. Herein, I will make the case that it is inevitable both today and in the future that an individual's exposure to aluminum is impacting upon their health and is already contributing to, if not causing, chronic diseases such as Alzheimer's disease. This is the logical, if uncomfortable, consequence of living in the aluminum age.

Full Report

http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4209859/

"Herein, I will make the case that it is inevitable both today and in the future that an individual's exposure to aluminum is impacting upon their health and is already contributing to, if not causing, chronic diseases such as Alzheimer's disease. This is the logical, if uncomfortable, consequence of living in the aluminum age."

Environmental Science And Pollution Research International • November 2014

Effects of aluminium and bacterial lipopolysaccharide on oxidative stress and immune parameters in roach, Rutilus rutilus L

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Abstract

Aluminium is used in diverse anthropogenic processes at the origin of pollution events in aquatic ecosystems. In the Champagne region (France), high concentrations of aluminium (Al) are detected due to vine-growing practices. In fish, little is known about the possible immune-related effects at relevant environmental concentrations. The present study analyzes the simultaneous effects of aluminium and bacterial lipopolysaccharide (LPS), alone and in combination, on toxicological biomarkers in the freshwater fish species Rutilus rutilus. For this purpose, roach treated or not with LPS were exposed to environmental concentrations of aluminium (100 µg/L) under laboratory-controlled conditions for 2, 7, 14 and 21 days. After each exposure time, we assessed hepatic lipoperoxidation, catalase activity, glutathione reductase activity and total glutathione content. We also analyzed cellular components related to the LPS-induced inflammatory response in possible target tissues, i.e. head kidney and spleen. Our results revealed a significant prooxidant effect in the liver cells and head kidney leukocytes of roach exposed to 100 µg of Al/L for 2 days. In liver, we observed more lipoperoxidation products and lower endogenous antioxidant activity levels such as glutathione reductase activity and total glutathione content. These prooxidant effects were associated with a higher oxidative burst in head kidney leukocytes, and they were all the more important in fish stimulated by LPS injection. These findings demonstrate that environmental concentrations of Al induce oxidative and immunotoxic effects in fish and are associated to an immunomodulatory process related to the inflammatory response.

http://www.ncbi.nlm.nih.gov/pubmed/24996940

“These findings demonstrate that environmental concentrations of Aluminum induce oxidative and immunotoxic effects in fish and are associated to an immunomodulatory process related to the inflammatory response.”

Science Reports • September 2014

Unequivocal identification of intracellular aluminium adjuvant in a monocytic THP-1 cell line

Author information

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Abstract

Aluminium-based adjuvants (ABA) are the predominant adjuvants used in human vaccinations. While a consensus is yet to be reached on the aetiology of the biological activities of ABA several studies have identified shape, crystallinity and size as critical factors affecting their adjuvanticity. In spite of recent advances, the fate of ABA following their administration remains unclear. Few if any studies have demonstrated the unequivocal presence of intracellular ABA. Herein we demonstrate for the first time the unequivocal identification of ABA within a monocytic T helper 1 (THP-1) cell line, using lumogallion as a fluorescent molecular probe for aluminium. Use of these new methods revealed that particulate ABA was only found in the cell cytoplasm. Transmission electron microscopy revealed that ABA were contained within vesicle-like structures of approximately 0.5-1 μm in diameter.

Full Report

http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4155332/

“In spite of recent advances, the fate of Aluminium-based adjuvants following their administration remains unclear. Herein we demonstrate for the first time the unequivocal identification of ABA within a monocytic T helper 1 cell line, using lumogallion as a fluorescent molecular probe for aluminium. Use of these new methods revealed that particulate Aluminium-based adjuvants was only found in the cell cytoplasm.”

“This short “Opinion” paper will overview and comment on

the current massive mobilization of aluminum into the earth’s biosphere.”

Frontiers In Neurology • December 2014

The mobilization of aluminum into the biosphere

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Abstract

Aluminum is currently the most widely used non-ferrous metal, and its extraction and purification from geological stores exceeds that of any other metal except iron (1, 2). In 2013, global primary aluminum production was ~52 million tons (104 billion pounds) or about 15 pounds for very person on the earth (1–4). The global outlook for aluminum demand from developing countries such as Brazil, China, India, and Indonesia is rapidly increasing, due to new applications for aluminum and aluminum alloys in infrastructural support, transportation including automobiles, aviation and aerospace applications, electrical transmission, and the generation of energy, including catalytic zeolites in the petroleum and petrochemical industries (5). Interestingly, the largest “machine” built by humankind is the domestic and international networks for the transmission of electricity. Although traditionally-used copper has a higher electrical conductivity, aluminum is only slightly less so, being lighter, more ductile, and less expensive; aluminum is now widely used for both high-voltage tower construction and the electrical transmission wires themselves (2–5). It has been estimated that within the next 10 years aluminum production will exceed that of the previous 150 years (1–3). This prolific de novo generation of aluminum combined with its highly efficient recycling means this metal is becoming increasingly present in our biosphere, defined as the sum of all ecosystems and living organisms on the earth. This short “Opinion” paper will overview and comment on the current massive mobilization of aluminum into the earth’s biosphere.

http://journal.frontiersin.org/article/10.3389/fneur.2014.00262/full

Immunology Research • December 2014

Autoimmune/inflammatory syndrome induced by adjuvants (ASIA): clues and pitfalls in the pediatric background

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Abstract

The development and increasing diffusion of new vaccinations and global immunization protocols have aroused burning debates about safety of adjuvants and their immunogenicity-enhancing effect in vaccines. Shoenfeld and Agmon-Levin have grouped under the term "autoimmune/inflammatory syndrome induced by adjuvants" (ASIA) a complex of variable signs and symptoms that may occur after a previous exposure to different adjuvants and also external environmental triggers, even eliciting specific overt immune-mediated disorders. This entity subsumes five medical conditions: post-vaccination phenomena, gulf war syndrome, macrophagic myofasciitis syndrome, siliconosis, and sick building syndrome, but the relevance and magnitude of the syndrome in the pediatric age is fundamentally limited to post-vaccination autoimmune or inflammatory disorders. The occurrence of vaccine-triggered phenomena represents a diagnostic challenge for clinicians and a research conundrum for many investigators. In this paper, we will analyze the general features of ASIA and focus on specific post-vaccination events in relation with the pediatric background. In the presence of a favorable genetic background, many autoimmune/inflammatory responses can be triggered by adjuvants and external factors, showing how the man himself might breach immune tolerance and drive many pathogenetic aspects of human diseases. Nonetheless, the elective application of ASIA diagnostic criteria to the pediatric population requires further assessment and evaluations. Additional studies are needed to help clarify connections between innate or adaptive immunity and pathological and/or protective autoantibodies mostly in the pediatric age, as children and adolescents are mainly involved in the immunization agendas related to vaccine-preventable diseases.

http://www.ncbi.nlm.nih.gov/pubmed/25395340

"In the presence of a favorable genetic background, many autoimmune/inflammatory responses can be triggered by adjuvants and external factors, showing how the man himself might breach immune tolerance and drive many pathogenetic aspects of human diseases."

Reproductive Toxicology • December 2014

Aluminum content of human semen: implications for semen quality

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Abstract

A deterioration of human semen quality has been observed over recent decades. A possible explanation could be an increased exposure to environmental pollutants, including aluminum. Our aim was to measure the aluminum concentration in the semen of 62 patients and to carry out a preliminary evaluation on its impact on specific semen parameters. For each patient, semen analyses were performed according to WHO guidelines. A graphite furnace atomic absorption spectrometry method was used to determine semen aluminum concentration. A cytological analysis using an aluminum-specific fluor, lumogallion, was also performed. The mean aluminum concentration in human semen was 339 μg/L. Patients with oligozoospermia had a statistically higher aluminum concentration than others. No significant difference was observed for other semen parameters. Cytological analysis showed the presence of aluminum in spermatozoa. This study provided unequivocal evidence of high concentrations of aluminum in human semen and suggested possible implications for spermatogenesis and sperm count.

http://www.ncbi.nlm.nih.gov/pubmed/25461904

“This study provided unequivocal evidence of high concentrations of aluminum in human semen and suggested possible implications for spermatogenesis and sperm count.”

Journal of Alzheimer's Disease • 2014

Chronic aluminum intake causes Alzheimer's disease: applying Sir Austin Bradford Hill's causality criteria

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Industrialized societies produce many convenience foods with aluminum additives that enhance various food properties and use alum (aluminum sulfate or aluminum potassium sulfate) in water treatment to enable delivery of large volumes of drinking water to millions of urban consumers. The present causality analysis evaluates the extent to which the routine, life-long intake, and metabolism of aluminum compounds can account for Alzheimer's disease (AD), using Austin Bradford Hill's nine epidemiological and experimental causality criteria, including strength of the relationship, consistency, specificity, temporality, dose-dependent response, biological rationale, coherence with existing knowledge, experimental evidence, and analogy. Mechanisms that underlie the risk of low concentrations of aluminum relate to (1) aluminum's absorption rates, allowing the impression that aluminum is safe to ingest and as an additive in food and drinking water treatment, (2) aluminum's slow progressive uptake into the brain over a long prodromal phase, and (3) aluminum's similarity to iron, in terms of ionic size, allows aluminum to use iron-evolved mechanisms to enter the highly-active, iron-dependent cells responsible for memory processing. Aluminum particularly accumulates in these iron-dependent cells to toxic levels, dysregulating iron homeostasis and causing microtubule depletion, eventually producing changes that result in disconnection of neuronal afferents and efferents, loss of function and regional atrophy consistent with MRI findings in AD brains. AD is a human form of chronic aluminum neurotoxicity. The causality analysis demonstrates that chronic aluminum intake causes AD.

http://europepmc.org/abstract/med/24577474

"Aluminum particularly accumulates in these iron-dependent cells to toxic levels, dysregulating iron homeostasis and causing microtubule depletion, eventually producing changes that result in disconnection of neuronal afferents and efferents, loss of function and regional atrophy consistent with MRI findings in AD brains. AD is a human form of chronic aluminum neurotoxicity. The causality analysis demonstrates that chronic aluminum intake causes AD."

Immunotherapy • 2014

Are there negative CNS impacts of aluminum adjuvants used in vaccines and immunotherapy?

Author information

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Abstract

In spite of a common view that aluminum (Al) salts are inert and therefore harmless as vaccine adjuvants or in immunotherapy, the reality is quite different. In the following article we briefly review the literature on Al neurotoxicity and the use of Al salts as vaccine adjuvants and consider not only direct toxic actions on the nervous system, but also the potential impact for triggering autoimmunity. Autoimmune and inflammatory responses affecting the CNS appear to underlie some forms of neurological disease, including developmental disorders. Al has been demonstrated to impact the CNS at every level, including by changing gene expression. These outcomes should raise concerns about the increasing use of Al salts as vaccine adjuvants and for the application as more general immune stimulants.

http://www.ncbi.nlm.nih.gov/pubmed/25428645

“Aluminum has been demonstrated to impact the Central Nervous System at every level, including by changing gene expression. These outcomes should raise concerns about the increasing use of Aluminum salts as vaccine adjuvants and for the application as more general immune stimulants.”

“Currently, ethylmercury (EtHg) and adjuvant-Aluminum are the dominating interventional exposures encountered by fetuses, newborns, and infants due to immunization with Thimerosal-containing vaccines (TCVs). Despite their long use as active agents of medicines and fungicides, the safety levels of these substances have never been determined, either for animals or for adult humans—much less for fetuses, newborns, infants, and children.”

International Journal Of Environmental Research And Public Health • January 2015

Exposure to mercury and aluminum in early life: developmental vulnerability as a modifying factor in neurologic and immunologic effects

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Abstract

Currently, ethylmercury (EtHg) and adjuvant-Al are the dominating interventional exposures encountered by fetuses, newborns, and infants due to immunization with Thimerosal-containing vaccines (TCVs). Despite their long use as active agents of medicines and fungicides, the safety levels of these substances have never been determined, either for animals or for adult humans—much less for fetuses, newborns, infants, and children. I reviewed the literature for papers reporting on outcomes associated with (a) multiple exposures and metabolism of EtHg and Al during early life; (b) physiological and metabolic characteristics of newborns, neonates, and infants relevant to xenobiotic exposure and effects; (c) neurobehavioral, immunological, and inflammatory reactions to Thimerosal and Al-adjuvants resulting from TCV exposure in infancy. Immunological and neurobehavioral effects of Thimerosal-EtHg and Al-adjuvants are not extraordinary; rather, these effects are easily detected in high and low income countries, with co-exposure to methylmercury (MeHg) or other neurotoxicants. Rigorous and replicable studies (in different animal species) have shown evidence of EtHg and Al toxicities. More research attention has been given to EtHg and findings have showed a solid link with neurotoxic effects in humans; however, the potential synergic effect of both toxic agents has not been properly studied. Therefore, early life exposure to both EtHg and Al deserves due consideration.

Full Report

http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4344667

Frontiers In Neurology • February 2015

Biopersistence and brain translocation of aluminum adjuvants of vaccines

Author information

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Abstract

Aluminum oxyhydroxide (alum) is a crystalline compound widely used as an immunological adjuvant of vaccines. Concerns linked to the use of alum particles emerged following recognition of their causative role in the so-called macrophagic myofasciitis (MMF) lesion detected in patients with myalgic encephalomyelitis/chronic fatigue/syndrome. MMF revealed an unexpectedly long-lasting biopersistence of alum within immune cells in presumably susceptible individuals, stressing the previous fundamental misconception of its biodisposition. We previously showed that poorly biodegradable aluminum-coated particles injected into muscle are promptly phagocytosed in muscle and the draining lymph nodes, and can disseminate within phagocytic cells throughout the body and slowly accumulate in brain. This strongly suggests that long-term adjuvant biopersistence within phagocytic cells is a prerequisite for slow brain translocation and delayed neurotoxicity. The understanding of basic mechanisms of particle biopersistence and brain translocation represents a major health challenge, since it could help to define susceptibility factors to develop chronic neurotoxic damage. Biopersistence of alum may be linked to its lysosome-destabilizing effect, which is likely due to direct crystal-induced rupture of phagolysosomal membranes. Macrophages that continuously perceive foreign particles in their cytosol will likely reiterate, with variable interindividual efficiency, a dedicated form of autophagy (xenophagy) until they dispose of alien materials. Successful compartmentalization of particles within double membrane autophagosomes and subsequent fusion with repaired and re-acidified lysosomes will expose alum to lysosomal acidic pH, the sole factor that can solubilize alum particles. Brain translocation of alum particles is linked to a Trojan horse mechanism previously described for infectious particles (HIV, HCV), that obeys to CCL2, signaling the major inflammatory monocyte chemoattractant.

Full Report

http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4318414/

“This strongly suggests that long-term adjuvant biopersistence within phagocytic cells is a prerequisite for slow brain translocation and delayed neurotoxicity.”

Biotechnic And Histochemistry • February 2015

A histological study of toxic effects of aluminium sulfate on rat hippocampus

Author information

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Abstract

Aluminium has toxic effects on many organ systems of the human body. Aluminium toxicity also is a factor in many neurodegenerative diseases. We investigated changes in numbers of hippocampal neurons in rats exposed to aluminium using an optical fractionator and we investigated aluminium-induced apoptosis using the transferase mediated dUTP nick end labeling (TUNEL) assay. Twenty-four female rats were divided equally into control, sham and aluminium-exposed groups. The control group received no treatment. The two treatment groups were injected intraperitoneally with 1 ml 0.9% saline without (sham) and with 3 mg/ml aluminium sulfate every day for two weeks. Following the treatments, the brains were removed, the left hemisphere was used for hippocampal neuron counting using an optical fractionator and the right hemisphere was investigated using hippocampal TUNEL assay to determine the apoptotic index. The number of neurons in the stratum pyramidale of the hippocampus was significantly less in the aluminium group than in the control and sham groups; there was no significant difference between the control and sham groups. The apoptotic index also was significantly higher in the aluminium group than in the other two groups. We quantified the toxic effects of aluminium on the rat hippocampus and determined that apoptosis was the mechanism of aluminium-induced neuron death in the hippocampus.

http://www.ncbi.nlm.nih.gov/pubmed/25314162

“Aluminium has toxic effects on many organ systems of the human body. We quantified the toxic effects of aluminium on the rat hippocampus and determined that apoptosis was the mechanism of aluminium-induced neuron death in the hippocampus.”

Journal Of Trace Elements In Medicine And Biology • April 2015

The binding, transport and fate of aluminium in biological cells

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Abstract

Aluminium is the most abundant metal in the Earth's crust and yet, paradoxically, it has no known biological function. Aluminium is biochemically reactive, it is simply that it is not required for any essential process in extant biota. There is evidence neither of element-specific nor evolutionarily conserved aluminium biochemistry. This means that there are no ligands or chaperones which are specific to its transport, there are no transporters or channels to selectively facilitate its passage across membranes, there are no intracellular storage proteins to aid its cellular homeostasis and there are no pathways which evolved to enable the metabolism and excretion of aluminium. Of course, aluminium is found in every compartment of every cell of every organism, from virus through to Man. Herein we have investigated each of the 'silent' pathways and metabolic events which together constitute a form of aluminium homeostasis in biota, identifying and evaluating as far as is possible what is known and, equally importantly, what is unknown about its uptake, transport, storage and excretion.

http://www.ncbi.nlm.nih.gov/pubmed/25498314

"Of course, aluminium is found in every compartment of every cell of every organism, from virus through to Man. Herein we have investigated each of the 'silent' pathways and metabolic events which together constitute a form of aluminium homeostasis in biota, identifying and evaluating as far as is possible what is known and, equally importantly, what is unknown about its uptake, transport, storage and excretion."

PLoS One • June 2015

Bumblebee pupae contain high levels of aluminium

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Abstract

The causes of declines in bees and other pollinators remains an on-going debate. While recent attention has focussed upon pesticides, other environmental pollutants have largely been ignored. Aluminium is the most significant environmental contaminant of recent times and we speculated that it could be a factor in pollinator decline. Herein we have measured the content of aluminium in bumblebee pupae taken from naturally foraging colonies in the UK. Individual pupae were acid-digested in a microwave oven and their aluminium content determined using transversely heated graphite furnace atomic absorption spectrometry. Pupae were heavily contaminated with aluminium giving values between 13.4 and 193.4 μg/g dry wt. and a mean (SD) value of 51.0 (33.0) μg/g dry wt. for the 72 pupae tested. Mean aluminium content was shown to be a significant negative predictor of average pupal weight in colonies. While no other statistically significant relationships were found relating aluminium to bee or colony health, the actual content of aluminium in pupae are extremely high and demonstrate significant exposure to aluminium. Bees rely heavily on cognitive function and aluminium is a known neurotoxin with links, for example, to Alzheimer's disease in humans. The significant contamination of bumblebee pupae by aluminium raises the intriguing spectre of cognitive dysfunction playing a role in their population decline.

Full Report: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4456414/

"the actual content of aluminium in pupae are extremely high and demonstrate significant exposure to aluminium."

Pharmacology Research • October 2015

Vaccines, adjuvants and autoimmunity

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Abstract

Vaccines and autoimmunity are linked fields. Vaccine efficacy is based on whether host immune response against an antigen can elicit a memory T-cell response over time. Although the described side effects thus far have been mostly transient and acute, vaccines are able to elicit the immune system towards an autoimmune reaction. The diagnosis of a definite autoimmune disease and the occurrence of fatal outcome post-vaccination have been less frequently reported. Since vaccines are given to previously healthy hosts, who may have never developed the disease had they not been immunized, adverse events should be carefully accessed and evaluated even if they represent a limited number of occurrences. In this review of the literature, there is evidence of vaccine-induced autoimmunity and adjuvant-induced autoimmunity in both experimental models as well as human patients. Adjuvants and infectious agents may exert their immune-enhancing effects through various functional activities, encompassed by the adjuvant effect. These mechanisms are shared by different conditions triggered by adjuvants leading to the autoimmune/inflammatory syndrome induced by adjuvants (ASIA syndrome). In conclusion, there are several case reports of autoimmune diseases following vaccines, however, due to the limited number of cases, the different classifications of symptoms and the long latency period of the diseases, every attempt for an epidemiological study has so far failed to deliver a connection. Despite this, efforts to unveil the connection between the triggering of the immune system by adjuvants and the development of autoimmune conditions should be undertaken. Vaccinomics is a field that may bring to light novel customized, personalized treatment approaches in the future.

http://www.ncbi.nlm.nih.gov/pubmed/26275795

“In this review of the literature, there is evidence of vaccine-induced autoimmunity and adjuvant-induced autoimmunity in both experimental models as well as human patients.”

Journal Of Inorganic Biochemistry • November 2015

Highly delayed systemic translocation of aluminum-based adjuvant in CD1 mice following intramuscular injections

Author information

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Abstract

Concerns regarding vaccine safety have emerged following reports of potential adverse events in both humans and animals. In the present study, alum, alum-containing vaccine and alum adjuvant tagged with fluorescent nanodiamonds were used to evaluate i) the persistence time at the injection site, ii) the translocation of alum from the injection site to lymphoid organs, and iii) the behavior of adult CD1 mice following intramuscular injection of alum (400µgAl/kg). Results showed for the first time a strikingly delayed systemic translocation of adjuvant particles. Alum-induced granuloma remained for a very long time in the injected muscle despite progressive shrinkage from day 45 to day 270. Concomitantly, a markedly delayed translocation of alum to the draining lymph nodes, major at day 270 endpoint, was observed. Translocation to the spleen was similarly delayed (highest number of particles at day 270). In contrast to C57BL/6J mice, no brain translocation of alum was observed by day 270 in CD1 mice. Consistently neither increase of Al cerebral content, nor behavioral changes were observed. On the basis of previous reports showing alum neurotoxic effects in CD1 mice, an additional experiment was done, and showed early brain translocation at day 45 of alum injected subcutaneously at 200µgAl/kg. This study confirms the striking biopersistence of alum. It points out an unexpectedly delayed diffusion of the adjuvant in lymph nodes and spleen of CD1 mice, and suggests the importance of mouse strain, route of administration, and doses, for future studies focusing on the potential toxic effects of aluminum-based adjuvants.

http://www.ncbi.nlm.nih.gov/pubmed/26384437

“Concerns regarding vaccine safety have emerged following reports of potential adverse events in both humans and animals. This study confirms the striking biopersistence of alum. It points out an unexpectedly delayed diffusion of the adjuvant in lymph nodes and spleen of CD1 mice ...”

"The well-recognized manifestations of systemic aluminum toxicity include fracturing osteomalacia, dialysis encephalopathy, and microcytic hypochromic anemia. More recently, aluminum loading has been demonstrated in premature infants receiving intravenous fluid therapy."

American Academy Of Pediatrics • December 2015
Committee on Nutrition

Aluminum Toxicity in Infants and Children

Abstract

During the last 15 years, accumulating evidence has implicated aluminum in disorders associated with chronic renal failure.1-6 The well-recognized manifestations of systemic aluminum toxicity include fracturing osteomalacia, dialysis encephalopathy, and microcytic hypochromic anemia. More recently, aluminum loading has been demonstrated in premature infants receiving intravenous fluid therapy.7 Although the clinical importance of this finding is unclear, it warrants careful attention. The association between aluminum excess and neurologic dysfunction, which has been reported in patients with chronic renal failure, suggests the possibility that aluminum overload may contribute to the pathogenesis of CNS damage in the sick premature infant.7,8

Aluminum Exposure

Aluminum, which is the most abundant metal in the earth's crust, is ubiquitous in its distribution.7 There is constant exposure to this element through ingestion of water and food and exposure to dust particles.10 Because aluminum sulfate (alum) is used as a flocculating agent in the purification of municipal water supplies, drinking water may contain high levels of aluminum (up to 1,000 µg/L). Aluminum cans, containers, and cooking utensils, as well as aluminum-containing medications, are also potential sources of oral intake of aluminum. Increase in aluminum intake as a result of transfer through the skin is probably negligible; however, exposure is common due to use of aluminum in deodorants.10 Some inhaled aluminum is retained in pulmonary tissue and in the peribronchial lymph nodes, but it is largely excluded from other tissues. Pulmonary aluminum concentration increases with age; unlike aluminum levels in other tissues, the concentration in the lung does not correlate with that in other tissues.

http://pediatrics.aappublications.org/content/78/6/1150

Springer Plus • 2015

The mechanisms of action of vaccines containing aluminum adjuvants: an in vitro vs in vivo paradigm

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Abstract

Adjuvants such as the aluminum compounds (alum) have been dominantly used in many vaccines due to their immunopotentiation and safety records since 1920s. However, how these mineral agents influence the immune response to vaccination remains elusive. Many hypotheses exist as to the mode of action of these adjuvants, such as depot formation, antigen (Ag) targeting, and the induction of inflammation. These hypotheses are based on many in vitro and few in vivo studies. Understanding how cells interact with adjuvants in vivo will be crucial to fully understanding the mechanisms of action of these adjuvants. Interestingly, how alum influences the target cell at both the cellular and molecular level, and the consequent innate and adaptive responses, will be critical in the rational design of effective vaccines against many diseases. Thus, in this review, mechanisms of action of alum have been discussed based on available in vitro vs in vivo evidences to date.

Full Report

http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4406982/

“Adjuvants such as the aluminum compounds (alum) have been dominantly used in many vaccines due to their immunopotentiation and safety records since 1920s. However, how these mineral agents influence the immune response to vaccination remains elusive.”

Chapter Four
The Human Papilloma Virus Vaccine
2008 - 2015

Dr. Harper was the lead scientist for Mercks Gardasil vaccine. She explained in a presentation at the 4th International Public Conference on Vaccination in October of 2009 that the cervical cancer risk in the U.S. is already extremely low, and that vaccinations are unlikely to have any effect upon the rate of cervical cancer in the United States. In fact, 70% of all HPV infections resolve themselves without treatment in a year and the number rises to well over 90% in two years. Harper also mentioned the safety angle. All trials of the vaccines were done on children aged 15 and above, despite them currently being marketed for 9-year-olds.

So far, 15,037 girls have reported adverse side effects from Gardasil alone to the Vaccine Adverse Event Reporting System (V.A.E.R.S.), and this number only reflects parents who underwent the hurdles required for reporting adverse reactions. At the time of writing, over 100 girls are officially known to have died from this vaccine.

The reported side effects include Guillian Barré Syndrome (paralysis lasting for years, or permanently — sometimes eventually causing suffocation), lupus, seizures, blood clots, brain inflammation and more. Parents are usually not made aware of these risks. Dr. Harper, the vaccine developer, claimed that she was speaking out, so that she might finally be able to sleep at night.

“About eight in every ten women who have been sexually active will have H.P.V. at some stage of their life. Normally there are no symptoms, and in 98 per cent of cases it clears itself.”

- Dr. Diane Harper

Spanish attorney Don Manuel Saez Ochoa filed a criminal complaint against Merck-Sanofi Pasteur Laboratories and the Spanish National Health Authorities in the Spanish courts in June of 2014. The complaint alleges that Merck failed to use an inert placebo during clinical trials thereby manipulating data and thus Gardasil was marketed under false pretences. Merck-Sanofi Pasteur and Spain’s National and Regional (La Rioja) health authorities are charged with the following:

- fraudulent marketing and/or administration of an inadequately tested vaccine;
- failure to inform the public about the potential risks of using Gardasil;
- clear infringement of the right to informed consent;
- ignoring new medical conditions in those who used Gardasil despite the similarity of their symptoms and the relatively short period of time between vaccine administration and the onset of symptoms;
- ignoring established and new scientific evidence illustrating the potential harmful effects of Gardasil ingredients and manufacturing methods;
- callous disregard for those suffering new medical conditions post-Gardasil;
- failure to inform the public that HPV infections are simply one of the risk factors involved in the development of cervical cancer;
- failure to inform the public that 90% of all HPV infections clear on their own without medical intervention;
- failure to inform the publlic about alternative methods of controlling cervical cancer;
- and criminal liability for the injuries resulting from the administration of Gardasil.

Thousands of young women around the world are finding themselves in the same position. They have gone from being happy, active, and healthy to facing a multitude of autoimmune problems and neurological disorders. For them, the ‘possible’ adverse effects of Gardasil have become an all too harsh and brutal reality.

It is time for those responsible to be held accountable for their actions. Criminal prosecution is quite possibly the only way to accomplish that goal. Perhaps six to twelve years in prison would remind those responsible what it means to conduct yourself in an ethical manner.

Perhaps they would remember that their first duty is to maintain the public health, not destroy it. On July 30, the Judge decided to open criminal proceedings and an investigation of the facts. The first criminal case in Spain regarding Gardasil injuries and potential criminal liability now begins.

Canadian Medical Association Journal • September 2008

The human papillomavirus vaccine and risk of anaphylaxis

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Abstract

In this issue of CMAJ, Brotherton and colleagues1 report a comprehensive investigation revealing higher than expected rates of apparent anaphylaxis following vaccination with the quadrivalent human papillomavirus (HPV) vaccine in Australian children. The cause of these reactions remains somewhat unclear and needs further investigation. Of note, rates of anaphylaxis, if confirmed, may not be as high in other populations. Further investigations may assist in clarifying differences between the Australian study and other reports.

The HPV vaccine is associated with high rates of fainting in adolescents, which can result in serious head injuries. These adverse events emphasize the need for recommendations to keep adolescents and children under close observation (preferably sitting) for at least 15 minutes after vaccination.

Full Report

http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2527389/

“The HPV vaccine is associated with high rates of fainting in adolescents, which can result in serious head injuries.”

Pharmacotherapy • September 2008

Development of unilateral cervical and supraclavicular lymphadenopathy after human papilloma virus vaccination

Author information

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Abstract

A 26-year-old woman developed significant unilateral anterior cervical and supraclavicular lymphadenopathy 3 days after receiving her first dose (of a total of three doses) of human papilloma virus (HPV) vaccine. She had no history of lymphadenopathy after other previous immunizations, and had received no vaccines other than HPV at that time. The left-sided lymphadenopathy developed after she was vaccinated in the left deltoid muscle. The spatial and temporal relationships between the appearance of the lymphadenopathy and receipt of the vaccine in the absence of other causal agents strongly suggest that the HPV vaccine was the causal agent. Use of the Naranjo adverse drug reaction probability scale indicated that the HPV vaccine was a probable (score of 6) cause of the patient's adverse reaction. The patient received her second dose of the HPV vaccine 2 months later without further lymphadenopathy. To prevent unnecessary lymph node biopsies and patient concern, clinicians should be aware that lymphadenopathy may occur after HPV vaccination.

http://www.ncbi.nlm.nih.gov/pubmed/?term=18752390

"clinicians should be aware that lymphadenopathy may occur after HPV vaccination."

Multiple Sclerosis • January 2009

CNS demyelination and quadrivalent HPV vaccination

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Abstract

Vaccination is generally considered safe in patients with multiple sclerosis (MS). We report five patients who presented with multifocal or atypical demyelinating syndromes within 21 days of immunization with the quadrivalent human papilloma virus (HPV) vaccine, Gardasil. Although the target population for vaccination, young females, has an inherently high risk for MS, the temporal association with demyelinating events in these cases may be explained by the potent immuno-stimulatory properties of HPV virus-like particles which comprise the vaccine. A prospective case-control study of patients with MS or clinically isolated demyelinating syndromes receiving the Gardasil vaccine may provide relevant safety data in this population.

http://www.ncbi.nlm.nih.gov/pubmed/?term=18805844

"We report five patients who presented with multifocal or atypical demyelinating syndromes within 21 days of immunization with the quadrivalent human papilloma virus (HPV) vaccine, Gardasil ... association with demyelinating events in these cases may be explained by the potent immuno-stimulatory properties of HPV virus-like particles which comprise the vaccine."

Obstetrics & Gynecology • February 2009

Cervical cancers after human papillomavirus vaccination

Author information

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Abstract

BACKGROUND

Current randomized clinical trials have shown that the quadrivalent human papillomavirus (HPV) vaccine can reduce the morbidity of precancerous lesions associated with HPV infection of vaccine-related subtypes. However, to date, there is no definite evidence showing the vaccine reduces the incidence of invasive cervical carcinoma.

CASES

We present two cases—one young, vaccinated woman who developed cervical carcinoma that was unrelated to HPV and another who developed cervical carcinoma secondary to infection with an HPV subtype not covered by the vaccine. Both patients were treated successfully and remained well without evidence of cancer.

CONCLUSION

Long-term follow-up data are needed to evaluate the prophylactic effectiveness of the current HPV vaccine. These cases could represent non-vaccine-related HPV infections. Young women must be thoroughly counseled about the efficacy and limitations of the vaccine and about continuing lifelong screening even after vaccination.

http://www.ncbi.nlm.nih.gov/pubmed/?term=19155953

“However, to date, there is no definite evidence showing the vaccine reduces the incidence of invasive cervical carcinoma.”

Vaccine • August 2009

Quadrivalent Human Papillomavirus recombinant vaccine associated lipoatrophy

Author information

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Abstract

Involutional lipoatrophy, a loss of subcutaneous fat, may be idiopathic, associated with inflammatory skin conditions, or trauma, and has also been reported following injections of medications including insulin, corticosteroids and penicillin. There have also been reports in association with Diptheria Pertussis Tetanus (DPT) vaccine. We report on two cases of lipoatrophy associated with the new Quadrivalent Human Papillomavirus (HPV) recombinant vaccine (Gardasil).

http://www.ncbi.nlm.nih.gov/pubmed/19555713

“Involutional lipoatrophy, a loss of subcutaneous fat, may be idiopathic, associated with inflammatory skin conditions, or trauma, and has also been reported following injections of medications including insulin, corticosteroids and penicillin. There have also been reports in association with Diptheria Pertussis Tetanus (DPT) vaccine. We report on two cases of lipoatrophy associated with the new Quadrivalent Human Papillomavirus (HPV) recombinant vaccine (Gardasil).”

4th International Public Conference on Vaccination • October 2nd through 4th, 2009

No actual evidence that the vaccine can prevent any cancer

Dr. Diane Harper
Lead Vaccine Researcher
Merck Gardasil And Cervarix Vaccines

Abstract

Dr. Diane Harper was the lead researcher in the development of the human papilloma virus vaccines, Gardasil and Cervarix. She is the latest to come forward and question the safety and effectiveness of these vaccines. She made the surprising announcement at the 4th International Public Conference on Vaccination, which took place in Reston, Virginia on Oct. 2nd through 4th, 2009.

Her speech was supposed to promote the Gardasil and Cervarix vaccines, but she instead turned on her corporate bosses in a very public way. When questioned about the presentation, audience members remarked that they came away feeling that the vaccines should not be used. “I came away from the talk with the perception that the risk of adverse side effects is so much greater than the risk of cervical cancer, I couldn’t help but question why we need the vaccine at all.” – Joan Robinson

Dr. Harper explained in her presentation that the cervical cancer risk in the U.S. is already extremely low, and that vaccinations are unlikely to have any effect upon the rate of cervical cancer in the United States. In fact, 70% of all H.P.V. infections resolve themselves without treatment in a year, and the number rises to well over 90% in two years. Harper also mentioned the safety angle. All trials of the vaccines were done on children aged 15 and above, despite them currently being marketed for 9-year-olds.

So far, 15,037 girls have reported adverse side effects from Gardasil alone to the Vaccine Adverse Event Reporting System (V.A.E.R.S.), and this number only reflects parents who underwent the hurdles required for reporting adverse reactions. At the time of writing, 44 girls are officially known to have died from these vaccines.

The reported side effects include Guillian Barré Syndrome (paralysis lasting for years, or permanently — sometimes eventually causing suffocation), lupus, seizures, blood clots, and brain inflammation. Parents are usually not made aware of these risks. Dr. Harper, the vaccine developer, claimed that she was speaking out, so that she might finally be able to sleep at night.

“About eight in every ten women who have been sexually active will have H.P.V. at some stage of their life. Normally there are no symptoms, and in 98 per cent of cases it clears itself. But in those cases where it doesn’t, and isn’t treated, it can lead to pre-cancerous cells which may develop into cervical cancer.” - Dr. Diane Harper

One must understand how the establishment’s word games are played to truly understand the meaning of the above quote, and one needs to understand its unique version of “science”. When they report that untreated cases “can” lead to something that “may” lead to cervical cancer, it really means that the relationship is merely a hypothetical conjecture that is profitable if people actually believe it. In other words, there is no demonstrated relationship between the condition being vaccinated for and the rare cancers that the vaccine might prevent, but it is marketed to do that nonetheless. In fact, there is no actual evidence that the vaccine can prevent any cancer.

From the manufacturers own admissions, the vaccine only works on 4 strains out of 40 for a specific venereal disease that dies on its own in a relatively short period, so the chance of it actually helping an individual is about about the same as the chance of him being struck by a meteorite. Why do nine-year-old girls need vaccinations for extremely rare and symptomless venereal diseases that the immune system usually kills anyway?

http://www.whydontyoutrythis.com/2013/07/the-lead-vaccine-developer-comes-clean-so-she-can-sleep-at-night.html

Dermatology • July 2010

The quadrivalent human papillomavirus vaccine: erythema multiforme and cutaneous side effects after administration

Author information

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Abstract

The quadrivalent human papillomavirus (qHPV) vaccine, the first vaccine for use in the prevention of cervical cancer and condyloma acuminatum, was approved in June 2006. In 2008, the mass media reported suspected links between the qHPV vaccine and serious adverse events; however, several studies have found that the vaccine is safe and the main adverse events are mild local reactions. Erythema multiforme (EM) is an acute self-limited cutaneous or mucocutaneous syndrome characterized by the abrupt onset of symmetric target lesions. The clinical manifestations and histological features of EM, Stevens-Johnson syndrome and toxic epidermal necrolysis show considerable overlap, and they are classically considered to represent a spectrum of skin disorders. We present a case of EM following qHPV vaccination to review the cutaneous side effects of this vaccine and the possibility of more serious side effects with the administration of booster doses.

http://www.ncbi.nlm.nih.gov/pubmed/?term=20861606

“We present a case of Erythema multiforme following qHPV vaccination to review the cutaneous side effects of this vaccine and the possibility of more serious side effects with the administration of booster doses.”

Journal Of Vaccines & Vaccination • November 2010

Review of Gardasil

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Abstract

Human papillomavirus (HPV) is necessary for the development of cervical cancer. Cervical cancer is the second most common cancer in women worldwide but 80% occurs in developing countries, not countries with Pap screening programs. Pap screening programs in industrialized countries have reduced the incidence of cervical cancer to 4-8/100,000 women. HPV vaccines may be a promising strategy for cervical cancer in women without access to screening programs. In industrialized countries, the benefit of HPV vaccines focuses on individual abnormal Pap test reduction not cancer prevention. The focus of this review is to cover the side effects of Gardasil in perspective with the limited population benefit cervical cancer reduction in countries with organized Pap screening programs. In addition, information about Gardasil benefits, risks and unknowns for individual patient decision making for vaccination is presented. Gardasil offers protection against CIN 2+ lesions caused by HPV 16/18 and against genital warts caused by HPV 6/11 for at least 5 years. Combining Gardasil with repeated cytology screenings may reduce the proportion of abnormal cytology screens and hence reduce the associated morbidity with the subsequent colposcopies and excisional procedures.

http://www.ncbi.nlm.nih.gov/pubmed/23805398

"Pap screening programs
in industrialized countries
have reduced the incidence of cervical cancer
to 4-8/100,000 women.

HPV vaccines
may be a promising strategy
for cervical cancer in women
without access to screening programs."

Dermatology • November 2010

Erythema multiforme following vaccination for human papillomavirus

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Abstract

Erythema multiforme (EM) is an acute self-limited immune-mediated reaction manifested by target skin lesions with mucous membrane involvement. The most common causes are infections and drugs. Vaccinations have been reported as a triggering factor, and they may be a frequent cause of EM in childhood. A 19-year-old female developed several target lesions of the hands and feet 10 days after the second dose of human papillomavirus (HPV) vaccine. Clinico-histologically, a diagnosis of EM minor was made. Treatment with topical corticosteroids and oral antihistamines resulted in complete clearance of the rash. Four months later, she received the last booster dose of the vaccine. A few subtle lesions appeared and disappeared spontaneously after a few days. Gardasil is a non-infectious vaccine, developed for the prevention of cervical cancer, precancerous genital lesions and genital warts. It delivers the major capsid (L1) protein of HPV types 6, 11, 16 and 18. Mild local reactions are the main adverse events. The only serious events are very rare cases of anaphylaxis. In our patient, the temporal relationship between the development of EM and the vaccination suggests that the HPV vaccine probably was the causal agent. This is the first published case of EM following HPV vaccination.

http://www.ncbi.nlm.nih.gov/pubmed/?term=19887766

“In our patient,

the temporal relationship between

the development of Erythema multiforme

and the vaccination suggests that the

HPV vaccine probably was the causal agent.

This is the first published case of

Erythema multiforme following HPV vaccination.”

Vaccine • January 2011

Guillain-Barré syndrome after Gardasil vaccination: data from Vaccine Adverse Event Reporting System 2006-2009

Author information

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Abstract

Using data from Vaccine Adverse Event Reporting System, we identified 69 reports of Guillain-Barré Syndrome (GBS) after Gardasil vaccination that occurred in the United States between 2006 and 2009. The onset of symptoms was within 6 weeks after vaccination in 70% of the patients in whom the date of vaccination was known. The estimated weekly reporting rate of post-Gardasil GBS within the first 6 weeks (6.6 per 10,000,000) was higher than that of the general population, and higher than post-Menactra and post-influenza vaccinations. Further prospective active surveillance for accurate ascertainment and identification of high-risk groups of GBS after Gardasil vaccination is warranted.

http://www.ncbi.nlm.nih.gov/pubmed/?term=20869467

"The estimated weekly reporting rate of post-Gardasil Guillain-Barré Syndrome within the first 6 weeks (6.6 per 10,000,000) was higher than that of the general population, and higher than post-Menactra and post-influenza vaccinations."

[for every 100 million women vaccinated it is known and recognized that there will be an estimated 66 cases of collateral damage in the form of Guillain-Barré Syndrome]

Vaccine • June 2011

Autoimmune hepatitis type 2 following anti-papillomavirus vaccination in a 11-year-old girl

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Abstract

In the last years numerous reports describing a possible association between administration of vaccines and development of autoimmune phenomena and overt autoimmune disease were published. Possible mechanisms of induction of autoimmune phenomena by vaccines and their excipients are probably similar to those implicated in induction by infectious agents. Here we report the case of an 11-year-old girl who developed autoimmune hepatitis type II after four weeks from vaccination against human papillomavirus. The possible relationships between the use of adjuvated vaccine against papillomavirus and autoimmune hepatitis are discussed. Although we do not provide evidence for a causal link, we suggest that the occurrence of the autoimmune hepatitis may be related to the stimulation of immune system by adjuvated-vaccine, that could have triggered the disease in a genetically predisposed individual. Therefore a monitoring of liver function test following administration of vaccine against papillomavirus may be useful in adolescent girl with signs of hepatopathy, as jaundice, dark urine or hepatomegaly, to early identify and to promptly treat autoimmune liver disorders.

http://www.ncbi.nlm.nih.gov/pubmed/?term=21596082

"In the last years **numerous** reports describing a possible association between administration of vaccines and development of autoimmune phenomena and overt autoimmune disease were published."

Lupus • February 2012

Systemic lupus erythematosus following HPV immunization or infection?

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Abstract

BACKGROUND AND PURPOSE

The link between autoimmunity and infectious agents has been strongly suggested by reports of lupus or lupus-like syndromes following immunization. This report describes three patients with either newly diagnosed systemic lupus erythematosus (SLE) or SLE flare, following vaccination for human papilloma virus (HPV). CASE 1: A 17-year-old female completed two doses of HPV vaccine uneventfully. Two months later, she developed arthralgias with pruritic rashes on both lower extremities, later accompanied by livedo reticularis, bipedal edema with proteinuria, anemia, leucopenia, hypocomplementemia and high titers of anti-nuclear antibody (ANA) and anti-double-stranded DNA (anti-dsDNA). Kidney biopsy showed International Society of Nephrology/Renal Pathology Society Class III lupus nephritis. She was started on high dose steroids followed by pulse cyclophosphamide therapy protocol for lupus nephritis, and subsequently went into remission. CASE 2: A 45-year-old housewife, previously managed for 11 years as having rheumatoid arthritis, had been in clinical remission for a year when she received two doses of HPV immunization. Four months later, she developed fever accompanied by arthritis, malar rash, oral ulcers, recurrent ascites with intestinal pseudo-obstruction, and behavioral changes. Cranial MRI showed vasculitic lesions on the frontal and parietal lobes. Laboratory tests showed anemia with leucopenia, hypocomplementemia, proteinuria, ANA positive at 1:320, and antibodies against dsDNA, Ro/SSA, La/SSB and histone. She improved following pulse methylprednisolone with subsequent oral prednisone combined with hydroxychloroquine. CASE 3: A 58-year-old housewife diagnosed with SLE had been in clinical remission for 8 years when she received two doses of HPV immunization. Three months later, she was admitted to emergency because of a 1-week history of fever, malar rash, easy fatigability, cervical lymph nodes, gross hematuria and pallor. Laboratory exams showed severe anemia, thrombocytopenia, active urine sediments, and hypocomplementemia. Despite pulse steroid therapy, blood transfusions, intravenous immunoglobulin and aggressive resuscitative measures, she expired a day after hospital admission.

SUMMARY

These cases narrate instances of the onset or exacerbation of lupus following HPV immunization suggesting adjuvant-induced autoimmunity. On the other hand, there are reports of higher incidence of HPV infection in SLE, with the infection per se possibly contributing to disease activity. Thus, the benefit of HPV immunization may still outweigh the risk among these individuals.

http://www.ncbi.nlm.nih.gov/pubmed/?term=22235047

“These cases narrate instances of the onset or exacerbation of lupus following HPV immunization suggesting adjuvant-induced autoimmunity.”

American Journal Of Public Health • May 2012

Pharmaceutical companies' role in state vaccination policymaking: the case of human papillomavirus vaccination

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Abstract

OBJECTIVES
We sought to investigate roles that Merck & Co Inc played in state human papillomavirus (HPV) immunization policymaking, to elicit key stakeholders' perceptions of the appropriateness of these activities, and to explore implications for relationships between health policymakers and industry.

METHODS
We used a series of state case studies combining data from key informant interviews with analysis of media reports and archival materials. We interviewed 73 key informants in 6 states that were actively engaged in HPV vaccine policy deliberations.

RESULTS
Merck promoted school-entry mandate legislation by serving as an information resource, lobbying legislators, drafting legislation, mobilizing female legislators and physician organizations, conducting consumer marketing campaigns, and filling gaps in access to the vaccine. Legislators relied heavily on Merck for scientific information. Most stakeholders found lobbying by vaccine manufacturers acceptable in principle, but perceived that Merck had acted too aggressively and nontransparently in this case.

CONCLUSIONS
Although policymakers acknowledge the utility of manufacturers' involvement in vaccination policymaking, industry lobbying that is overly aggressive, not fully transparent, or not divorced from financial contributions to lawmakers risks undermining the prospects for legislation to foster uptake of new vaccines.

http://www.ncbi.nlm.nih.gov/pubmed/?term=22420796

"Most stakeholders found lobbying by vaccine manufacturers acceptable in principle, but perceived that Merck had acted too aggressively and nontransparently in this case."

American Journal Of Public Health • September 2012

Who Profits From Uncritical Acceptance of Biased Estimates of Vaccine Efficacy and Safety?

Lucija Tomljenovic, PhD and Christopher A. Shaw, PhD
At the time of the writing, Lucija Tomljenovic and Christopher A. Shaw were with the Neural Dynamics Research Group
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Abstract

We read with great interest the analysis by Mello et al.1 on how Merck & Co., Inc. (Merck) influenced state human papillomavirus (HPV) vaccination policymaking. The exclusive reliance on Merck for scientific information on behalf of the legislators is unfortunate, especially in the light of independent research which has repeatedly warned that drug companies may manipulate clinical trial designs and subsequent data analysis and reporting to make their drugs look better and safer.2–4 Indeed, careful scrutiny of Gardasil clinical trials shows that their design, as well as data reporting and interpretation, were largely inadequate.4–6

Given this, the widespread public optimism regarding Gardasil's clinical benefits appears to rest on an extremely weak base built on a number of untested assumptions and significant misinterpretation of factual evidence. For example, the claim that Gardasil vaccination will result in approximately 70% reduction of cervical cancers7,8 is made despite the fact that the clinical trial data have not demonstrated to date that the vaccine has actually prevented a single case of cervical cancer (let alone cervical cancer death),4 nor that the current overly optimistic surrogate marker–based extrapolations are justified.6 A second equally fallacious claim is that lifelong protection arises from three vaccine doses,7,8 although clinical trial follow-up data do not extend beyond five years.9 The third claim is that Gardasil may induce only minor side effects of negligible clinical importance,7,8 although such conclusions are only supported by highly flawed safety trials design.4,10 Additionally, we note evidence of biased and selective reporting of results from clinical trials, that is, exclusion of particular vaccine efficacy figures from peer-reviewed publications, such as those related to study subgroups in which efficacy might be lower or even negative.4,5

All of the above issues suggest that the information presented by Merck to the public and the various state legislators concerning Gardasil safety and true prophylactic value were incomplete and inaccurate and thus inevitably misleading, particularly in light of data from various vaccine safety surveillance systems and case reports that continue to raise significant concerns regarding the safety of Gardasil (Table 1).4

Keeping in mind that "the primary interest of a pharmaceutical company is developing and selling pharmaceutical product,"1 one must ask whether rational vaccine policy decisions should be based on conclusions derived from an uncritical acceptance of flawed vaccine safety and efficacy estimates provided by the vaccine manufacturer. Failure to adhere to principles of evidence-based medicine with respect to Gardasil promotion and vaccination policymaking inevitably raises the question of whether we have learned anything from the Vioxx debacle.

Full Report with References: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3482043/

Age-Adjusted Rate Of Adverse Reactions (ADRs) Related To Gardasil Compared With All Other Vaccines In The United States Reported To The Vaccine Adverse Event Reporting System (VAERS) As Of March 25th, 2012.

Event	Gardasil	All Vaccines	Gardasil %
All	14,616	31,713	46.1
Serious	1,272	2,077	61.2
Deaths	37	58	63.8
Life-Threatening	289	444	65.1
Permanently Disabled	468	572	81.2
Prolonged Hospitalization	172	229	75.1
Emergency Room Visit	6,892	12,927	53.3

Note: Compared with all other vaccines, Gardasil alone is associated with >60% of all serious Adverse Reactions (including 63.8% of all deaths and 81.2% cases of permanent disability) in females younger than 30 years. In context, while females in this age group have a near-zero risk of dying from cervical cancer, they are faced with a risk of dying and a permanently disabling condition from a vaccine that has not prevented a single case of cervical cancer thus far. For a vaccine with uncertain benefits designed to prevent a disease that is preventable through Papanicolaou screening combined with the loop electrosurgical excision procedure, which together carry no such risks, the potental for harm to those vaccinated should be negligible. It is not.

"In context. while females in this age group have a near-zero risk of dying from cervical cancer, they are faced with a risk of dying and a permanently disabling condition from a vaccine that has not prevented a single case of cervical cancer thus far. For a vaccine with uncertain benefits designed to prevent a disease that is preventable through Papanicolaou screening combined with the loop electrosurgical precision procedure, which together carry no such risks, the potential for harm to those vaccinated should be negligible."

BMJ Case Report • September 2012

Premature ovarian failure 3 years after menarche in a 16-year-old girl following human papillomavirus vaccination

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Abstract

Its occurrence raises important questions about causation, which may signal other systemic concerns. This patient presented with amenorrhoea after identifying a change from her regular cycle to irregular and scant periods following vaccinations against human papillomavirus. She declined the oral contraceptives initially prescribed for amenorrhoea. The diagnostic tasks were to determine the reason for her secondary amenorrhoea and then to investigate for possible causes of the premature ovarian failure identified. Although the cause is unknown in 90% of cases, the remaining chief identifiable causes of this condition were excluded. Premature ovarian failure was then notified as a possible adverse event following this vaccination. The young woman was counselled regarding preservation of bone density, reproductive implications and relevant follow-up. This event could hold potential implications for population health and prompts further inquiry.

Full Report

http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4543769/

“Premature ovarian failure in a well adolescent is a rare event. This patient presented with amenorrhoea after identifying a change from her regular cycle to irregular and scant periods following vaccinations against human papillomavirus. This event could hold potential implications for population health and prompts further inquiry.”

Journal of Internal Medicine
Volume 272, Issue 5, pages 514–515 • November 2012

Letter to the Editor

No autoimmune safety signal after vaccination with quadrivalent HPV vaccine Gardasil?

L. Tomljenovic and C. A. Shaw

Dear sir,

Recently, the Journal of Internal Medicine published a study by Chao et al. [1] on autoimmune conditions following the routine use of Gardasil, which failed to identify any significant autoimmune safety concerns. This study was conducted in collaboration between two managed care organizations, Kaiser Permanente Southern California (KPSC) and Kaiser Permanente Northern California (KPNC), as a postlicensure commitment to the FDA, the European Medicines Agency (EMA) and other regulatory authorities to help evaluate the autoimmune safety of the vaccine. In particular, Chao et al. [1] noted that 'well-designed postlicensure safety studies for newly approved vaccines facilitate proper evaluation of their autoimmune safety' [emphasis added]. We certainly do agree with the authors that such studies are needed for determining whether or not new vaccines have adequate safety profiles. The study population for the autoimmune surveillance by the Kaiser's research team thus included 189 629 women of diverse ethnical and socio-economic background, 99% of whom were in the recommended age range for HPV vaccination (9–26 years) [1]. Nonetheless, two potential biases might have influenced the outcome of the safety analysis conducted by the authors.

First, the study included all women who received at least one dose of Gardasil, thus making this particular population sample less sensitive for the detection of serious adverse reactions (ADRs), as such events may be expected to occur less frequently if fewer doses of the vaccine are administered. As the authors did not report how many women actually completed the recommended three-dose HPV vaccination regimen, it is impossible to know what proportion of the study population was actually at high risk from vaccine-related serious ADRs. Secondly, the Safety Review Committee (SRC) that reviewed all safety data included a general paediatrician/clinical epidemiologist, a perinatologist/teratologist, a vaccinologist, a paediatric rheumatologist and a pharmacoepidemiologist [1]. In view of the fact that the autoimmune conditions of interest to be examined by this expert Committee included (i) rheumatologic/autoimmune disorders, (ii) autoimmune endocrine conditions and (iii) autoimmune neurological/ophthalmic disorders [1]; the question must be asked about why the Kaiser's research team failed to recruit an expert panel with similar expertise if, in fact, the study aimed to facilitate proper evaluation of autoimmune safety for Gardasil? It is thus surprising to note the absence of an immunologist/autoimmunologist, neurologist and ophthalmologist from the SRC especially because such experts were in fact present at a later stage, in the analysis of case reports selected by the SRC [1]. As demonstrated repeatedly in the scientific literature, inadequately designed research cannot be used to reliably evaluate the safety of any drug [2,3].

We have previously pointed out to existing HPV vaccine-related safety concerns as well as uncertainties about the efficacy of HPV vaccination against actual cervical cancer incidence [3, 4]. Whilst results from clinical trials show that Gardasil can reduce the incidence of a subset of abnormal CIN 2/3+ cytologies (i.e. those related to HPV-16/18) in women with no pre-existing HPV infections [5], the vaccine is unlikely to reduce the overall frequency of cervical cancers (at least not beyond what Pap screening has already accomplished) [6, 7], yet this is the primary aim for which the vaccine was developed [8]. Furthermore, current data show that antibodies against HPV-18 after Gardasil fall rapidly, with 35% of women having no measurable antibody titres by 5 years postinjection [6]. This outcome suggests that rather than preventing future cases of cervical cancer, Gardasil, at best, may only be effective in postponing them.

In addition, unlike screening and the loop electrosurgical excision procedure (LEEP), Gardasil offers no therapeutic benefits as it cannot cause regression of pre-existing HPV-16/18 infections or associated lesions. On the contrary, Gardasil may exacerbate cervical cancer disease in women with pre-existing HPV-6/11/16/18 infections [5]. It thus appears that the current widespread optimism regarding the putative long-term benefits of HPV vaccination has only been made possible by invalid and premature extrapolations from such often inadequate surrogate markers [3, 9, 10]. As recently noted by Gerhardus and Razum [9], the, 'unwarranted confidence in the new [HPV] vaccines led to the impression that there was no need to actually evaluate their effectiveness'.

On the other hand, abundant evidence now exists that HPV vaccines can cause serious adverse events, including death and long-term disabling autoimmune conditions [3, 6]. Moreover, because currently there are no active surveillance programs for monitoring vaccine safety outcomes anywhere in the world, the true rate of serious ADRs following Gardasil remains unknown. In context, whilst 12-year-old preadolescents are at zero risk of dying from cervical cancer, they are faced with a risk of death and a permanently disabling lifelong autoimmune or neurodegenerative condition from a vaccine that thus far has not prevented a single case of cervical cancer, let alone cervical cancer death. For vaccines with uncertain benefits designed to prevent a disease that is already preventable by Pap screening and LEEP, both of which carry no such risks, the potential for harm to those vaccinated should be negligible [3, 4].

Conflict of interest statement

Authors LT and CAS conducted a histological analysis of autopsy brain samples from a Gardasil-suspected death case

http://onlinelibrary.wiley.com/doi/10.1111/j.1365-2796.2012.02551.x/full

"the vaccine is unlikely to reduce the overall frequency of cervical cancers (at least not beyond what Pap screening has already accomplished), yet this is the primary aim for which the vaccine was developed. Furthermore, current data show that antibodies against HPV-18 after Gardasil fall rapidly, with 35% of women having no measurable antibody titres by 5 years postinjection. This outcome suggests that rather than preventing future cases of cervical cancer, Gardasil, at best, may only be effective in postponing them."

The Journal Of Law, Medicine & Ethics • Fall 2012

Too fast or not too fast: the FDA's approval of Merck's HPV vaccine Gardasil

Author information

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Abstract

There are not many public health issues where views are as extremely polarized as those concerning vaccines, and Merck's HPV vaccine Gardasil is a case in point. Ever since gaining the FDA's approval in 2006, Merck has been heavily criticized for their overly aggressive marketing strategies and lobbying campaigns aimed at promoting Gardasil as a mandatory vaccine. Subsequently, questions have been raised as to whether it was appropriate for vaccine manufacturers to partake in public health policies when their conflicts of interests are so obvious. Some of their advertising campaign slogans, such as "cervical cancer kills x women per year" and "your daughter could become one less life affected by cervical cancer," seemed more designed to promote fear rather than evidence-based decision making about the potential benefits of the vaccine. Although, conflicts of interests do not necessarily mean that the product itself is faulty, marketing claims should be carefully examined against factual science data. Currently Gardasil vaccination is strongly recommended by the U.S. and other health authorities while public concerns about safety and efficacy of the vaccine appear to be increasing. This discrepancy leads to some important questions that need to be resolved. The current review examines key issues of this debate in light of currently available research evidence.

http://www.ncbi.nlm.nih.gov/pubmed/23061593

"Some of their advertising campaign slogans, such as "cervical cancer kills x women per year" and "your daughter could become one less life affected by cervical cancer," seemed more designed to promote fear rather than evidence-based decision making about the potential benefits of the vaccine."

Pharmaceutical Regulatory Affairs • 2012

Death after Quadrivalent Human Papillomavirus (HPV) Vaccination: Causal or Coincidental?

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Abstract

Background

The proper understanding of a true risk from vaccines is crucial for avoiding unnecessary adverse reactions (ADRs). However, to this date no solid tests or criteria have been established to determine whether adverse events are causally linked to vaccinations.

Objectives

This research was carried out to determine whether or not some serious autoimmune and neurological ADRs following HPV vaccination are causal or merely coincidental and to validate a biomarker-based immunohistochemical (IHC) protocol for assessing causality in case of vaccination-suspected serious adverse neurological outcomes.

Results

In both cases, the autopsy revealed no anatomical, microbiological nor toxicological ndings that might have explained the death of the individuals. In contrast, our IHC analysis showed evidence of an autoimmune vasculitis potentially triggered by the cross-reactive HPV-16L1 antibodies binding to the wall of cerebral blood vessels in all examined brain samples. We also detected the presence of HPV-16L1 particles within the cerebral vasculature with some HPV-16L1 particles adhering to the blood vessel walls. HPV-18L1 antibodies did not bind to cerebral blood vessels nor any other neural tissues. IHC also showed increased T-cell signalling and marked activation of the classical antibody-dependent complement pathway in cerebral vascular tissues from both cases. This pattern of complement activation in the absence of an active brain infection indicates an abnormal triggering of the immune response in which the immune attack is directed towards self-tissue.

Conclusions

Our study suggests that HPV vaccines containing HPV-16L1 antigens pose an inherent risk for triggering potentially fatal autoimmune vasculopathies.

Practice implications

Cerebral vasculitis is a serious disease which typically results in fatal outcomes when undiagnosed and left untreated. The fact that many of the symptoms reported to vaccine safety surveillance databases following HPV vaccination are indicative of cerebral vasculitis, but are unrecognized as such (i.e., intense persistent migraines, syncope, seizures, tremors and tingling, myalgia, locomotor abnormalities, psychotic symptoms and cognitive de cits), is a serious concern in light of the present findings. It thus appears that in some cases vaccination may be the triggering factor of fatal autoimmune/neurological events. Physicians should be aware of this association.

“Our study suggests that HPV vaccines containing HPV-16L1 antigens pose an inherent risk for triggering potentially fatal autoimmune vasculopathies.”

Full Report:
http://sanevax.org/wp-content/uploads/2012/10/Tomljenovic-Shaw-Gardasil-Causal-Coincidental-2167-7689-S12-001.pdf

Current Pharmaceutical Design • 2013

Human papillomavirus (HPV) vaccines as an option for preventing cervical malignancies: (how) effective and safe?

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Abstract

We carried out a systematic review of HPV vaccine pre- and post-licensure trials to assess the evidence of their effectiveness and safety. We find that HPV vaccine clinical trials design, and data interpretation of both efficacy and safety outcomes, were largely inadequate. Additionally, we note evidence of selective reporting of results from clinical trials (i.e., exclusion of vaccine efficacy figures related to study subgroups in which efficacy might be lower or even negative from peer-reviewed publications). Given this, the widespread optimism regarding HPV vaccines long-term benefits appears to rest on a number of unproven assumptions (or such which are at odd with factual evidence) and significant misinterpretation of available data. For example, the claim that HPV vaccination will result in approximately 70% reduction of cervical cancers is made despite the fact that the clinical trials data have not demonstrated to date that the vaccines have actually prevented a single case of cervical cancer (let alone cervical cancer death), nor that the current overly optimistic surrogate marker-based extrapolations are justified. Likewise, the notion that HPV vaccines have an impressive safety profile is only supported by highly flawed design of safety trials and is contrary to accumulating evidence from vaccine safety surveillance databases and case reports which continue to link HPV vaccination to serious adverse outcomes (including death and permanent disabilities). We thus conclude that further reduction of cervical cancers might be best achieved by optimizing cervical screening (which carries no such risks) and targeting other factors of the disease rather than by the reliance on vaccines with questionable efficacy and safety profiles.

http://www.ncbi.nlm.nih.gov/pubmed/23016780

“We carried out a systematic review of HPV vaccine pre- and post-licensure trials to assess the evidence of their effectiveness and safety. We find that HPV vaccine clinical trials design, and data interpretation of both efficacy and safety outcomes, were largely inadequate. Given this, the widespread optimism regarding HPV vaccines long-term benefits appears to rest on a number of unproven assumptions (or such which are at odd with factual evidence) and significant misinterpretation of available data. Likewise, the notion that HPV vaccines have an impressive safety profile is only supported by highly flawed design of safety trials and is contrary to accumulating evidence from vaccine safety surveillance databases and case reports which continue to link HPV vaccination to serious adverse outcomes (including death and permanent disabilities).”

Infectious Agents & Cancer • 2013

HPV vaccines and cancer prevention, science versus activism

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Abstract

The rationale behind current worldwide human papilloma virus (HPV) vaccination programs starts from two basic premises, 1) that HPV vaccines will prevent cervical cancers and save lives and, 2) have no risk of serious side effects. Therefore, efforts should be made to get as many pre-adolescent girls vaccinated in order to decrease the burden of cervical cancer. Careful analysis of HPV vaccine pre- and post-licensure data shows however that both of these premises are at odds with factual evidence and are largely derived from significant misinterpretation of available data.

Letter

The recent Editorial by Silvia de Sanjosé* [1] is problematic from a variety of perspectives. Mainly, it attempts to portray a complex issue as a simple dichotomy between supposedly unjustified "anti-HPV vaccine activism" and alleged absolute science which has presumably provided indisputable evidence on HPV vaccine safety and efficacy.

In spite of much unwarranted and premature optimism, the fact is however that HPV vaccines have not thus far prevented a single case of cervical cancer (let alone cervical cancer death). Instead, what the clinical trials have shown is that HPV vaccines can prevent some of the pre-cancerous CIN 2/3 lesions associated with HPV-16 and HPV-18 infection, a large fraction of which would spontaneously resolve regardless of the vaccination status [2-4]. For example, in adolescent women aged 13 to 24 years, 38% of CIN 2 resolve after one year, 63% after two and 68% after three years [5]. Moreover, the validity of CIN 2 being a cancer precursor is questionable due to high misclassification rates and poor intra- and inter-observer reproducibility in diagnosis, as well as high regression rates [6-9]. According to Castle et al. [7] CIN 2 is the least reproducible of all histopathologic diagnoses and may in part reflect sampling error. While CIN 3 is a more reliable marker for cancer progression than CIN 2, the use of this marker is not without caveats [2,10].

Indeed, the optimistic assumption that HPV vaccination (even if proven effective against cervical cancer as claimed), will result in 70% reduction of cervical cancers appears to be largely based on premature, exaggerated and invalid surrogate marker-based extrapolations [2,11]. Crucially, these assumptions failed to take into account several important real-world factors such as:

(1) reliability of surrogate-markers (i.e., whether they can accurately measure what they are purport to measure);
(2) efficacy against oncogenic HPV strains not covered by the vaccine;
(3) possibility of increased frequency of infections with these types;
(4) efficacy in women acquiring multiple HPV types;
(5) effects in women with pre-existing HPV infections

It is also noteworthy that Merck's HPV vaccine Gardasil received priority Fast Track approval by the U.S. Food and Drug Administration (FDA) after a 6-month review process, despite the fact that it failed (and still continues to fail) to meet a single one of the four criteria required by the FDA for Fast Track approval. Gardasil is demonstrably neither safer nor more effective than Pap screening combined with the loop electrosurgical excision procedure (LEEP) in preventing cervical cancers, nor can it improve the diagnosis of serious cervical cancer outcomes [12]. In this regard, Gerhardus and Razum have recently noted that the "…unwarranted confidence in the newHPVvaccines led to the impression that there was no need to actually evaluate their effectiveness" [11].

Similarly, the notion that HPV vaccines have an impressive safety profile can only be supported by highly flawed design of safety trials [2,13] and is contrary to accumulating evidence from vaccine safety surveillance databases and case reports which continue to link HPV vaccination to serious adverse outcomes (including death and permanent disabilities) [2,4,14]. For example, compared to all other vaccines in the U.S. vaccination schedule, Gardasil alone is associated with 61% of all serious adverse reactions (including 63.8% of all deaths and 81.2% cases of permanent disability) in females younger than 30 years of age [12].

Although a report to a vaccine safety surveillance system does not by itself prove that the vaccine caused an adverse reaction, the unusually high frequency of adverse reactions related to HPV vaccines reported worldwide, as well as their consistent pattern (i.e. nervous system-related disorders rank the highest in frequency), points to a potentially causal relationship [2]. Furthermore, matching the data from vaccine surveillance databases is an increasing number of case reports documenting similar serious adverse reactions associated with HPV vaccine administration, with nervous system and autoimmune disorders being the most frequently reported in the medical literature [15-24].

In summary, the optimistic claims that HPV vaccines will prevent cervical cancers and save lives, and that they are extremely safe, rest on assumptions which are misinterpreted and presented to the public as factual evidence. We thus conclude that further reduction of cervical cancers might be best achieved by optimizing cervical screening (which carries no serious health risks) and targeting other factors of the disease rather than by the reliance on vaccines with questionable efficacy and safety profiles [2,25].

To those who wish to promote HPV vaccination as a means for reducing cervical cancer burden, perhaps the following should be asked:

1. HPV vaccines have not been demonstrated to prevent any cervical cancers so why are they being promoted as cervical cancer vaccines?

2. If the majority of HPV infections and a great proportion of pre-cancerous lesions clear spontaneously and without medical treatment and are thus not a reliable indication of cancer later in life, then how can these end-points be used as a reliable indicator of the number of cervical cancer cases that will be prevented by HPV vaccines?

3. How can the clinical trials make an accurate estimate of the risk associated with HPV-vaccines if they are methodologically biased to produce type-2 errors (false negatives [2,4,13])? [continued next page]

4. Can a passive monitoring system such as that used by most vaccine surveillance systems world-wide allow the medical regulatory agencies to make accurate estimates on the real frequency of HPV-vaccine related adverse reactions?

5. Can an accurate estimate of the real frequency of HPV-vaccine related adverse reactions be made if appropriate follow-up and thorough investigation of suspected vaccine related ADRs is not conducted but instead, these cases are a-priori dismissed as being unrelated to the vaccine?

6. Why are women not informed of the fact that in some circumstances (i.e., prior exposure to vaccine-targeted and non-targeted HPV types), HPV vaccination may accelerate the progression of cervical abnormalities [4,26-28]?

7. How can women make a fully informed decision about whether or not to consent to vaccination if crucial information regarding HPV vaccine efficacy and safety is not being disclosed to them?

8. Should the medical health regulators and authorities rely solely on data provided by the vaccine manufacturers to make vaccine-policy decisions and recommendations [12,29]?

Competing interests

The authors declare that they have no conflict of interests

Authors' contributions

LT was involved in choosing the topic and drafting the initial manuscript. CAS, JW, EV and TB were involved in critically revising the manuscript and additional content. The authors have read and approved the manuscript. This work was supported by the Dwoskin and Katlyn Fox Family Foundations.

Full Report with References

http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3565961/

"As for all vaccines, and in particular for newly marketed ones, the surveillance of adverse events represents an essential step in the evaluation of a vaccination programme."

[because all vaccines are part of a long-term human population-wide medical experiment]

" Gardasil is demonstrably neither safer nor more effective than Pap screening combined with the loop electrosurgical excision procedure (LEEP) in preventing cervical cancers, nor can it improve the diagnosis of serious cervical cancer outcomes."

Annals Of Medicine • March 2013

Human papillomavirus (HPV) vaccine policy and evidence-based medicine: are they at odds?

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Abstract

All drugs are associated with some risks of adverse reactions. Because vaccines represent a special category of drugs, generally given to healthy individuals, uncertain benefits mean that only a small level of risk for adverse reactions is acceptable. Furthermore, medical ethics demand that vaccination should be carried out with the participant's full and informed consent. This necessitates an objective disclosure of the known or foreseeable vaccination benefits and risks. The way in which HPV vaccines are often promoted to women indicates that such disclosure is not always given from the basis of the best available knowledge. For example, while the world's leading medical authorities state that HPV vaccines are an important cervical cancer prevention tool, clinical trials show no evidence that HPV vaccination can protect against cervical cancer. Similarly, contrary to claims that cervical cancer is the second most common cancer in women worldwide, existing data show that this only applies to developing countries. In the Western world cervical cancer is a rare disease with mortality rates that are several times lower than the rate of reported serious adverse reactions (including deaths) from HPV vaccination. Future vaccination policies should adhere more rigorously to evidence-based medicine and ethical guidelines for informed consent.

http://www.ncbi.nlm.nih.gov/pubmed/22188159

"... while the world's leading medical authorities state that HPV vaccines are an important cervical cancer prevention tool, clinical trials show no evidence that HPV vaccination can protect against cervical cancer. Similarly, contrary to claims that cervical cancer is the second most common cancer in women worldwide, existing data show that this only applies to developing countries. In the Western world cervical cancer is a rare disease with mortality rates that are several times lower than the rate of reported serious adverse reactions (including deaths) from HPV vaccination."

Clinical Rheumatology • September 2013

Human papillomavirus vaccine and systemic lupus erythematosus

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Abstract

To investigate the association between human papillomavirus (HPV) vaccination and autoimmune manifestations compatible with systemic lupus erythematosus (SLE) or SLE-like disease, the medical history of six women who presented with SLE or SLE-like disease following HPV immunization was collected. Data regarding type of vaccine, number of immunization, family and personal, clinical and serological features, as well as response to treatments were analyzed. In the reported cases, several common features were observed, such as personal or familial susceptibility to autoimmunity or adverse response to a prior dose of the vaccine, both of which may be associated with a higher risk of post-vaccination autoimmunity. Favorable response to immunosuppressant was observed in all patients. In the current study, a temporal association between immunization with HPV vaccine and the appearance of a spectrum of SLE-like conditions is reported. Additionally, among the patients described, several common features were observed that may enable better identification of subjects at risk. Further studies are required to assess the safety of immunization with the HPV vaccine in patients with autoimmune-rheumatic diseases or in subject at risk of autoimmunity as well as the potential beneficial effect of preventive immunosuppressants.

http://www.ncbi.nlm.nih.gov/pubmed/23624585

“In the current study, a temporal association between immunization with HPV vaccine and the appearance of a spectrum of SLE-like conditions is reported. Additionally, among the patients described, several common features were observed that may enable better identification of subjects at risk.”

Neuropediatrics • October 2013

Association of acute cerebellar ataxia and human papilloma virus vaccination: a case report

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Abstract

INTRODUCTION

We report the case of a patient who developed symptoms of acute cerebellar ataxia (ACA) after administration of the human papilloma virus (HPV)-16/18 vaccine.

PATIENT AND METHOD

This patient developed symptoms of ACA, including nausea, vertigo, severe limb and truncal ataxia, and bilateral spontaneous continuous horizontal nystagmus with irregular rhythm, 12 days after administration of the HPV-16/18 AS04-adjuvanted cervical cancer vaccine. After this, the patient received methylprednisolone pulse and intravenous immunoglobulin (IVIG) therapies as well as immunoadsorption plasmapheresis.

RESULTS

Severe ACA symptoms did not improve after methylprednisolone pulse and IVIG therapies, but the patient recovered completely after immunoadsorption plasmapheresis.

CONCLUSION

This temporal association strongly suggests that ACA was induced by the vaccination.

http://www.ncbi.nlm.nih.gov/pubmed/?term=23378179

“This temporal association strongly suggests that acute cerebellar ataxia was induced by the vaccination.”

American Journal Of Reproductive Immunology • October 2013

Human papilloma virus vaccine and primary ovarian failure: another facet of the autoimmune/inflammatory syndrome induced by adjuvants

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Abstract

PROBLEM

Post-vaccination autoimmune phenomena are a major facet of the autoimmune/inflammatory syndrome induced by adjuvants (ASIA) and different vaccines, including HPV, have been identified as possible causes.

METHOD OF STUDY

The medical history of three young women who presented with secondary amenorrhea following HPV vaccination was collected. Data regarding type of vaccine, number of vaccination, personal, clinical and serological features, as well as response to treatments were analyzed.

RESULTS

All three patients developed secondary amenorrhea following HPV vaccinations, which did not resolve upon treatment with hormone replacement therapies. In all three cases sexual development was normal and genetic screen revealed no pertinent abnormalities (i.e., Turner's syndrome, Fragile X test were all negative). Serological evaluations showed low levels of estradiol and increased FSH and LH and in two cases, specific auto-antibodies were detected (antiovarian and anti thyroid), suggesting that the HPV vaccine triggered an autoimmune response. Pelvic ultrasound did not reveal any abnormalities in any of the three cases. All three patients experienced a range of common non-specific post-vaccine symptoms including nausea, headache, sleep disturbances, arthralgia and a range of cognitive and psychiatric disturbances. According to these clinical features, a diagnosis of primary ovarian failure (POF) was determined which also fulfilled the required criteria for the ASIA syndrome.

CONCLUSION

We documented here the evidence of the potential of the HPV vaccine to trigger a life-disabling autoimmune condition. The increasing number of similar reports of post HPV vaccine-linked autoimmunity and the uncertainty of long-term clinical benefits of HPV vaccination are a matter of public health that warrants further rigorous inquiry.

http://www.ncbi.nlm.nih.gov/pubmed/23902317

"We documented here the evidence of the potential of the HPV vaccine to trigger a life-disabling autoimmune condition. The increasing number of similar reports of post HPV vaccine-linked autoimmunity and the uncertainty of long-term clinical benefits of HPV vaccination are a matter of public health that warrants further rigorous inquiry."

Current Drug Safety • March 2014

Human papilloma virus vaccine associated uveitis

Author information

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Abstract

PURPOSE
To report a possible association between human papilloma virus (HPV) vaccination and uveitis.

METHODS
Spontaneous reports from the National Registry of Drug-Induced Ocular Side effects, World Health Organization and Food and Drug Administration were collected on uveitis associated with human papilloma virus vaccination. A MEDLINE search was performed using keywords “uveitis,” “iritis,” “iridocyclitis,” “human papilloma virus,” “Cervarix”, and “Gardasil.”

MAIN OUTCOME MEASURES
Data garnered from spontaneous reports included the age, gender, adverse drug reaction (ADR), date of administration, concomitant administration of other vaccinations, time until onset of ADR, other systemic reactions, and dechallenge and rechallenge data.

RESULTS
A total of 24 case reports of uveitis associated with human papilloma virus vaccination were identified, all cases were female, and the median age was 17. Median time from HPV vaccination to reported ADR was 30 days (range 0-476 days).

DISCUSSION
According to World Health Organization criteria, the relationship between human papilloma virus vaccination and uveitis is “possible.” Causality assessments are based on the time relationship of drug administration, uveitis development and rechallenge data.

CONCLUSIONS
Clinicians should be aware of a possible bilateral uveitis and papillitis following HPV vaccination.

http://www.ncbi.nlm.nih.gov/pubmed/24191906

“A total of 24 case reports of uveitis associated with human papilloma virus vaccination were identified, all cases were female, and the median age was 17. According to World Health Organization criteria, the relationship between human papilloma virus vaccination and uveitis is “possible.”

European Journal Of Neurology • September 2014

Postural tachycardia syndrome following human papillomavirus vaccination

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Abstract

BACKGROUND AND PURPOSE
Postural tachycardia syndrome (POTS) is a heterogeneous disorder of the autonomic nervous system that may have an autoimmune etiology.

METHODS
Six patients who developed new onset POTS 6 days to 2 months following human papillomavirus vaccination are reported.

RESULTS
Three patients also had neurocardiogenic syncope, and three patients were diagnosed with possible small fiber neuropathy. Symptoms in all patients improved over 3 years with pharmacotherapy and non-pharmacological measures but residual symptoms persisted. Molecular mimicry with formation of cross-reacting autoantibodies to the potential targets of the autonomic ganglia, neurons, cardiac proteins or vascular receptors is considered as a possible pathogenesis of new onset POTS after immunization.

CONCLUSION
Correct diagnosis of POTS and awareness that POTS may occur after vaccination in young women is essential for prompt and effective management of this condition.

http://www.ncbi.nlm.nih.gov/pubmed/24102827

“Six patients who developed new onset Postural tachycardia syndrome 6 days to 2 months following human papillomavirus vaccination are reported.”

Journal Of Investigative Medicine
High Impact Case Reports • October 2014

Adolescent Premature Ovarian Insufficiency Following Human Papillomavirus Vaccination: A Case Series Seen in General Practice

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Abstract

Three young women who developed premature ovarian insufficiency following quadrivalent human papillomavirus (HPV) vaccination presented to a general practitioner in rural New South Wales, Australia. The unrelated girls were aged 16, 16, and 18 years at diagnosis. Each had received HPV vaccinations prior to the onset of ovarian decline. Vaccinations had been administered in different regions of the state of New South Wales and the 3 girls lived in different towns in that state. Each had been prescribed the oral contraceptive pill to treat menstrual cycle abnormalities prior to investigation and diagnosis. Vaccine research does not present an ovary histology report of tested rats but does present a testicular histology report. Enduring ovarian capacity and duration of function following vaccination is unresearched in preclinical studies, clinical and postlicensure studies. Postmarketing surveillance does not accurately represent diagnoses in adverse event notifications and can neither represent unnotified cases nor compare incident statistics with vaccine course administration rates. The potential significance of a case series of adolescents with idiopathic premature ovarian insufficiency following HPV vaccination presenting to a general practice warrants further research. Preservation of reproductive health is a primary concern in the recipient target group. Since this group includes all prepubertal and pubertal young women, demonstration of ongoing, uncompromised safety for the ovary is urgently required. This matter needs to be resolved for the purposes of population health and public vaccine confidence.

http://www.ncbi.nlm.nih.gov/pubmed/26425627

“Three young women who developed premature ovarian insufficiency following quadrivalent human papillomavirus (HPV) vaccination presented to a general practitioner in rural New South Wales, Australia. The potential significance of a case series of adolescents with idiopathic premature ovarian insufficiency following HPV vaccination presenting to a general practice warrants further research. This matter needs to be resolved for the purposes of population health and public vaccine confidence.”

Human Vaccines And Immunotherapeutics • 2014

Comparison of adaptive and innate immune responses induced by licensed vaccines for Human Papillomavirus

Author information

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Abstract

Two HPV virus-like particle (VLP) vaccines, HPV-16/18 (GlaxoSmithKline, Cervarix®) and HPV-6/11/16/18 (Merck, Gardasil®), are currently licensed in the United States. Given the similar antigenic content but different adjuvant formulations in the 2 vaccines, they provide an efficient method for evaluating adjuvants and comparing the kinetics of the innate and adaptive immune responses. We randomized women to receive either Cervarix® or Gardasil®, followed 6 month vaccination delivery schedules per manufacturer's recommendations, and analyzed the humoral immune response, T cell response, and circulating plasma cytokine levels in response to vaccination. Cervarix® recipients had higher anti-HPV-16 antibody and neutralization titers at month 7, and elevated anti-HPV-18 antibody and neutralization titers at months 7 and 12. Antibody avidity was similar for the 2 vaccines. HPV-31 was the only phylogenetically related non-vaccine HPV type, for which there is evidence of cross-protection, to be cross-neutralized and only in response to Cervarix®. Comparing CD4+ T cell cytokine responses at month 12, there was a trend of increased levels of IL-2 and TNF-□ in the Cervarix® groups versus the Gardasil® groups that was consistent across all 4 tested HPV types (16/18/33/45). Elevated levels of circulating plasma cytokine/chemokines were observed post first vaccination in Gardasil® recipients and proinflammatory cytokines were elevated following 1st and 3rd Cervarix® vaccinations. Cervarix® and Gardasil® are both highly immunogenic vaccines. Higher antibody levels and CD4 T cell responses were achieved with Cervarix® after 3 doses, although similar affinity maturation was measured for the 2 vaccines. The clinical implications of the differences in immune responses are unknown.

http://www.ncbi.nlm.nih.gov/pubmed/?term=25483691

[proving vaccines are continuous, long-term human experiments]

HPV vaccine is neither safe nor effective

The following letter to the editor of the Baltimore Sun, with references, was written by Emily Tarsell, LCPC, and Dr. William Reichel on August 9, 2015

Dear Editor:

Your recent article in The Baltimore Sun, Medicine Briefs for August 2, 2015, states that "not enough pediatricians are strongly recommending HPV vaccine." It appears there are excellent medical and scientific reasons why many doctors do not.

Since hpv vaccines were introduced seven years ago, it has been assumed that this vaccine will prevent cervical cancer. Yet it has never been demonstrated to prevent any cancer, cervical or otherwise (1, 2, 3).

It has also been assumed for 7 years that this vaccine is safe. Yet there have been thousands of adverse event reports. The CDC itself admits there are 3x as many adverse events for the hpv vaccine Gardasil as there are for all other vaccines combined.(4) Compared to all other vaccines in the US schedule, Gardasil alone is associated with 61% of all serious adverse events including 63.8% of all deaths and 81.2% of all permanent disabilities in females under 30 years of age. (5)

In fact, Japan, India and France have removed hpv vaccines from their recommended list due to safety and ef cacy concerns.(6, 7, 8, 11) Unethical practices and serious post hpv vaccination injuries and deaths prompted the Supreme Court of India to initiate an ongoing investigation of the Bill and Melin- da Gates Foundation. (7) The Health Welfare and Labor Ministry of Japan conducted a national inves- tigation regarding post hpv vaccine injuries in their country. The outcome was the removal of funding and removal of recommendations regarding hpv vaccines. (8, 9, 10, 11) They concluded that the harm experienced is overwhelmingly greater than the bene t expected.

Prompted by medical reports of post hpv vaccination arrhythmia and motor neuron disabilities in children in Denmark, the European Medicines Agency is conducting an investigation of hpv injection adverse events. (12) Law suits for hpv injuries and deaths have also been led in Spain, France and Columbia.

Some studies have linked serious hpv vaccine adverse events to the aluminum adjuvant which is a known neurotoxin. (13, 14, 15, 16) Yet the latest version of hpv vaccine, Gardasil 9, contains double the amount of aluminum adjuvant than its predecessor.

We already have proven, safe and effective ways to prevent cervical cancer with pap screening which carries no serious health risk. So the doctors who do not recommend hpv vaccination are the ones who have done their research. The public should be grateful to those who have taken their oath seriously.

Sincerely,

William Reichel, MD Emily Tarsell, LCPC

References

1. Tomljenovic L, Shaw CA, Spinosa JP: Human Papillomavirus (HPV) Vaccines as an option for preventing cervical malignancies: (How) effective and safe? Curr Pharm Des 2012, :CPD-EPUB-20120924-13.Epub ahead of print.
2. Tomljenovic L, Shaw CA: Who profits from uncritical acceptance of biased estimates of vaccine efficacy and safety? Am J Public Health 2012, 102(9):e13–e14.
3. Tomljenovic L, Shaw CA: Human papillomavirus (HPV) vaccine policy and evidence-based medicine: are they at odds? Ann Med 2011, doi:10.3109/07853890.2 011.645353
4. Slade BA, Leidel L, Vellozzi C, et al. Postlicensure safety surveillance for quadrivalent human papillomavirus recombinant vaccine. JAMA. 2009; 302 (7): 750- 757.
5. Tomljenovic L, Wilyman J, Vanamee E, Bark T,Shaw CA. HPV vaccines and cancer prevention, science versus activism. Infectious Agents and Cancer 2013,8:6. http://www.infectagentscancer.com/content/8/1/6.
6. Vactruth. French Medical Doctors Say, "Delist & Suspend HPV Vaccines. December 28, 2011 http://www.medocean.re/2011/09/le-gardasil-a-l%E2%80%99as- semblee-nationale/.Accessed January 2012.
7. Sarojini N B, Sandhya Srinivasan, Madhavi Y, Srinivasan S, Anjali Shenoifie HPV Vaccine: Science, Ethics and Regulation. Economic & Political Weekly EPW november 27, 2010 vol xlv no 48.
8. Erickson N. Japan and the hpv vaccine controversy. www.sanevax.org. Accessed 4/29/2014.
9. Kyodo. Cervarix vaccine issues trigger health notice. Japan Times. June 15,2013. http://www.japantimes.co.jp/news/2013/06/15/national/cervix-vaccine-issues-trigger-health-notice/#.VMfXlWjF8fX. Accessed 4/29/2014.
10. Ministry of Health, Labor and Welfare. Shimbun A. Analysis: Experts at loss over pain from cervical cancer vaccination. Asia and Japan Watch. June 18, 2013. http://ajw.asahi.com/article/behind_news/social_a airs/AJ201306180057. Ac- cessed 1/27/15
11. Archive of proceedings and events regarding an investigation into hpv vaccines safety and efficacy by the Japanese Ministry of Health, Labor and Welfare. Medwatcher Japan. http://www.yakugai.gr.jp/en/activity/index.php?year=2014. Accessed 1/26/15.
12. Chustecka Z. Safety Profile of HPV Vaccines Under Review in Europe. Med- scape.July 13. 2015. http://www.medscape.com/viewarticle/847841src=wnl_edit_ newsal&uac=148182AN&impID=759675&faf=1 Accessed July 20, 2015.
13. Lee, SH. Detection of human papillomavirus (HPV) L1gene DNA possibly bound to particulate aluminum adjuvant in the HPV-vaccine Gardasil. Journal of Inorganic Biochemistry.117 (2012) 85-92. www.elsevier.com/locate/jinorgbio.
14. Shoenfeld Y, Agmon-Levin N. 'ASIA' – Autoimmune/in ammatory syndrome induced by adjuvants. Journal of Autoimmunity (2010), 2010; XXX: 1-5.
15. Tomljenovic L, Shaw CA. Mechanisms of Aluminum adjuvant toxicity and autoimmunity in pediatric populations. Lupus 2012; 21:223-230.
16. Shaw CA, Petrik MS. Aluminum hydroxide injections lead to motor de cits and motor neuron degeneration. J Inorg Biochem 2009; 103: 1555-1562.

"Since hpv vaccines were introduced seven years ago, it has been assumed that this vaccine will prevent cervical cancer. Yet it has never been demonstrated to prevent any cancer, cervical or otherwise. It has also been assumed for 7 years that this vaccine is safe. Yet there have been thousands of adverse event reports. The CDC itself admits there are 3x as many adverse events for the hpv vaccine Gardasil as there are for all other vaccines combined."

Danish Medical Journal • April 2015

Suspected side effects to the quadrivalent human papilloma vaccine

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Abstract

Introduction

The quadrivalent vaccine that protects against human papilloma virus types 6, 11, 16 and 18 (Q-HPV vaccine, Gardasil) was included into the Danish childhood vaccination programme in 2009. During the past years, a collection of symptoms primarily consistent with sympathetic nervous system dysfunction have been described as suspected side effects to the Q-HPV vaccine.

Methods

We present a description of suspected side effects to the Q-HPV vaccine in 53 patients referred to our Syncope Unit for tilt table test and evaluation of autonomic nervous system function.

Results

All patients had symptoms consistent with pronounced autonomic dysfunction including different degrees of orthostatic intolerance, severe non-migraine-like headache, excessive fatigue, cognitive dysfunction, gastrointestinal discomfort and widespread pain of a neuropathic character.

Conclusion

We found consistency in the reported symptoms as well as between our findings and those described by others. Our findings neither confirm nor dismiss a causal link to the Q-HPV vaccine, but they suggest that further research is urgently warranted to clarify the pathophysiology behind the symptoms experienced in these patients and to evaluate the possibility and the nature of any causal link and hopefully establish targeted treatment options.

http://www.ncbi.nlm.nih.gov/pubmed/25872549

“During the past years, a collection of symptoms primarily consistent with sympathetic nervous system dysfunction have been described as suspected side effects to the Q-HPV vaccine. All patients had symptoms consistent with pronounced autonomic dysfunction including different degrees of orthostatic intolerance, severe non-migraine-like headache, excessive fatigue, cognitive dysfunction, gastrointestinal discomfort and widespread pain of a neuropathic character.”

Brain And Nerve • July 2015

Neurologic Complications in HPV Vaccination

Author information

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Department of Medicine (Neurology and Rheumatology)
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Abstract

A relatively high incidence of chronic limb pain, frequently complicated by violent, tremulous involuntary movements, has been noted in Japanese girls following human papillomavirus vaccination. The average incubation period after the first dose of the vaccine was 5.47 ± 5.00 months. Frequent manifestations included headaches, general fatigue, coldness of the feet, limb pain, and weakness. The skin temperature of the girls with limb symptoms was slightly lower in the fingers and moderately lower in the toes. Digital plethysmograms revealed a reduced peak of the waves, especially in the toes. Limb symptoms of the affected girls were compatible with the diagnostic criteria for complex regional pain syndrome. The Schellong test identified a significant number of patients with orthostatic hypotension and a few with postural orthostatic tachycardia syndrome. Electron-microscopic examinations of the intradermal nerves showed an abnormal pathology in the unmyelinated fibers in two of the three girls examined. The symptoms observed in this study can be explained by abnormal peripheral sympathetic responses. The most common previous diagnosis in the patients was psychosomatic disease. Recently, delayed manifestation of cognitive dysfunction in the post-vaccinated girls has attracted attention. The symptoms include memory loss and difficulty in reading textbooks and/or calculation.

http://www.ncbi.nlm.nih.gov/pubmed/26160812

“A relatively high incidence of chronic limb pain, frequently complicated by violent, tremulous involuntary movements, has been noted in Japanese girls following human papillomavirus vaccination.”

Expert Opinion On Drug Safety • July 2015

The safety of human papilloma virus-blockers and the risk of triggering autoimmune diseases

Author information

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Abstract

INTRODUCTION

With the safety of human papilloma virus vaccine (HPVv) being questioned, this article aims to assess the risks and benefits of the commercially available HPVv. Within the last decade, two vaccines (Gardasil and Cervarix) have been put on the market to prevent infection with the most oncogenic HPV subtypes. Both vaccines contain aluminum adjuvants that are meant to cause a hyper stimulated immune response to prevent HPV infection.

AREAS COVERED

The purpose of this paper is to consider the safety of these two vaccines based on the data from the U.S. Vaccine Adverse Event Reporting System (VAERS) and case reports.

EXPERT OPINION

The current HPVv are both effective and generally safe. However, it should be noted that autoimmune side effects have been reported in several studies. Further research should be done to understand the relationship between HPVv and autoimmunity.

http://www.ncbi.nlm.nih.gov/pubmed/26216756

“However, it should be noted that autoimmune side effects have been reported in several studies. Further research should be done to understand the relationship between HPVv and autoimmunity.”

Human Vaccines & Immunotherapy • October 2015

Compensation programs after withdrawal of the recommendation for HPV vaccine in Japan

Author information

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Abstract

HPV vaccinations were recommended with the backing of a Japanese government subsidy program in 2010, and were included in the National Immunization Program in April 2013. However, the Ministry of Health, Labour, and Welfare withdrew the recommendation for the HPV vaccination in June 2013. We investigated HPV vaccine injury compensation programs for both the national and local governments. Approximately 3.38 million girls were vaccinated, and 2,584 complained of health problems. The majority of these received the vaccine shot as a non-routine vaccination. In total, 98 people developed health problems and applied for assistance from 2011 to 2014, but no cases have been processed since October 2014. Several local governments are providing their own compensation program for cases of vaccine adverse reactions, but the number is extremely low (16 of 1,741 municipalities and 1 of 47 prefectures). The local governments that are providing compensation are largely those where HPV vaccine victim support groups are prominent. The confusion regarding the national program for HPV vaccine injury was caused by the discrepancy between the compensation programs for those vaccinated under the immunization law and for those who received voluntary vaccinations. The establishment of a new compensation program might be key to finding a lasting resolution.

http://www.ncbi.nlm.nih.gov/pubmed/26513303

HPV Vaccination Crisis In Japan link:

http://www.researchgate.net/publication/279181953_HPV_vaccination_crisis_in_Japan

“the Ministry of Health, Labour, and Welfare withdrew the recommendation for the HPV vaccination in June 2013.”

Clinical Rheumatology • November 2015

HPV vaccination syndrome
A questionnaire-based study

Author information

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Abstract

Isolated cases and small series have described the development of complex regional pain syndrome, postural orthostatic tachycardia, and fibromyalgia after human papillomavirus (HPV) vaccination. These illnesses are difficult to diagnose and have overlapping clinical features. Small fiber neuropathy and dysautonomia may play a major role in the pathogenesis of these entities. We used the following validated questionnaires to appraise the chronic illness that might appear after HPV vaccination: The 2010 American College of Rheumatology Fibromyalgia Diagnostic Criteria, COMPASS 31 dysautonomia questionnaire, and S-LANSS neuropathic pain form. These questionnaires and a "present illness" survey were e-mailed to persons who had the onset of a chronic ailment soon after HPV vaccination. Forty-five filled questionnaires from individuals living in 13 different countries were collected in a month's period. Mean (±SD) age at vaccination time was 14 ± 5 years. Twenty-nine percent of the cases had immediate (within 24 h) post-vaccination illness onset. The most common presenting complaints were musculoskeletal pain (66 %), fatigue (57 %), headache (57 %), dizziness/vertigo (43 %), and paresthesias/allodynia (36 %). Fifty-three percent of affected individuals fulfill the fibromyalgia criteria. COMPASS-31 score was 43 ± 21, implying advanced autonomic dysfunction. Eighty-three percent of the patients who had ongoing pain displayed S-LANSS values >12, suggesting a neuropathic component in their pain experience. After a mean period of 4.2 ± 2.5 years post-vaccination, 93 % of patients continue to have incapacitating symptoms and remain unable to attend school or work. In conclusion, a disabling syndrome of chronic neuropathic pain, fatigue, and autonomic dysfunction may appear after HPV vaccination.

http://www.ncbi.nlm.nih.gov/pubmed/26354426

"Isolated cases and small series have described the development of complex regional pain syndrome, postural orthostatic tachycardia, and fibromyalgia after human papillomavirus (HPV) vaccination. In conclusion, a disabling syndrome of chronic neuropathic pain, fatigue, and autonomic dysfunction may appear after HPV vaccination."

Chapter Five
75 Years Of Vaccine Science
1939 - 2016

Both common observation and official statistics confirm that there have been dramatic increases in chronic physical and mental illnesses in American children, such as autism, asthma, and allergies since the introduction of the MMR vaccine in 1978. Government health officials have denied a relationship with vaccines, but U.S. Congressional hearings on vaccine safety (1999 to Dec. 2004) revealed a total absence of vaccine safety tests that would meet current scientific standards, so that it can be assumed that many vaccine reactions are taking place unrecognized. Prior to the introduction of vaccines, the Th1 cellular immune system of the gastrointestinal and respiratory systems served as the primary defense systems with the Th2 humoral immune system in the bone marrow, serving a secondary role. There is a school of thought that the "minor childhood diseases" of earlier times, including measles, mumps, chicken pox, and rubella, which involved the epithelial tissues of skin, respiratory, and/or gastrointestinal tracts, served a necessary purpose in challenging, strengthening, and establishing the dominance of the Th1 cellular immune system during early childhood. Current vaccines against these diseases, in contrast, being directed at stimulating antibody production in the bone marrow, are bypassing the cellular immune system and thereby tending to reverse the roles of the cellular and humoral systems, with the former suffering from a lack of challenge. In addition, the cellular immune system is being further compromised by the powerfully immunosuppressive effects of the MMR vaccine. The time is overdue to totally rethink and redirect our current childhood vaccine program.

~ Dr. Harold Buttram

JAMA • Vol 112, No. 19 • May 13, 1939

Diphtheria immunity in Chicago

by Herman N. Bundesen, MD., Sc.D.,
William I. Fishbein, MD., John L. White, MD

Abstract

Although diphtheria mortality and morbidity have been gradually decreasing in most parts of the United States for the past twenty-five years, they have not been reduced to the level which it was hoped would be attained. Antitoxin, control of carriers and the Schick test were important. The discovery of toxoid added new impetus to the efforts to control this disease. It was believed that the inoculation of a large proportion of the child population would result in almost complete eradication of diphtheria. The results obtained with the use of toxoid did not, however, approximate expectations. The present study explains to some extent this failure.

http://jama.jamanetwork.com/article.aspx?articleid=288193&resultClick=3

“It was believed that the inoculation of a large proportion of the child population would result in almost complete eradication of diphtheria. The results obtained with the use of toxoid did not, however, approximate expectations. The present study explains to some extent this failure.”

JAMA • Vol 114, No. 19 • May 11, 1940

Allergy induced by immunization with Tetanus Toxoid

by Robert A. Cooke, MD., Stanley Hampton, MD.,
William B. Sherman, MD., Arthur Stull. Ph.D.

Abstract

A toxoid for the active immunization of human beings against tetanus infection has been developed within the past few years and its efficiency as a producer of tetanus antitoxin has been well established. It has followed directly in the wake of the development of diphtheria toxoid, and today a refined alum precipitated formaldehyde detoxified tetanus toxoid standardized under rules of the National Institute of Health is commercially available. It is not within the scope of this paper to discuss the aspects of its development or its antitoxin producing capacity, all of which may be found in such recent papers, with references, as those of Bergey and Etris,1 Jones and Moss,2 Hall,3 Gold4 and Cowles.5

http://jama.jamanetwork.com/article.aspx?articleid=1160278&resultClick=3

“It has followed directly in the wake of the development of diphtheria toxoid, and today a refined alum precipitated formaldehyde detoxified tetanus toxoid standardized under rules of the National Institute of Health is commercially available.”

Pediatrics • April 1948

Encephalopathies Following Prophylactic Pertussis Vaccine

Randolph K. Byers, Frederic C. Moll

Abstract

Inspection of the records of the Children's Hospital for the past ten years has disclosed 15 instances in which children developed acute cerebral symptoms within a period of hours after the administration of pertussis vaccine. The children varied between 5 and 18 months in age and, in so far as it is possible to judge children of this age range, were developing normally according to histories supplied by their parents. None had had convulsions previously. Many different lots of vaccine, made by eight different manufacturers over a period of eight years, were implicated. The inoculations were given throughout the usual geographic range of children coming to this hospital. All but one, at the time of follow-up or death, showed evidence of impairment of the nervous system, which might still have been in the healing stage in three or four.

During the same period about half as many children were seen in the hospital suffering from the encephalopathy secondary to smallpox vaccination, and about twice as many from the encephalopathy complicating pertussis itself.

A variety of etiologic considerations were suggested by consideration of the reported cases and references to the literature. That constitutional factors may have been involved was suggested by both the preponderance of males as opposed to females, and by the high incidence of abnormalities of the nervous system in the family histories. The clinical course and cytologic abnormalities of spinal fluids found in acute cases indicated an encephalopathy. The literature suggested that this process might have resulted from either the activity of a specific toxin or from an antigen-antibody response. Against the former of these hypotheses was the unstable nature of the heretofore recognized toxins which could hardly survive in properly aged vaccines. The rapid onset of symptoms, occasionally within minutes of the first injection, seemed strong evidence against the second. The present study has left these etiologic considerations unanswered, but it has called attention to a risk of the prophylactic use of pertussis vaccine not hitherto recognized.

In view of the impressive evidence of the effectiveness of prophylactic pertussis vaccine now accumulating, it seems likely that babies are safer vaccinated than not. Further studies should be made to prove this point definitely, for the encephalopathy following pertussis vaccine seems more devastating than the vast majority of the nervous lesions following the use of smallpox vaccine.

http://pediatrics.aappublications.org/content/1/4/437?sid=0d16c0ef-0e60-4827-883e-d89933f51dfc&variant=abstract&sso=1&sso_redirect_count=5&nfstatus=401&nftoken=00000000-0000-0000-0000-000000000000&nfstatusdescription=ERROR%3A%20No%20local%20token&nfstatus=401&nftoken=00000000-0000-0000-0000-000000000000&nfstatusdescription=ERROR%3a+No+local+token

"In view of the impressive evidence of the effectiveness of prophylactic pertussis vaccine now accumulating, it seems likely that babies are safer vaccinated than not. Further studies should be made to prove this point definitely, for the encephalopathy following pertussis vaccine seems more devastating than the vast majority of the nervous lesions following the use of smallpox vaccine."

JAMA • Vol 152, No. 14 • August 1, 1953

Precautions In Pediatric Immunization Procedures

by Louis W. Sauer, M.D., Ph.D.

Abstract

During the past decade, the simultaneous immunization against diphtheria, tetanus, and pertussis has become quite well established on laboratory and clinical evidence. To retard the elimination of antigen (DTP) from the body and to enhance antitoxin and antibody development, various forms of aluminum have been used as adjuvant. Most private patients are now adequately protected by the customary primary series of three or four monthly doses, and subsequent recall (stimulating or booster) doses. Needless deaths due to pertussis are still occurring, however, in infants and children from families with low incomes and orphanages in congested cities and in rural areas. To reach these children, mass immunization clinics should function at well baby clinics, primary schools, and mobile units. The diverse difficulties encountered in the execution of these immunization procedures are problems due to earlier immunization, febrile reactions, alum cyst, postinoculation encephalopathy, paralytic poliomyelitis of the injected limb, and unfavorable results.

http://jama.jamanetwork.com/article.aspx?articleid=287046&resultClick=3

“The diverse difficulties encountered in the execution of these immunization procedures are problems due to earlier immunization, febrile reactions, alum cyst, postinoculation encephalopathy, paralytic poliomyelitis of the injected limb, and unfavorable results.”

Science • January 1969

Secretory activity and oncogenicity of a cell line (MDCK) derived from canine kidneyand

A cell line (MDCK) of dog kidney origin grows on a glass surface as a mosaic of epithelium with many multicellular hemispherical vesicles. The cells lining the blisters actively secrete into the cyst cavities. Suspensions of these cells injected intravenously in the chick embryo produce brain metastases resembling adenocarcinoma.

[Editors Note: The MDCK (NBL-2) (ATCC® CCL-34™) cell line has been used since 1958 to produce influenza and other vaccines]

http://www.sciencemag.org/content/163/3866/472.long

Information on the MDCK cell line

http://www.atcc.org/products/all/CCL-34.aspx

"A cell line (MDCK) of dog kidney origin grows on a glass surface as a mosaic of epithelium with many multicellular hemispherical vesicles. The cells lining the blisters actively secrete into the cyst cavities. Suspensions of these cells injected intravenously in the chick embryo produce brain metastases resembling adenocarcinoma."

[In a departure from the use of traditional egg-based vaccines the FDA approved Flucelvax for Novartis on November 20th, 2012. Flucelvax was the first mammalian cell-based influenza vaccine in the US. The Madin-Darby canine kidney cell line is cultured to produce the vaccine. The primary advantage of MDCK over traditional egg-based manufacturing is rapid growth.]

“The observations of this study as well as those of similar studies suggest that vaccine failures contributed to the genesis of the epidemic.”

Canadian Medical Association Journal • November 1975

Analysis of a measles epidemic: possible role of vaccine failures

W. E. Rawls, M. L. Rawls, and M. A. Chernesky

Abstract

A measles epidemic occurred in the Greensville (Ont.) Unit schools during January and February 1975. There were 47 cases of measles in 403 students: 26 (55%) of the children had a history of being vaccinated and 18 (38%) had not been vaccinated. Among children known to have been vaccinated at less than 1 year of age 7 of 13 contracted measles, while among the 48 children who had not been vaccinated 18 contracted measles. The attack rate among vaccinees increased with increasing time since vaccination. The observations of this study as well as those of similar studies suggest that vaccine failures contributed to the genesis of the epidemic. It is recommended that all children initially vaccinated at less than 1 year of age should be revaccinated with live attenuated measles virus vaccine.

Full Report

http://www.ncbi.nlm.nih.gov/pmc/articles/PMC1956577/

Journal Of Experimental Medicine • September 1977

Autoimmunity to type II collagen an experimental model of arthritis

Trentham DE, Townes AS, Kang AH.

Abstract

We have found that intradermal injection of native type II collagen extracted from human, chick or rat cartilage induces an inflammatory arthritis in approximately 40% of rats of several strains whether complete Freund's adjuvant or incomplete Freund's adjuvant is used. Type I or III collagen extracted from skin, cartilage proteoglycans and alpha1(II) chains were incapable of eliciting arthritis, as was type II collagen injected without adjuvant. The disease is a chronic proliferative synovitis, resembling adjuvant arthritis in rats and rheumatoid arthritis in humans. Native type II co-lagen modified by limited pepsin digestion still produces arthritis, suggesting that type-specific determinants residing in the helical region of the molecule are responsible for the induction of disease. Since homologous type II collagen emulsified in oil without bacterial preparations regularly causes the disease, this new animal model of arthritis represents a unique example of experimentally-inducible autoimmunity to a tissue component.

Full Report

http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2180804/pdf/je1463857.pdf

"this new animal model of arthritis represents a unique example of experimentally-inducible autoimmunity to a tissue component."

Gastroenterology • February 1980

HBe-Antigen in the course and prognosis of hepatitis B infection: a prospective study

Schulman AN, Fagen ND, Brezina M,
Silver H, Nitzze A, Morton D, Gitnick GL.

Abstract

The prognostic significance of the HBe-antigen (HBeAg) in the course and outcome of type B hepatitis was studied prospectively in 71 susceptible oncology patients. The patients had been exposed to tumor cell vaccines inadvertently contaminated with hepatitis B surface antigen (HBsAg)-containing plasma. Forty-five patients (63%) were infected. These 45 showed three types of acute seroresponse: HBsAg and HBeAg, 28 patients (62%); HBsAg alone, 8 patients (18%); and a primary antibody to HBsAg (anti-HBs) response, 9 patients (20%). There was no significant difference in acute course and outcome between the two HBs-antigenemic groups. All primary anti-HBs responders had asymptomatic infections. Seventeen patients receiving chemotherapy during the period of hepatitis B exposure were significantly more prone to symptomatic infection with acute HBs-antigenemia, and 2 of these patients developed chronic active hepatitis. The HBeAg is common early in acute hepatitis B among solid tumor patients and at this stage in disease has no prognostic significance independent of HBsAg.

http://www.ncbi.nlm.nih.gov/pubmed/?term=7350048

“The patients had been exposed to tumor cell vaccines inadvertently contaminated with hepatitis B surface antigen-containing plasma. Forty-five patients (63%) were infected.”

Reviews Of Infectious Diseases • May 1980

Vaccine adjuvants

Edelman R.

Abstract

Nonreplicating, purified subunit or synthetic viral vaccines of the future are likely to be weak immunogens that will require immunopotentiation if they are to be effective. These marginal vaccines could be improved by combination with potent and safe immunologic adjuvants. The use of adjuvants should also reduce the amount of purified antigen required for successful immunization, thus making vaccine production more economical and more feasible. It may be possible to combine the recently developed relatively nontoxic synthetic immunoregulators of low molecular weight with antigens in order to modulate preselected compartments of the immune system. To date, the question of adjuvant safety has not been resolved and represents the major obstacle to the orderly development of adjuvanted vaccines. The fear of inducing cancer and other immediate or long-term perturbations of the immune system must be patently and rationally overcome by basic and applied experimentation and by the development of appropriate guidelines for studies in humans.

http://www.ncbi.nlm.nih.gov/pubmed/?term=6997966

“Nonreplicating, purified subunit or synthetic viral vaccines of the future are likely to be weak immunogens that will require immunopotentiation if they are to be effective.”

“These data suggest that Tween 80 has an effect on the Central Nervous System which could lead to misinterpretation of results in toxicology studies that use this compound as a dosage vehicle.”

Life Sciences • June 1982

Effect of Tween 80 on exploratory behavior and locomotor activity in rats

Brubaker CM, Taylor DH, Bull RJ.

Abstract

Exploratory behavior and locomotor activity is enhanced in male rat pups (aged 10 to 20 days) whose dams received a chronic dose (1.25 ml/l) of Tween 80 via their drinking water. This enhancement manifests itself during the diurnal period of the day. These data suggest that Tween 80 has an effect on the CNS which could lead to misinterpretation of results in toxicology studies that use this compound as a dosage vehicle.

http://www.ncbi.nlm.nih.gov/pubmed/7202094

Biochimica et Biophysica Acta • October 1983

Effect of pertussis toxin on the hormonal regulation of cyclic AMP levels in hamster fat cells

by Martínez-Olmedo MA, García-Sáinz JA.

Abstract

Pertussis toxin was purified approx. 1800-fold from pertussis vaccine. Administration of as little as 1 microgram of toxin/100 g body weight to hamsters markedly decreased the sensitivity of their adipocytes to agents that inhibit adenylate cyclase through receptor-mediated, GTP-dependent mechanisms such as alpha 2-adrenergic amines, prostaglandins, phenylisopropyladenosine and nicotinic acid. On the contrary, the inhibitory effect of 2',5'-dideoxyadenosine on cyclic AMP accumulation was not affected by the toxin. Activation of adenylate cyclase by isoproterenol, ACTH or forskolin was not diminished by the toxin but the maximum cyclic AMP accumulation was consistently increased. Furthermore, the dose-response curves for ACTH and forskolin were clearly shifted to the left in adipocytes from toxin-treated hamsters as compared to control adipocytes. It is concluded that pertussis toxin blocks the transfer of inhibitory information from the receptors to adenylate cyclase.

http://www.ncbi.nlm.nih.gov/pubmed/6313062

"It is concluded that pertussis toxin blocks the transfer of inhibitory information from the receptors to adenylate cyclase."

New England Journal Of Medicine • January 1984

Abnormal T-lymphocyte subpopulations in healthy subjects after tetanus booster immunization

Eibl MM, Mannhalter JW, Zlabinger G.

“By way of explanation, a vaccine safety test is one in which before-and-after vaccine tests are performed, specifically designed to test for possible adverse effects on the neurological, immunological, hematologic, genetic, and other systems of the body, in sufficient numbers of test subjects and controls to be statistically significant. As an example, in a little noted study from Germany by Eibl et al. [11], a significant, though temporary, drop of T-Helper lymphocytes was found in 11 healthy adults following routine tetanus booster vaccinations. Special concern rests in the fact that, in four of the subjects, T-helper lymphocytes fell to levels seen in active AIDS patients.”

Report available for purchase:

http://www.ncbi.nlm.nih.gov/pubmed/?term=6228737

“As an example, in a little noted study from Germany by Eibl et al. [11], a significant, though temporary, drop of T-Helper lymphocytes was found in 11 healthy adults following routine tetanus booster vaccinations. Special concern rests in the fact that, in four of the subjects, T-helper lymphocytes fell to levels seen in active AIDS patients.”

"This outbreak demonstrates that transmission of measles can occur within a school population with a documented immunization level of 100%. This level was validated during the outbreak investigation."

CDC • June 22, 1984

MMWR Weekly

From December 9, 1983, to January 13, 1984, 21 cases of measles occurred in Sangamon County, Illinois.* Nine of the cases were confirmed serologically. The outbreak involved 16 high school students, all of whom had histories of measles vaccination after 15 months of age documented in their school health records. Of the five remaining cases, four occurred in unvaccinated preschool children, two of whom were under 15 months of age, and one case occurred in a previously vaccinated college student (Figure 5).

The affected high school had 276 students and was in the same building as a junior high school with 135 students. A review of health records in the high school showed that all 411 students had documentation of measles vaccination on or after the first birthday, in accordance with Illinois law.

Measles vaccination histories were obtained from the school health records of all 276 senior high school students. Risk of infection was not significantly associated with type of vaccine, medical provider, age at most recent vaccination, or revaccination. All the students with measles had received their most recent vaccinations after 15 months of age. However, the measles attack rate increased with increasing years since most recent vaccination ($p = 0.024$) (Table 3). The attack rate was four times greater for students vaccinated 10 or more years before the outbreak than for students vaccinated more recently (p 0.05). When these data are corrected for the number of vaccinations, the trend was still observed and achieved a borderline level of statistical significance ($p = 0.07$). Age at first or last vaccination was not a confounding variable.

The index patient, Student A, was a 17-year-old male in the 11th grade; he was present in school with a productive cough for 3 consecutive days before his onset of rash. The source of his infection was not identified. Nine students with first-generation cases developed onset of rash 10-14 days after exposure to Student A (Figure 5). The attack rate was 6% (16/276) for senior high school students and 0% (0/135) for junior high school students. The highest attack rate was 12% (9/74) for the 11th grade students (p 0.02).

Repeated and close exposure to Student A was associated with a greater risk of illness (Table 4). The eight patients with first-generation cases who attended the high school were used to analyze the degree of exposure to Student A. The measles attack rate was 3% for students who did have classroom exposure to Student A versus 2% for those who did not. Moreover, the attack rate was 21% for students whom Student A identified as "close friends" from the school enrollment roster, compared with 2% for students not so identified (p 0.001).

Editorial Note

This outbreak demonstrates that transmission of measles can occur within a school population with a documented immunization level of 100%. This level was validated during the outbreak investigation. Previous investigations of measles outbreaks among highly immunized populations have revealed risk factors such as improper storage or handling of vaccine, vaccine administered to children under 1 year of age, use of globulin with vaccine, and use of killed virus vaccine (1-5). However, these risk factors did not adequately explain the occurrence of this outbreak.

If waning immunity is not a problem, this outbreak suggests that measles transmission can occur within the 2%-10% of expected vaccine failures (5,7). However, transmission was not sustained beyond 36 days in this outbreak, and community spread was principally among unvaccinated preschool children. The infrequent occurrence of measles among highly vaccinated persons suggests that this outbreak may have resulted from chance clustering of otherwise randomly distributed vaccine failures in the community. That measles transmission can occur among vaccine failures makes it even more important to ensure persons are adequately vaccinated. Had there been a substantial number of unvaccinated or inadequately vaccinated students in the high school and the community, transmission in Sangamon County probably would have been sustained.

http://www.cdc.gov/mmwr/preview/mmwrhtml/00000359.htm

Acta Paediatrica Scandinavica • July 1984

Bordetella pertussis whole cell vaccines efficacy and toxicity

Trollfors B.

Abstract

The literature concerning efficacy and side effects of pertussis vaccines is reviewed. With few exceptions, most vaccines induce a protective immunity lasting for 2 to 5 years. The large-scale use of pertussis vaccines has markedly contributed to the decrease in pertussis morbidity in small children but in some countries the incidence has increased in older children. Not even countries with immunisation rates of 90-95% have managed to eradicate pertussis or prevent disease in infants below the age of immunisation. The pertussis-associated mortality is currently very low in the industrialised countries and no differences can be discerned when countries with high, low and zero immunisation rates are compared. Local and benign systemic reactions are commonly seen after immunisation. The vaccines also sometimes cause convulsions, a shock-like state and, rarely, serious neurological reactions.

http://www.ncbi.nlm.nih.gov/pubmed/6380211

“The pertussis-associated mortality is currently very low in the industrialised countries and no differences can be discerned when countries with high, low and zero immunisation rates are compared. Local and benign systemic reactions are commonly seen after immunisation. The vaccines also sometimes cause convulsions, a shock-like state and, rarely, serious neurological reactions.”

Journal Of Toxicology And Environmental Health • 1984

Formaldehyde and hepatotoxicity: a review

Beall JR, Ulsamer AG.

Abstract

Exposure to formaldehyde appears to be associated with hepatoxicity in many species, including humans, following injection, ingestion, or inhalation. Macroscopic, microscopic, and biochemical manifestations in the liver include alterations in weight, centrilobular vacuolization, focal cellular necrosis, and increased alkaline phosphatase concentrations. Time-related changes in the pattern of the effects are suggested as one goes from acute exposure by inhalation at greater concentrations to repeated exposure at lesser concentrations. Although the hepatic changes are generally not extensive and can be reversible following acute exposure, the potential exists for them to progressively become more serious with repeated exposures. There are several possible mechanisms for the toxicity. Depending on the route of exposure could include direct effects on hepatocytes and/or indirect effects through the circulatory and immune systems. The catabolism of formaldehyde includes conversion to CO2 by reactions involving glutathione. Many hepatotoxic chemicals require glutathione for detoxification. Formaldehyde may then have the potential to cause additive toxicity with such chemicals in some circumstances.

http://www.ncbi.nlm.nih.gov/pubmed/?term=6389892

“Exposure to formaldehyde appears to be associated with hepatoxicity in many species, including humans, following injection, ingestion, or inhalation.”

“The results of the present study indicate that polysorbate 80 can neither be used as a solvent for isolated tissue experiments nor when considered for intravenous administration.”

Arzneimittelforschung • 1985

Polysorbate 80: a pharmacological study

Varma RK, Kaushal R, Junnarkar AY, Thomas GP,
Naidu MU, Singh PP, Tripathi RM, Shridhar DR.

Abstract

Polyoxyethylene (20) sorbitan monooleate (polysorbate 80, Tween 80), a surfactant, has been widely used as a solvent for pharmacological experiments. In the present study, polysorbate 80 was found to have toxicity of a low order in both the mice and rats when given by i.p. and p.o. routes. It produced mild to moderate depression of the central nervous system with a marked reduction in locomotor activity and rectal temperature, exhibited ataxia and paralytic activity and potentiated the pentobarbital sleeping time. On intravenous administration in dogs, it had a dose-dependent hypotensive effect. Polysorbate 80 did not have a direct stimulant or relaxant effect on either guinea pig ileum or rat uterus, however, it antagonised the contractions induced by acetylcholine, histamine, barium, 5-hydroxytryptamine and carbachol in a dose-dependent manner. A direct relaxant effect was observed on rabbit jejunum. A dose-dependent myocardial depressant effect was observed on guinea pig and rabbit paired atrial preparations. On the electrically-driven guinea pig left atrial preparation, polysorbate 80 exhibited a dose-dependent negative inotropic action. Polysorbate 80 did not induce diuresis in rats upto a dose of 2.5 ml/kg. The results of the present study indicate that polysorbate 80 can neither be used as a solvent for isolated tissue experiments nor when considered for intravenous administration. However, polysorbate 80 can be employed safely as a vehicle for neuropsychopharmacological experiments in doses not exceeding 1 ml/kg.

http://www.ncbi.nlm.nih.gov/pubmed/4026903

Pediatrics • April 1986

Polysorbate 80 and E-Ferol toxicity

Alade SL, Brown RE, Paquet A Jr.

Abstract

The relatively recent introduction and use of an intravenous form of a vitamin E preparation (E-Ferol) has been associated with the development of an unusual syndrome and fatalities among low birth weight (less than 1,500 g), premature infants in neonatal intensive care units. We have observed an inhibitory effect by this vitamin E preparation on the in vitro response of human lymphocytes to phytohemagglutinin (PHA). E-Ferol suppressed the expected response to low doses of PHA. However, this suppression was not due to the alpha-tocopherol acetate (vitamin E) component, because alpha-tocopherol acetate by itself was not inhibitory; in fact, it often enhanced the PHA response. Because a mixture of polysorbate 80 and polysorbate 20 is used as a carrier in E-Ferol, these components were also tested and were found to be responsible for the suppression, especially the polysorbate 80. Concurrent with this suppression of PHA-induced mitogenesis was a decrease in the percentage of T11 lymphocytes.

http://www.ncbi.nlm.nih.gov/pubmed/3960626

“The relatively recent introduction and use of an intravenous form of a vitamin E preparation has been associated with the development of an unusual syndrome and fatalities among low birth weight (less than 1,500 g), premature infants in neonatal intensive care units ... polysorbate 80 and polysorbate 20 ... were found to be responsible for the suppression, especially the polysorbate 80.”

Laboratory Animal Science • March 1989

An evaluation of distress following intraperitoneal immunization with Freund's adjuvant in mice

Author information

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Abstract

Intraperitoneal immunization with Freund's adjuvant is frequently used to stimulate antibody production in mice. To evaluate the clinical and pathological effects of this technique, mice were immunized intraperitoneally with complete Freund's adjuvant and albumin, and the injection repeated 3-4 weeks later using incomplete Freund's adjuvant. This regimen induced a mean antibody titer against albumin of 1:280 within 7 days after booster immunization and increased the abdominal width, abdominal circumference and spleen weights of immunized animals. Food intake and body weight decreased after immunization, but returned to control levels within 1-2 weeks. Open-field activity was not affected. Neutrophilia, eosinophilia and monocytosis were present 7 days after immunization and persisted for the duration of the study. Gross and histopathological lesions included multiple granulomatous abdominal adhesions and lymphoid hyperplasia. Thus, intraperitoneal immunization with Freund's adjuvant and albumin produced some adverse effects in the animal (weight loss, neutrophilia and granulomatous peritonitis). However, the animals did not appear to be severely or chronically impaired, since food intake, body weight and locomotor activity were within normal limits for most of the post-immunization period.

http://www.ncbi.nlm.nih.gov/pubmed/?term=2709800

"intraperitoneal immunization with Freund's adjuvant and albumin produced some adverse effects in the animal (weight loss, neutrophilia and granulomatous peritonitis)."

American Journal Of Public Health • April 1989

The role of secondary vaccine failures in measles outbreaks

Author information

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Abstract

An outbreak of measles in 1985-86 in a community where measles vaccine trials had been carried out from 1974-76 allowed the assessment of the role of secondary vaccine failures in previously immunized children. A total of 188 children from the vaccine trial were followed. Of these, 175 seroconverted initially while 13 (6 per cent) required re-immunization (primary failure). A total of 13 cases of measles, eight of which were laboratory and/or physician-confirmed, were reported in this cohort. Of these, nine cases occurred in the 175 subjects who had hemagglutination inhibition test (HI) and neutralizing antibody responses following the initial immunization. These nine cases represent secondary vaccine failures. An additional four cases occurred in the 13 subjects with primary vaccine failure. We conclude that secondary vaccine failures occur and that while primary failures account for most cases, secondary vaccine failures contribute to the occurrence of measles cases in an epidemic. A booster dose of measles vaccine may be necessary to reduce susceptibility to a sufficiently low level to allow the goal of measles elimination to be achieved.

http://www.ncbi.nlm.nih.gov/pubmed/2929807

“These nine cases represent secondary vaccine failures. An additional four cases occurred in the 13 subjects with primary vaccine failure. We conclude that secondary vaccine failures occur and that while primary failures account for most cases, secondary vaccine failures contribute to the occurrence of measles cases in an epidemic.”

Scope • 1990

Short-term Toxicity Tests for Non-genotoxic Effects
Toxicity Tests with Mammalian Cell Cultures

B. Ekwall, V. Silano, A. Paganuzzi-Stammati, F. Zucco

Introduction

Cell culture can be used to screen for toxicity both by estimation of the basal functions of the cell (i.e. those processes common to all types of cells) or by tests on specialized cell functions (Ekwall, 1983b). General toxicity tests, aimed mainly at detection of the biological activity of test substances, can be carried out on many cell types (e.g. fibroblasts, HeLa and hepatoma cells). A number of parameters including vital staining, cytosolic enzyme release, cell growth and cloning efficien- cy are used as end-points to measure toxicity. Organ-specific toxic effects are tested using specialized cells by measuring alterations in membrane and metabolism integ- rity and/or in specific cell functions (e.g. glycogen metabolism in primary hepatocyte cultures, beating rate in mixed myocardial cells or myocytes, and phagocytosis in macrophages).

http://dge.stanford.edu/SCOPE/SCOPE_41/SCOPE_41_2.02_Chapter_7_75-98.pdf

[shows that as far back as 1990

we could test for non-genotoxic cellular toxicity]

Neuropediatrics • November 1990

Workshop on neurologic complications of pertussis and pertussis vaccination

Author information

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Abstract

A multidisciplinary workshop held from September 29 to October 1, 1989, at Airlie House, Warrenton, Virginia, considered the neurologic complications of whooping cough and pertussis vaccine. Pertussis mortality in the U.S. in 2-3/1000 cases. Seizures occur in 1.9% of cases, and encephalopathy in 0.3%. Reviewing all data, it appears likely that a combination of one or more bacterial toxins, asphyxia, CO2 retention and loss of cerebral vascular autoregulation is responsible for neurologic symptoms. The timing of the encephalopathy suggests that it results from increased lysis of bacteria, and release of endotoxin. The encephalopathy is not confined to the paroxysmal phase. In evaluating side-reactions to the vaccine, the following must be kept in mind: 1. Vaccines are not standardized between manufacturers. 2. For a given manufacturer, vaccines are not standard from one batch to the next. 3. Unless the vaccine is properly prepared and refrigerated, its potency and reactivity varies with shelf life. In fact, the whole question of vaccine detoxification has never been systematically investigated. Listed in order of increasing severity, observed adverse reactions include irritability, persistent, unusually high pitched crying, somnolence, seizures, a shock-like “hypotensive, hyporesponsive” state, and an encephalopathy. Since the neurologic picture is not specific for pertussis vaccination, its temporal relationship to the vaccination is the critical variable for determining causation. Although the majority of seizures following pertussis vaccination are associated with fever, it was the consensus of the neurologists attending the workshop, that these do not represent febrile convulsions, but are non-benign convulsions. The incidence of post-vaccine encephalopathy is difficult to ascertain.

(Abstract truncated at 250 words)

http://www.ncbi.nlm.nih.gov/pubmed/1981251

Full Report

https://www.thieme-connect.com/DOI/DOI?10.1055/s-2008-1071488

“1. Vaccines are not standardized between manufacturers.

2. For a given manufacturer, vaccines are not standard from one batch to the next.

3. Unless the vaccine is properly prepared and refrigerated, its potency and reactivity varies with shelf life. In fact, the whole question of vaccine detoxification has never been systematically investigated.”

Pediatric Infectious Disease Journal • March 1991

Aseptic meningitis as a complication of mumps vaccination

Author information

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Abstract

In 1989 a nationwide surveillance of neurologic complications after the administration of mumps vaccine was conducted in Japan, based on the notification of cases and the testing of mumps viruses isolated from cerebrospinal fluid for their relatedness to the vaccine by nucleotide sequence analysis. Among 630,157 recipients of measles-mumps-rubella trivalent (MMR) vaccine containing the Urabe Am9 mumps vaccine, there were at least 311 meningitis cases suspected to be vaccine-related. In 96 of these 311 cases, mumps virus related to the vaccine was isolated from cerebrospinal fluid. The unusually high incidence may have been partly a result of the adverse media publicity of the problem at the time of surveillance. We analyzed clinical features of 165 and 27 laboratory-confirmed mumps vaccine-related meningitis cases that occurred among the recipients of MMR and monovalent mumps vaccines, respectively, during a 1-year period after the introduction of MMR vaccine. The incidence of vaccine-related meningitis was similar among the recipients of MMR and monovalent Urabe Am9 mumps vaccines. Meningitis was generally mild and there were no sequelae from the illness. The complication was more frequent among male than among female children.

http://www.ncbi.nlm.nih.gov/pubmed/2041668

“Among 630,157 recipients of measles-mumps-rubella trivalent (MMR) vaccine containing the Urabe Am9 mumps vaccine, there were at least 311 meningitis cases suspected to be vaccine-related. In 96 of these 311 cases, mumps virus related to the vaccine was isolated from cerebrospinal fluid.”

Lancet • September 1991

Chronic fatigue syndrome: clinical condition associated with immune activation

Author information

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Abstract

There is much conflicting immunological and viral data about the causes of chronic fatigue syndrome (CFS); some findings support the notion that CFS may be due to one or more immune disorders that have resulted from exposure to an infectious agent. In the present study, flow cytometry and several different monoclonal antibodies recognising T, B, and natural killer (NK) cell populations as well as activation and cell adhesion antigens were used to study 147 individuals with CFS. Compared with healthy controls, a reduced CD8 suppressor cell population and increased activation markers (CD38, HLA-DR) on CD8 cells were found. The differences were significant ($p = 0.01$) in patient with major symptoms of the disease. These immunological indices were not observed in 80 healthy individuals, in 22 contacts of CFS patients, or in 43 patients with other diseases. No correlation of these findings in CFS patients with any known human viruses could be detected by serology. The findings suggest that immune activation is associated with many cases of CFS.

http://www.ncbi.nlm.nih.gov/pubmed/?term=1679864

"No correlation of these findings in chronic fatigue syndrome (CFS) patients with any known human viruses could be detected by serology. The findings suggest that immune activation is associated with many cases of CFS."

Vaccine • October 1991

Adverse reactions after injection of adsorbed diphtheria-pertussis-tetanus (DPT) vaccine are not due only to pertussis organisms or pertussis components in the vaccine

Author information

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Abstract

Reactions to adsorbed diphtheria-pertussis-tetanus (DPT) vaccine have mostly been attributed to the pertussis organisms or pertussis components in the vaccine. Nevertheless reactions may also be due to other factors such as sensitization induced by aluminium adjuvants and impurities present in crude toxoids that cannot be removed by purification of toxoids after formalinization. Aluminium compounds such as aluminium phosphate and aluminium hydroxide are the most commonly used adjuvants with vaccines for human use. Due to the increasing concern about the toxicity of aluminium, other adjuvants like calcium phosphate may be evaluated as an alternative to aluminium adjuvants. To minimize reactions after immunization with DPT vaccine due to impurities in the toxoids, the use of toxoided purified toxins is suggested.

http://www.ncbi.nlm.nih.gov/pubmed/?term=1759487

“... reactions may also be due to other factors such as sensitization induced by aluminium adjuvants and impurities present in crude toxoids that cannot be removed by purification of toxoids after formalinization.”

Journal Of Autoimmunity • December 1991

Adjuvant oils induce arthritis in the DA rat. I. Characterization of the disease and evidence for an immunological involvement

Author information

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Uppsala University, Sweden

Abstract

An intradermal injection of Freund's incomplete adjuvant oil (FIA) without further additives was shown to induce erosive polyarthritis in dark Agouti (DA) rats, but not in Lewis rats. Histological examination revealed joint inflammation, first with polymorphonuclear cells and synovial hyperplasia, and subsequently, with multi-nucleated giant cells. Both constituents of FIA, mineral oil and Arlacel A, as well as Pristane oil were arthritogenic, whereas vegetable oil were not. Re-administration of adjuvant oil after recovery failed to induce arthritis, thus making possible a role of specific immunity in this new form of arthritis in rats.

http://www.ncbi.nlm.nih.gov/pubmed/?term=1812893

"Freund's incomplete adjuvant oil (FIA)

was shown to induce erosive polyarthritis in ... rats ..."

Washington DC National Academies Press (US) 1991
The National Academies Collection
Reports funded by National Institutes of Health

Howson CP, Howe CJ, Fineberg HV, editors

Adverse Effects of Pertussis and Rubella Vaccines: A Report of the Committee to Review the Adverse Consequences of Pertussis and Rubella Vaccines

Excerpt

Parents have come to depend on vaccines to protect their children from a variety of diseases. Some evidence suggests, however, that vaccination against pertussis (whooping cough) and rubella (German measles) is, in a small number of cases, associated with increased risk of serious illness. This book examines the controversy over the evidence and offers a comprehensively documented assessment of the risk of illness following immunization with vaccines against pertussis and rubella. Based on extensive review of the evidence from epidemiologic studies, case histories, studies in animals, and other sources of information, the book examines: The relation of pertussis vaccines to a number of serious adverse events, including encephalopathy and other central nervous system disorders, sudden infant death syndrome, autism, Guillain-Barre syndrome, learning disabilities, and Reye syndrome. The relation of rubella vaccines to arthritis, various neuropathies, and thrombocytopenic purpura. The volume, which includes a description of the committee's methods for evaluating evidence and directions for future research, will be important reading for public health officials, pediatricians, researchers, and concerned parents.

Full Report

http://www.ncbi.nlm.nih.gov/pubmed/25121241

"that the evidence is consistent with a causal relation between DPT vaccine and acute encephalopathy, shock and "unusual shock-like state," and between RA 27/3 rubella vaccine and chronic arthritis; and that the evidence indicates a causal relation between DPT vaccine and anaphylaxis, between the pertussis component of DPT vaccine and protracted, inconsolable crying, and between RA 27/3 rubella vaccine and acute arthritis."

[RA 27/3 rubella is still in use today]

JAMA • January 1992

Adverse events following pertussis and rubella vaccines
Summary of a report of the Institute of Medicine

Author information

Howson CP1, Fineberg HV.

Institute of Medicine
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Abstract

In August 1991, the Institute of Medicine released a report entitled Adverse Effects of Pertussis and Rubella Vaccines, which examined 18 adverse events in relation to diphtheria-tetanus-pertussis (DTP) vaccine and four adverse events in relation to the currently used rubella vaccine strain, RA 27/3. The committee spent 20 months reviewing a wide range of information sources, including case series and individual case reports, both published and unpublished, epidemiologic studies, studies in animals, and other laboratory studies. The committee found that the evidence indicates a causal relation between DTP vaccine and anaphylaxis and between the pertussis component of DTP vaccine and extended periods of inconsolable crying or screaming. The committee also reported that the evidence indicates a causal relation between the rubella vaccine and acute arthritis in adult women. The committee found the available evidence weaker but still consistent with a causal relation between DTP vaccine and two conditions--acute encephalopathy and hypotonic, hyporesponsive episodes--and between rubella vaccine and chronic arthritis in adult women. Estimated incidence rates of these adverse events following vaccination are provided, where possible. The committee found that the evidence does not indicate a causal relation between the DTP vaccine and infantile spasms, hypsarrhythmia, Reye's syndrome, and sudden infant death syndrome. The committee found insufficient evidence to indicate either the presence or absence of a causal relation between DTP vaccine and chronic neurologic damage, aseptic meningitis, erythema multiforme or other rash, Guillain-Barré syndrome, hemolytic anemia, juvenile diabetes, learning disabilities and attention-deficit disorder, peripheral mononeuropathy, or thrombocytopenia, and between rubella vaccine and radiculoneuritis and other neuropathies or thrombocytopenic purpura. The committee's evaluative methods are briefly described and a summary of research needs is provided.

http://www.ncbi.nlm.nih.gov/pubmed/1727962

"The committee found that the evidence indicates a causal relation between DTP vaccine and anaphylaxis and between the pertussis component of DTP vaccine and extended periods of inconsolable crying or screaming.

The committee also reported that the evidence indicates a causal relation between the rubella vaccine and acute arthritis in adult women.

The committee found the available evidence weaker but still consistent with a causal relation between DTP vaccine and two conditions—acute encephalopathy and hypotonic, hyporesponsive episodes—and between rubella vaccine and chronic arthritis in adult women."

National Toxicology Program Technical Report Series • January 1992

NTP Toxicology and Carcinogenesis Studies of Polysorbate 80 (CAS No. 9005-65-6) in F344/N Rats and B6C3F1 Mice (Feed Studies)

Abstract

Polysorbate 80 is a nonionic surfactant used widely as an additive in foods, pharmaceutical preparations, and cosmetics as an emulsifier, dispersant, or stabilizer. Toxicity and carcinogenicity studies were conducted by administering polysorbate 80 (which met all compendial specifications) in feed to groups of F344/N rats and B6C3F1 mice of each sex for 14 days, 13 weeks, and 2 years. Genetic toxicology studies were conducted in Salmonella typhimurium. 14-Day Studies: Groups of five rats and five mice of each sex received diets containing 0, 3,000, 6,000, 12,500, 25,000, or 50,000 ppm polysorbate 80. All animals survived to the end of the studies. The mean body weight change of male rats that received 50,000 ppm was significantly lower than that of the controls. The mean body weight changes in all other groups of dosed rats and in all groups of dosed mice were similar to those of the respective controls. No clinical findings or changes in absolute or relative organ weights in rats or mice were related to polysorbate 80 administration. 13-Week Studies: Groups of 10 rats and 10 mice of each sex received diets containing 0, 3,100, 6,200, 12,500, 25,000, or 50,000 ppm polysorbate 80. All animals survived to the end of the studies. The final mean body weights of dosed rats and mice were similar to those of the controls. No clinical findings, changes in absolute or relative organ weights, or gross or microscopic lesions in rats or mice were related to polysorbate 80 administration. 2-Year Studies: Doses for the 2-year studies were selected based on the lack of observed compound-related effects at the dose levels used in the 13-week studies. Groups of 60 rats and 60 mice of each sex received diets containing 0, 25,000, or 50,000 ppm polysorbate 80 for up to 103 weeks. 15-Month Interim Evaluations: Interim evaluations were performed on 7 to 10 rats and mice from each dose group at 15 months. There were no significant changes in absolute or relative organ weights. Incidences of hyperplasia and inflammation of the forestomach were increased in female mice that received 50,000 ppm. No other chemical-related lesions occurred in rats or male mice evaluated at 15 months. Body Weights, Clinical Findings, and Survival in the 2-Year Studies: The mean body weights in male and female rats and male mice administered polysorbate 80 were similar to those of the controls throughout the studies. The final mean body weight of female mice receiving 50,000 ppm was 11%lower than that of the controls. No clinical findings were associated with administration of polysorbate 80. The survival of dosed male rats was lower than that of the controls (0 ppm, 29/50; 25,000 ppm, 18/50; 50,000 ppm, 18/50); the survival of dosed female rats and male and female mice was similar to that of the respective controls (female rats: 23/50, 25/50, 25/50; male mice: 33/49, 34/50, 32/50; female mice: 30/50, 28/50, 26/50). Neoplasms and Nonneoplastic Lesions in the 2-Year Studies: The incidence of adrenal medulla pheochromocytoma was marginally increased in high-dose male rats (21/50, 19/50, 29/50). The incidence of hyperplasia of the adrenal medulla was increased in low-dose male rats but not in high-dose male rats (11/50, 22/50, 12/50). No chemical-related increases in the incidences of neoplasms occurred in male or female mice. The incidences of squamous hyperplasia and inflammation of the forestomach were significantly increased in high-dose male and female mice; forestomach ulcers were significantly increased in high-dose females. Genetic Toxicology: Polysorbate 80 was not mutagenic in Salmonella typhimurium strains TA100, TA1535, TA1537, and TA98 with or without exogenous metabolic activation (S9). Conclusions: Under the conditions of these 2-year feed studies, there was equivocal evidence of carcinogenic activity for polysorbate 80 in male F344/N rats based on an increased incidence of pheochromocytomas of the adrenal medulla. There was no evidence of carcinogenic activity for polysorbate 80 in female F344/N rats or in male or female B6C3F1 mice given 25,000 or 50, or 50,000 ppm. Administration of polysorbate 80 was associated with inflammation and squamous hyperplasia of the forestomach in male and female mice, and with ulcers of the forestomach in female mice.

http://www.ncbi.nlm.nih.gov/pubmed/12616296

“Administration of polysorbate 80 was associated with inflammation and squamous hyperplasia of the forestomach in male and female mice, and with ulcers of the forestomach in female mice.”

American Journal Of Diseases Of Children • February 1992

Vitamin A levels and severity of measles New York City

Author information

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Abstract

Recent studies show that vitamin A levels decrease during measles and that vitamin A therapy can improve measles outcome in children in the developing world. Vitamin A levels of children with measles have not been studied in developed countries. We therefore measured vitamin A levels in 89 children with measles younger than 2 years and in a reference group in New York City, NY. Vitamin A levels in children with measles ranged from 0.42 to 3.0 mumol/L; 20 (22%) were low. Children with low levels were more likely to have fever at a temperature of 40 degrees C or higher (68% vs 44%), to have fever for 7 days or more (54% vs 23%), and to be hospitalized (55% vs 30%). Children with low vitamin A levels had lower measles-specific antibody levels. No child in the reference group had a low vitamin A level. Our data show that many children younger than 2 years in New York City have low vitamin A levels when ill with measles, and that such children seem to have lower measles-specific antibody levels and increased morbidity. Clinicians may wish to consider vitamin A therapy for children younger than 2 years with severe measles. Additional studies of vitamin A in measles and other infectious diseases, and in vaccine efficacy trials, should be done.

http://www.ncbi.nlm.nih.gov/pubmed/?term=1285727

“Recent studies show that vitamin A levels decrease during measles and that vitamin A therapy can improve measles outcome in children in the developing world. Vitamin A levels of children with measles have not been studied in developed countries.”

[vitamin A and vaccination will be studied in Africa 20 years from now and those reports are included herein]

Clinical Infectious Disease • August 1992

Chronic arthritis after rubella vaccination

Author information

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Abstract

In August 1991 the Institute of Medicine released a report entitled “Adverse Effects of Pertussis and Rubella Vaccines” that examined, among other relations, the relation between immunization with the RA 27/3 rubella vaccine strain and chronic arthritis. The committee spent 20 months reviewing a wide range of information sources including case series and individual case reports published in peer-reviewed journals and reported by vaccine manufacturers; unpublished case reports from physicians, parents, and other concerned persons; epidemiological studies; and laboratory studies. There were no animal studies available. The committee found that the evidence is consistent with a causal relation between the RA 27/3 rubella vaccine strain and chronic arthritis in adult women, although the evidence is limited in scope. Proving that rubella vaccination can cause chronic arthritis will require a better understanding of pathogenetic mechanisms and additional well-designed studies. We briefly describe the committee’s evaluative methods and present the evidence underlying its conclusion.

http://www.ncbi.nlm.nih.gov/pubmed/1520764

“The committee found that the evidence is consistent with a causal relation between the RA 27/3 rubella vaccine strain and chronic arthritis in adult women ...”

“Tween 80 accelerated maturation, prolonged the oestrus cycle, and induced persistent vaginal oestrus.”

Food And Chemical Toxicology • March 1993

Delayed effects of neonatal exposure to Tween 80 on female reproductive organs in rats

Author information

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Abstract

Neonatal female rats were injected ip (0.1 ml/rat) with Tween 80 in 1, 5 or 10% aqueous solution on days 4-7 after birth. Treatment with Tween 80 accelerated maturation, prolonged the oestrus cycle, and induced persistent vaginal oestrus. The relative weight of the uterus and ovaries was decreased relative to the untreated controls. Squamous cell metaplasia of the epithelial lining of the uterus and cytological changes in the uterus were indicative of chronic oestrogenic stimulation. Ovaries were without corpora lutea, and had degenerative follicles.

http://www.ncbi.nlm.nih.gov/pubmed/8473002

Archives of Disease in Childhood • 1994

Ocular contamination with BCG vaccine

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Abstract

The complications of BCG vaccination in both the immunocompetent, with local and lymph node ulceration, and in the immunocompromised, with disseminated infection, are familiar to most paediatricians. Moreover, the risks to the doctor from needlestick injury are well known. There are probably few other risks for the vaccinator but we describe a case of ocular contamination with BCG vaccine. During attempted intradermal injection of BCG vaccine into a struggling neonate's upper arm, the syringe slipped out of the infant's skin discharging its contents into the attending doctor's eye. The doctor had received BCG vaccine in childhood. Despite lavage of the eye with water, a painful follicular conjunctivitis developed 24 hours later. There was a rapid response to topical steroids, and the inflammatory response settled completely over the subsequent week. Although it was assumed that this was a delayed-type hypersensitivity response, anti-BCG cover was given with a one month course of oral isoniazid.

Full Report:

https://app.box.com/s/ev8bhi6vb3rofhrkavum3v3hpt2xlil9

"During attempted intradermal injection of BCG vaccine into a struggling neonate's upper arm, the syringe slipped out of the infant's skin discharging its contents into the attending doctor's eye."

National Academies Press US • 1994

DPT Vaccine and Chronic Nervous System Dysfunction: A New Analysis

Institute of Medicine US Committee to Study New Research on Vaccines

Editors

Kathleen R. Stratton, Cynthia J. Howe, and Richard B. Johnston, Jr.
Washington, DC

EXECUTIVE SUMMARY

An Institute of Medicine (IOM) committee recently concluded that the evidence is consistent with a causal relation between vaccination with DPT and acute encephalopathy (IOM, 1991), and the excess risk was estimated to range from 0 to 10.5 per million DPT immunizations. However, the same IOM committee also concluded that the evidence was insufficient to indicate a causal relation between DPT and permanent neurologic damage (IOM, 1991). In fact, the relation between DPT and chronic nervous system dysfunction had not been studied in a rigorous scientific manner until recently. Because the evidence has been so limited, the appearance of a single new report, a 10-year follow-up to the National Childhood Encephalopathy Study (NCES; Miller et al., 1993), prompted the U.S. Public Health Service to ask IOM to convene the Committee to Study New Research on Vaccines with the charge of studying the new data and, if warranted, reevaluating the causal relation between DPT and chronic nervous system dysfunction.

The NCES reported that the occurrence of hospitalization for serious neurologic disorders among 2- to 35-month-old children is very strongly related to the occurrence of death or nervous system dysfunction (neurologic, behavioral, educational, motor, sensory, or self-care impairment) up to age 10 years (Madge et al., 1993; Miller et al., 1993). Children who experienced the rare but serious acute neurologic disorder within 7 days after receiving DPT were no more or less likely to experience documented chronic nervous system dysfunction or to have died within 10 years of the acute disorder than children who had not received DPT within 7 days prior to the onset of the disorder. There were no special characteristics associated with the acute or chronic nervous system illnesses linked to DPT exposure.

The NCES did not investigate the possibility of a direct relation between DPT and chronic nervous system dysfunction, that is, in the absence of a serious acute neurologic illness that occurs within 7 days after receiving DPT. The NCES provides data only on the limited case of a possible relation between DPT and chronic nervous system dysfunction in those children in whom a serious acute neurologic illness followed DPT vaccination within 7 days.

The committee posits three plausible scenarios whereby the acute neurologic illnesses that follow DPT might be related to chronic nervous system dysfunction.

1. DPT administration might cause serious acute neurologic illness and subsequent chronic dysfunction in children who otherwise might not have experienced either an acute neurologic illness or chronic dysfunction in the absence of DPT.

2. DPT might trigger (and thereby be an immediate or proximate cause) an acute neurologic illness and subsequent chronic dysfunction in children with underlying brain or metabolic abnormalities. Such children might experience acute neurologic illness and subsequent chronic dysfunction in association with some trigger other than DPT.

3. DPT might cause an acute neurologic illness in children with underlying brain or metabolic abnormalities that would themselves eventually have led to chronic dysfunction even in the absence of an acute neurologic illness.

The committee believes its conclusions take into account the fact that the data do not support any one of these scenarios over the others. Because the NCES did not (and probably could not) rule out the possibility that only-children with underlying brain or metabolic abnormalities react to stimuli such as DPT with acute neurologic illness, and no other studies establish or rule out such a possibility, the committee concludes that the evidence is insufficient to indicate whether or not DPT increases the overall risk in children of chronic nervous system dysfunction.

The National Childhood Encephalopathy Study data are consistent with the possibility that some children without underlying brain or metabolic abnormalities might experience serious acute neurologic illness within 7 days after receiving DPT and that acute neurologic illness will have chronic nervous system sequelae. The NCES data also are consistent with the possibility that some children with underlying brain or metabolic abnormalities (which foster a “triggering” by DPT of an acute neurologic illness) might go on to develop chronic nervous system dysfunction due to a DPT-triggered acute illness. Therefore, the committee concludes that the balance of evidence is consistent with a causal relation between DPT and the forms of chronic nervous system dysfunction described in the NCES in those children who experience a serious acute neurologic illness within 7 days after receiving DPT vaccine. This serious acute neurologic response to DPT is a rare event. The excess risk has been estimated to range from 0 to 10.5 per million immunizations (IOM, 1991). The evidence does not “establish” or “prove” a causal relation. The evidence remains insufficient to indicate the presence or absence of a causal relation between DPT and chronic nervous system dysfunction under any other circumstances. That is, because the NCES is the only systematic study of long-term dysfunctions after DPT, the committee can only comment on the causal relation between DPT and those long-term dysfunctions under the conditions studied by the NCES. In particular, it should be noted that the long-term dysfunctions associated with DPT followed a serious acute neurologic illness that occurred in children within 7 days after receiving DPT.

http://www.ncbi.nlm.nih.gov/books/NBK225452/

Acta Paediatrica • February 1994

Immunosuppression after measles vaccination

Author information

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Abstract

The influence of conventional live attenuated measles vaccine on cellular immune responsiveness was investigated in Sweden and Guinea-Bissau. Sixteen children in a residential area in Bissau and 16 living in southern Stockholm were examined before and 8-10 days after vaccination. Lymphoproliferation was measured to concanavalin A (con-A), PPD and tetanus toxoid (TT) using a whole-blood 3H-thymidine incorporation assay. Stimulation indices were significantly lower after vaccination than before, in the case of con-A ($p = 0.03$) and TT ($p = 0.01$) in the Guinean children and in the case of PPD ($p = 0.009$) and TT ($p = 0.03$) in the Swedish children. Stimulation of lymphocytes from measles-immune children with measles antigens resulted in weak lymphoproliferative responses. These observations may be relevant to the increased mortality found in children immunized with high-titre measles vaccines, as compared to controls, in recent studies. The study confirms the applicability and usefulness under field conditions of the whole blood version of the thymidine incorporation assay.

http://www.ncbi.nlm.nih.gov/pubmed/?term=8193495

“These observations may be relevant to the increased mortality found in children immunized with high-titre measles vaccines, as compared to controls, in recent studies.”

Journal Of Clinical Pharmacology • February 1994

Adverse drug reactions in neonates

Author information

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Abstract

Adverse drug reactions (ADR) are uncommon causes of admission of neonates to the neonatal intensive care unit. The neonate, however, is potentially at significant risk for adverse drug reactions because of underdeveloped mechanisms and systems for handling drugs (the Gray Baby Syndrome with chloramphenicol as a classic example), the fact that infants in neonatal intensive care units are often critically ill with multiple organ system dysfunction, that they may be on multiple drugs, and that they may present with an adverse drug reaction as a result of exposure while still a fetus. There is also a history of misadventures in the neonatal intensive care unit and newborn nurseries due to exposure to antibacterial agents that produced systemic effects from percutaneous absorption. In this review, an overview of the mechanisms of adverse drug reactions will be presented, followed by a general review of the experience of adverse drug reactions in neonates and some specific examples of current adverse drug reactions and a suggested approach for the prevention and evaluation of adverse drug reactions in neonates.

http://www.ncbi.nlm.nih.gov/pubmed/?term=8163712

“The neonate, however,
is potentially at significant risk
for adverse drug reactions because
of underdeveloped mechanisms and
systems for handling drugs ...”

“Eighty-seven previously vaccinated school-aged children with measles that met the Advisory Committee on Epidemiology’s clinical case definition for measles.”

Canadian Medical Association Journal • April 1994

Measles outbreak in 31 schools: risk factors for vaccine failure and evaluation of a selective revaccination strategy

Author information

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Abstract

OBJECTIVE
To examine the risk factors for measles vaccine failure and to evaluate the effectiveness of a selective revaccination strategy during a measles outbreak.

DESIGN
Matched case-control study.

SETTING
Thirty-one schools in Mississauga, Ont.

SUBJECTS
Eighty-seven previously vaccinated school-aged children with measles that met the Advisory Committee on Epidemiology’s clinical case definition for measles. Two previously vaccinated control subjects were randomly selected for each case subject from the same homeroom class.

INTERVENTIONS
All susceptible contacts were vaccinated, and contacts who had been vaccinated before Jan. 1, 1980, were revaccinated. When two or more cases occurred in a school all children vaccinated before 1980 were revaccinated.

MAIN OUTCOME MEASURES
Risk of measles associated with age at vaccination, time since vaccination, vaccination before 1980 and revaccination.

RESULTS
Subjects vaccinated before 12 months of age were at greater risk of measles than those vaccinated later (adjusted odds ratio [OR] 7.7, 95% confidence interval [CI] 1.6 to 38.3; p = 0.01). Those vaccinated between 12 and 14 months of age were at no greater risk than those vaccinated at 15 months or over. Subjects vaccinated before 1980 were at greater risk than those vaccinated after 1980 (adjusted OR 14.5, 95% CI 1.5 to 135.6). Time since vaccination was not a risk factor. Revaccination was effective in reducing the risk of measles in both subjects vaccinated before 1980 and those vaccinated after 1980 (adjusted OR reduced to 0.6 [95% CI 0.1 to 5.3] and 0.3 [95% CI 0.13 to 2.6] respectively). However, only 18 cases were estimated to have been prevented by this strategy.

CONCLUSIONS
Adherence to routine measles vaccination for all eligible children is important in ensuring appropriate coverage with a single dose. The selective revaccination strategy’s high labour intensiveness and low measles prevention rate during the outbreak bring into question the effectiveness of such a strategy.

http://www.ncbi.nlm.nih.gov/pubmed/8137189

Vaccine • April 1994

Adverse reactions after diphtheria-tetanus booster in 10-year-old schoolchildren in relation to the type of vaccine given for the primary vaccination

Author information

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Abstract

This prospective open study investigated adverse reactions in 527 schoolchildren to a diphtheria-tetanus (DT) booster given within a national vaccination programme at 10 years of age. Evaluation was based on those whose immunization records showed that they had received either three doses of an adsorbed DT vaccine (n = 388) or a non-adsorbed DT-pertussis vaccine (DTP) (n = 69) for primary series vaccination. No differences in systemic reactions to the booster between the two groups were observed. Local reactions were significantly ($p < 0.001$) more common 1 day after vaccination in children who had received DT for primary series vaccination: redness, 73% compared with 23%; swelling, 56% versus 15%; and itching, 47% versus 21%. One and 2 weeks after the booster, itching was still more pronounced in the group who had received DT for primary series vaccination ($p < 0.001$ and 0.014, respectively). The study indicates that there was a real basis for the increase in spontaneous notifications of local side-effects to the school DT booster in Sweden. The most likely cause for the increase seems to be the aluminium adjuvant in the vaccine given for primary vaccination, a late and unexpected consequence of a change in the infant immunization programme.

http://www.ncbi.nlm.nih.gov/pubmed/?term=8023551

"This prospective open study investigated adverse reactions in 527 schoolchildren to a diphtheria-tetanus (DT) booster ... The most likely cause for the increase seems to be the aluminium adjuvant in the vaccine given for primary vaccination, a late and unexpected consequence of a change in the infant immunization programme."

JAMA • May 1994

Adverse events associated with childhood vaccines other than pertussis and rubella. Summary of a report from the Institute of Medicine

Author information

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Abstract

In September 1993, the Institute of Medicine released a report entitled Adverse Events Associated With Childhood Vaccines: Evidence Bearing on Causality. The report examined putative serious adverse consequences associated with administration of diphtheria and tetanus toxoids; measles, mumps, and measles-mumps-rubella vaccines; oral polio vaccine and inactivated polio vaccine; hepatitis B vaccines; and Haemophilus influenzae type b (Hib) vaccines. The committee spent 18 months reviewing all available scientific and medical data, from individual case reports (published and unpublished) to controlled clinical trials. The committee found that the evidence favored the rejection of a causal relation between diphtheria and tetanus toxoids and encephalopathy, infantile spasms, and sudden infant death syndrome, and between conjugate Hib vaccines and susceptibility to Hib disease. The committee found that the evidence favored acceptance of a causal relation between diphtheria and tetanus toxoids and Guillain-Barré syndrome and brachial neuritis, between measles vaccine and anaphylaxis, between oral polio vaccine and Guillain-Barré syndrome, and between unconjugated Hib vaccine and susceptibility to Hib disease. The committee found that the evidence established causality between diphtheria and tetanus toxoids and anaphylaxis, between measles vaccine and death from measles vaccine-strain viral infection, between measles-mumps-rubella vaccine and thrombocytopenia and anaphylaxis, between oral polio vaccine and poliomyelitis and death from polio vaccine-strain viral infection, and between hepatitis B vaccine and anaphylaxis. For five vaccine-related adverse events, there was no evidence identified. For the remaining 33 vaccine-related adverse events, the evidence was inadequate to accept or reject a causal relation.

http://www.ncbi.nlm.nih.gov/pubmed/8182813

“The committee found that the evidence favored acceptance of a causal relation between diphtheria and tetanus toxoids and Guillain-Barré syndrome and brachial neuritis, between measles vaccine and anaphylaxis, between oral polio vaccine and Guillain-Barré syndrome, and between unconjugated Hib vaccine and susceptibility to Hib disease.

The committee found that the evidence established causality between diphtheria and tetanus toxoids and anaphylaxis, between measles vaccine and death from measles vaccine-strain viral infection, between measles-mumps-rubella vaccine and thrombocytopenia and anaphylaxis, between oral polio vaccine and poliomyelitis and death from polio vaccine-strain viral infection, and between hepatitis B vaccine and anaphylaxis.”

“In 1993 we found 17 cases of Adverse Events Following Immunization (AEFI)

out of 1440 children between 0 and 2 years of age ...”

Przeglad Epidemiologiczny • 1994

Adverse events following immunization: AEFI in 17 children between 0 and 2 years of age

Author information

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Abstract

Adverse Events Following Immunization (AEFI) are disadvantageous side effects of preventive vaccination. In 1993 we found 17 cases of AEFI out of 1440 children between 0 and 2 years of age who had received BCG, diphtheria-tetanus-pertussis, measles or poliomyelitis vaccine. They were classified as reactions in 14 children (0.9%) or complications in 3 children (0.2%). Twelve adverse reactions followed DTP vaccination (0.8%), two followed BCG vaccination (0.14%), another two measles vaccination (0.14%) and one followed poliomyelitis vaccination (0.07%). Both generalized and local symptoms were present and they regressed with no further complications. Two children who had received BCG were noted to have a deeply placed abscess at the injection site remaining scar as well as axillary, submandibular and cervical lymph nodes enlargement within 6 months. In a 3 months old child, after the first injection of DTP vaccine, convulsions and consciousness disorder occurred. Transfontanel ultrasonography revealed intraventricular haemorrhage. After one year of intensive neurological care child’s health state was improved. In spite of using still more and more safe vaccines none of them is the ideal one—the one with no adverse events following vaccination. Vaccination technics, distribution and storage of vaccines are to be improved which may result in decrease number of AEFI.

http://www.ncbi.nlm.nih.gov/pubmed/7597191

CDC • MMWR • 1996

Update: Vaccine Side Effects, Adverse Reactions, Contraindications, and Precautions Recommendations of the Advisory Committee on Immunization Practices (ACIP)

Summary

This report provides updated information concerning the potential adverse events associated with vaccination for hepatitis B, poliomyelitis, measles, mumps, diphtheria, tetanus, and pertussis. This information incorporates findings from a series of recent literature reviews, conducted by an expert committee at the Institute of Medicine (IOM), of all evidence regarding the possible adverse consequences of vaccines administered to children. This report contains modifications to the previously published recommendations of the Advisory Committee on Immunization Practices (ACIP) and is based on an ACIP review of the IOM findings and new research on vaccine safety. In addition, this report incorporates information contained in the "Recommendations of the Advisory Committee on Immunization Practices: Use of Vaccines and Immune Globulins in Persons with Altered Immunocompetence" (MMWR 1993;42{No. RR-4}) and the "General Recommendations on Immunization: Recommendations of the Advisory Committee on Immunization Practices (ACIP)" (MMWR 1994;43{No. RR-1}). Major changes to the previous recommendations are highlighted within the text, and specific information concerning the following vaccines and the possible adverse events associated with their administration are included: hepatitis B vaccine and anaphylaxis; measles vaccine and a) thrombocytopenia and b) possible risk for death resulting from anaphylaxis or disseminated disease in immunocompromised persons; diphtheria and tetanus toxoids and pertussis vaccine (DTP) and chronic encephalopathy; and tetanus-toxoid-containing vaccines and a) Guillain-Barre syndrome, b) brachial neuritis, and c) possible risk for death resulting from anaphylaxis. These modifications will be incorporated into more comprehensive ACIP recommendations for each vaccine when such statements are revised. Also included in this report are interim recommendations concerning the use of measles and mumps vaccines in:

a. persons who are infected with human immunodeficiency virus and
b. persons who are allergic to eggs; ACIP is still evaluating these recommendations.

http://www.cdc.gov/mmwr/preview/mmwrhtml/00046738.htm

Pediatric Infectious Disease Journal • January 1996

Measles outbreaks in the United States, 1987 through 1990

Author information

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Abstract

BACKGROUND
During 1989 and 1990 reported measles cases in the United States increased 6- to 9-fold over the annual mean of 3000 between 1985 and 1988. To evaluate recent epidemiology we summarized measles outbreaks.

METHODS
Confirmed measles cases reported to the National Notifiable Disease Surveillance System during 1987 through 1990 were analyzed. An outbreak was defined as > or = 5 epidemiologically linked cases.

RESULTS
There were 815 outbreaks, accounting for 94% of the 52,846 cases reported. Similar to 1985 and 1986, 3 patterns of measles transmission during outbreaks were identified: (1) predominantly among unvaccinated pre-school age children < 5 years of age (38% of outbreaks); (2) predominantly among vaccinated school age children 5 to 17 years of age (40%); and (3) predominantly among unvaccinated and vaccinated post-school age persons > or = 18 years of age (22%). Most outbreaks were small (median, 12 cases), but very large outbreaks occurred (maximum size, 10,670). Although school age outbreaks (58%) predominated during 1987 and 1988, preschool age (40%) and post-school age (23%) outbreaks were more important during 1989 and 1990.

CONCLUSIONS
Recent epidemiology suggests that to achieve elimination of measles, ACIP recommendations must be fully implemented, including (1) routine administration of the first dose of measles vaccine from 12 to 15 months of age and (2) use of a routine two-dose schedule to prevent school age and post-school age outbreaks.

http://www.ncbi.nlm.nih.gov/pubmed/8684873

“There were 815 outbreaks,

accounting for 94% of the 52,846 cases reported.

3 patterns of measles transmission during

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(1) predominantly among unvaccinated

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(2) predominantly among vaccinated

school age children 5 to 17 years of age (40%)

(3) predominantly among unvaccinated

and vaccinated post-school age persons (22%) ...”

Carcinogenesis • January 1996

DNA—protein crosslinks, a biomarker of exposure to formaldehyde—in vitro and in vivo studies

Author information

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Abstract

Formaldehyde (FA) is a widely produced industrial chemical. Sufficient evidence exists to consider FA as an animal carcinogen. In humans the evidence is not conclusive. DNA-protein crosslinks (DPC) may be one of the early lesions in the carcinogenesis process in cells following exposures to carcinogens. It has been shown in in vitro tests that FA can form DPC. We examined the amount of DPC formation in human white blood cells exposed to FA in vitro and in white blood cells taken from 12 workers exposed to FA and eight controls. We found a significant difference (P = 0.03) in the amount of DPC among exposed (mean +/- SD 28 +/- 5%, minimum 21%, maximum 38%) than among the unexposed controls (mean +/- SD 22 +/- 6%, minimum 16%, maximum 32%). Of the 12 exposed workers, four (33%) showed crosslink values above the upper range of controls. We also found a linear relationship between years of exposure and the amount of DPC. We conclude that our data indicate a possible mechanism of FA carcinogenicity in humans and that DPC can be used as a method for biological monitoring of exposure to FA.

Full Report

http://carcin.oxfordjournals.org/content/17/1/121.long

“We conclude that our data indicate a possible mechanism of Formaldehyde carcinogenicity in humans ...”

Acta Paediatrica Japan • June 1996

Adverse events associated with MMR vaccines in Japan

Author information

Kimura M1, Kuno-Sakai H, Yamazaki S,
Yamada A, Hishiyama M, Kamiya H, Ueda K,
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Abstract

The largest nationwide active surveillance of four Measles-Mumps-Rubella (MMR) vaccines was conducted in Japan. A total of 1255 pediatricians actively participated in the study, which comprised 8.6% of all members of the Japanese Pediatric Society. The total number of registered recipients of MMR vaccines was 38 203. They were arbitrarily given one of the MMR vaccines produced by three makers (Takeda, Osaka city, Kitasato Minato-ku. Tokyo and Biken Suita city, Japan) or the standard MMR vaccine made of designated strains (Kitasato's measles-AIK-C, Biken's mumps-Urabe Am9 and Takeda's rubella-To336) produced by Takeda, Kitasato and Biken and were observed for 35 days. The rates of virologically confirmed aseptic meningitis per 10,000 recipients were 16.6, 11.6, 3.2 and 0 for the standard MMR, Takeda MMR, Kitasato MMR and Biken MMR vaccines, respectively. The incidence of convulsions between 15 and 35 days was the highest with the standard MMR vaccine and the incidence of fever associated with vomiting occurring between 15 and 35 days (symptoms relevant to aseptic meningitis) were also the highest with the standard MMR vaccine. The incidence of parotid swelling was the lowest with Takeda MMR vaccine. This surveillance revealed that incidences of aseptic meningitis after administration of the standard MMR vaccine and of Biken MMR vaccine were different. This posed questions about the manufacturing consistency of the Urabe Am9 mumps virus vaccines. On the other hand, the National Institute of Health found that the biological characteristics of the Urabe Am9 mumps virus contained in the standard MMR vaccine and in the Biken MMR vaccine were different. The Biken Company reported that the mumps vaccine in the standard MMR vaccine was a mixture of two Urabe Am9 mumps vaccine bulks; one identical to that contained in the Biken MMR vaccine and the other produced by a different manufacturing process.

http://www.ncbi.nlm.nih.gov/pubmed/8741307

"The incidence of convulsions between 15 and 35 days was the highest with the standard MMR vaccine and the incidence of fever associated with vomiting occurring between 15 and 35 days (symptoms relevant to aseptic meningitis) were also the highest with the standard MMR vaccine. The incidence of parotid swelling was the lowest with Takeda MMR vaccine. This surveillance revealed that incidences of aseptic meningitis after administration of the standard MMR vaccine and of Biken MMR vaccine were different. This posed questions about the manufacturing consistency of the Urabe Am9 mumps virus vaccines."

Lancet • June 1996

Measles and atopy in Guinea-Bissau

Author information

Shaheen SO1, Aaby P, Hall AJ, Barker DJ, Heyes CB, Shiell AW, Goudiaby A.

1Medical Research Council Environmental Epidemiology Unit
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Abstract

BACKGROUND
Epidemiological studies have led to speculation that infections in early childhood may prevent allergic sensitisation but evidence to support this hypothesis is lacking. We investigated whether measles infection protects against the development of atopy in children of Guinea-Bissau, West Africa.

METHODS
We conducted a historical cohort study in Bandim, a semi-rural district of Bissau, the capital of Guinea-Bissau. 395 young adults, first surveyed in 1978-80 aged 0-6 years, were followed up in 1994. Our analyses were restricted to 262 individuals still living in Bandim for whom a measles history, documented in childhood, was judged to be reliable. We defined atopy as skin-prick test positivity (> or = 3 mm weal) to one or more of seven allergens.

FINDINGS
17 (12.8 percent) of 133 participants who had had measles infection were atopic compared with 33 (25.6 percent) of 129 of those who had been vaccinated and not had measles (odds ratio, adjusted for potential confounding variables 0.36 [95 percent CI 0.17-0.78], p=O.O1). Participants who had been breastfed for more than a year were less likely to have a positive skin test to housedust mite. After adjustment for breastfeeding and other variables, measles infection was associated with a large reduction in the risk of skin-prick test positivity to housedust mite (odds ratio for Dermatophagoides pteronyssinus 0.20 [0.05-0.81], p=0.02; D farinae 0.20 [0.06-0.71], p=0.01).

INTERPRETATION
Measles infection may prevent the development of atopy in African children.

http://www.ncbi.nlm.nih.gov/pubmed/8667923

“Measles infection may prevent

the development of atopy [allergies] in African children.”

[as Dr. Buttram stated, challenge viruses like measles and

chicken pox strengthen the child’s immune system]

“Triton X-100 efficiently induces the apoptotic cell death ...”

Yonsei Medical Journal • February 1997

Triton X-100 induces apoptosis in human hepatoma cell lines

Author information

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Abstract

The detergent Triton X-100 was used to establish a model for apoptosis in hepatoma cell lines. The electrophoresis of DNA extracted from 0.01% Triton X-100 treated hepatoma cell lines showed DNA ladder formation, a hallmark of apoptosis. The DNA fragmentation appeared within less than 60 min of the Triton X-100 treatment. Chromatin condensation and apoptotic bodies were observed by hematoxylin and eosin (H & E) stain, and fragmented nucleosome was detected by terminal deoxynucleotidyl transferase-mediated dUTP-biotin nick end labelling (TUNEL) test. Apoptosis was semi-quantitated by measuring the lactate dehydrogenase (LDH) level for cytotoxity. It was found that apoptosis had been induced in more than 90% of the cells treated with Triton X-100 for 150 min. These data show that Triton X-100 efficiently induces the apoptotic cell death in hepatoma cell lines.

http://www.ncbi.nlm.nih.gov/pubmed/9100483

Epidemiology • November 1997

Is infant immunization a risk factor for childhood asthma or allergy?

Author information

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1Department of Medicine
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Abstract

The Christchurch Health and Development Study comprises 1,265 children born in 1977. The 23 children who received no diphtheria/pertussis/tetanus (DPT) and polio immunizations had no recorded asthma episodes or consultations for asthma or other allergic illness before age 10 years; in the immunized children, 23.1% had asthma episodes, 22.5% asthma consultations, and 30.0% consultations for other allergic illness. Similar differences were observed at ages 5 and 16 years. These findings do not appear to be due to differential use of health services (although this possibility cannot be excluded) or confounding by ethnicity, socioeconomic status, parental atopy, or parental smoking.

http://www.ncbi.nlm.nih.gov/pubmed/9345669

“The 23 children who received no diphtheria/pertussis/tetanus (DPT) and polio immunizations had no recorded asthma episodes or consultations for asthma or other allergic illness before age 10 years; in the immunized children, 23.1% had asthma episodes, 22.5% asthma consultations, and 30.0% consultations for other allergic illness. Similar differences were observed at ages 5 and 16 years.”

Lancet • June 1996

Measles and atopy in Guinea-Bissau

Author information

Shaheen SO1, Aaby P, Hall AJ,
Barker DJ, Heyes CB, Shiell AW, Goudiaby A.

Medical Research Council Environmental Epidemiology Unit
University of Southampton, Southhampton General Hospital, UK

Abstract

BACKGROUND

Epidemiological studies have led to speculation that infections in early childhood may prevent allergic sensitisation but evidence to support this hypothesis is lacking. We investigated whether measles infection protects against the development of atopy in children of Guinea-Bissau, West Africa.

METHODS

We conducted a historical cohort study in Bandim, a semi-rural district of Bissau, the capital of Guinea-Bissau. 395 young adults, first surveyed in 1978-80 aged 0-6 years, were followed up in 1994. Our analyses were restricted to 262 individuals still living in Bandim for whom a measles history, documented in childhood, was judged to be reliable. We defined atopy as skin-prick test positivity (> or = 3 mm weal) to one or more of seven allergens.

FINDINGS

17 (12.8 percent) of 133 participants who had had measles infection were atopic compared with 33 (25.6 percent) of 129 of those who had been vaccinated and not had measles (odds ratio, adjusted for potential confounding variables 0.36 [95 percent CI 0.17-0.78], p=O. O1). Participants who had been breastfed for more than a year were less likely to have a positive skin test to housedust mite. After adjustment for breastfeeding and other variables, measles infection was associated with a large reduction in the risk of skin-prick test positivity to housedust mite (odds ratio for Dermatophagoides pteronyssinus 0.20 [0.05-0.81], p=0.02; D farinae 0.20 [0.06-0.71], p=0.01).

INTERPRETATION

Measles infection may prevent the development of atopy in African children.

http://www.ncbi.nlm.nih.gov/pubmed/?term=8667923

“Measles infection may prevent the development of atopy [allergies] in African children.”

Lancet • June 1997

Gulf War syndrome: is it due to a systemic shift in cytokine balance towards a Th2 profile

Author information

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Abstract

The symptoms of Gulf War syndrome are compatible with the hypothesis that the immune system of affected individuals is biased towards a Th2-cytokine pattern. Factors that could lead to a Th2 shift among Gulf War veterans include exposure to multiple Th2-inducing vaccinations under stressful circumstances and the way in which such vaccinations were administered, which would be expected to maximise Th2 immunogenicity. These factors may have led to a long-term systemic shift towards a Th2-cytokine balance and to mood changes related to the immunoendocrine state. Other vaccines that lead to similar long-term, non-specific shifts in cytokine balance are well-established. If our hypothesis is proven, treatment may be possible with regimens that induce a systemic Th1 bias.

http://www.ncbi.nlm.nih.gov/pubmed/9269228

“The symptoms of Gulf War syndrome are compatible with the hypothesis that the immune system of affected individuals is biased towards a Th2-cytokine pattern. Factors that could lead to a Th2 shift among Gulf War veterans include exposure to multiple Th2-inducing vaccinations under stressful circumstances and the way in which such vaccinations were administered, which would be expected to maximise Th2 immunogenicity.”

“Although the use of adjuvants in veterinary vaccines enhances the immunogenicity of vaccines, they have been responsible for a number of side effects.”

Seminars In Veterinary Medicine And Surgery (Small Animal) • August 1997

Vaccine adjuvants

Author information

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Abstract

Vaccine adjuvants provide enhanced immune responses to a variety of antigens. Unlike human vaccines that are limited to aluminum-based adjuvants, veterinary vaccines may contain a large number of substances either alone or in combination that act as vaccine adjuvants. Although the use of adjuvants in veterinary vaccines enhances the immunogenicity of vaccines, they have been responsible for a number of side effects. This article explores the rationale of currently used vaccine adjuvants and some of the adverse events associated with their use in veterinary medicine.

http://www.ncbi.nlm.nih.gov/pubmed/?term=9283246

Journal Of Paediatric Child Health • October 1997

Incidence of apnoea and bradycardia in preterm infants following DTPw and Hib immunization: a prospective study

Author information

Botham SJ1, Isaacs D, Henderson-Smart DJ.

Abstract

OBJECTIVE

To evaluate the incidence and severity of apnoea and bradycardia in hospitalized preterm infants following immunization at 2 months of age, and identify risk factors.

METHODOLOGY

A prospective study of 98 preterm infants, of gestational age 24-31 weeks, immunized at approximately 2 months post natal age with diphtheria-tetanus-whole cell pertussis vaccine (DTPw) in the neonatal intensive care unit (NICU) at King George V Hospital Sydney. Half the infants also received Haemophilus influenzae type b conjugate vaccine (Hib) simultaneously. All infants were monitored for apnoea and bradycardia in the 24 h periods pre- and post immunization.

RESULTS

Only one infant had apnoea and/or bradycardia pre-immunization compared with 17 post immunization. For 12 infants these events were brief, self-limiting and not associated with desaturations (oxygen saturation < 90%). However, for five infants (30%) these events were associated with oxygen desaturation and two of these infants required supplemental oxygen. The group that had apnoea and/or bradycardia and the group that did not were not significantly different in terms of gestational age, birth weight and other variables. Infants who received Hib together with DTPw were less likely to have apnoea and/or bradycardia than those given DTPw alone.

CONCLUSION

When considering immunization for preterm infants, the benefits of early immunization must be balanced against the risk of apnoea and bradycardia. We recommend that the cardio-respiratory function of hospitalized infants born at less than 31 weeks gestation be monitored for 48 h post immunization.

http://www.ncbi.nlm.nih.gov/pubmed/?term=9401886

“Only one infant had apnoea and/or bradycardia pre-immunization compared with 17 post immunization. For 12 infants these events were brief, self-limiting and not associated with desaturations (oxygen saturation < 90%). However, for five infants (30%) these events were associated with oxygen desaturation and two of these infants required supplemental oxygen.”

Epidemiology • November 1997

Is infant immunization a risk factor for childhood asthma or allergy?

Author information

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Abstract

The Christchurch Health and Development Study comprises 1,265 children born in 1977. The 23 children who received no diphtheria/pertussis/tetanus (DPT) and polio immunizations had no recorded asthma episodes or consultations for asthma or other allergic illness before age 10 years; in the immunized children, 23.1% had asthma episodes, 22.5% asthma consultations, and 30.0% consultations for other allergic illness. Similar differences were observed at ages 5 and 16 years. These findings do not appear to be due to differential use of health services (although this possibility cannot be excluded) or con-founding by ethnicity, socioeconomic status, parental atopy, or parental smoking.

http://www.ncbi.nlm.nih.gov/pubmed/?term=9345669

“The 23 children who received no diphtheria/pertussis/tetanus (DPT) and polio immunizations had no recorded asthma episodes or consultations for asthma or other allergic illness before age 10 years; in the immunized children, 23.1% had asthma episodes, 22.5% asthma consultations, and 30.0% consultations for other allergic illness.”

American Journal Of Human Genetics • 1998
Ecogenetics ’98

Variability in Immune Response to Pathogens: Using Measles Vaccine to Probe Immunogenetic Determinants of Response

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Abstract

“*The measles had not prevailed on the Faroes since 1781; they broke out early in April, 1846. Of the 7,782 inhabitants, about 6,000 were taken with measles) 225 persons in all died. Of the many old people still living on the Faroes who had had the measles in 1781, not one was attacked the second time.*”

Quote from P. L. Panum in the report titled
“Observations Made during the Epidemic of Measles
on the Faroe Islands in the Year 1846”

The Faroe Islands measles outbreak described above is of interest to geneticists in several regards: Why did some people survive and some die? Why was the case fatality rate so high? Why was the protective effect of prior exposure so high? Understanding the genetic influences on the phenotypes of protective and nonprotective an- tibody responses provides a unique window to under- stand the variability in host response to pathogens.

Vaccine Response as a Marker of Disease Susceptibility

Postimmunization antibody response can be used as a marker of disease susceptibility. For example, the level of antibody response after hepatitis B immunization predicts susceptibility to disease on exposure (Ellis 1993). In studies of measles, postimmunization measles antibody in the “low positive” range did not protect against clinical measles when subjects were exposed to the wild measles virus, whereas high levels were protective (Chen et al. 1990). Furthermore, nonresponders to a single dose of measles vaccine who demonstrated an antibody response only after a second immunization were still six times more likely than were responders to a single dose of measles vaccine to develop measles on exposure to wild virus (Mathias et al. 1989). Others examined “poor responders,” who were reimmunized and developed poor or low-level antibody responses only to lose detectable antibody and develop measles on exposure 2–5 years later. They concluded that there is a strong correlation between low antibody levels after a single dose of vaccine and high susceptibility to infection with exposure (Deseda-Tous et al. 1978).

Full Report

http://www.ncbi.nlm.nih.gov/pmc/articles/PMC1376909/pdf/9463343.pdf

Vaccine

Non-Responders

And

Low Responders

“... nonresponders to a single dose of measles vaccine who demonstrated an antibody response only after a second immunization were still six times more likely than were responders to a single dose of measles vaccine to develop measles on exposure to wild virus (Mathias et al. 1989). Others examined “poor responders,” who were reimmunized and developed poor or low-level antibody responses only to lose detectable antibody and develop measles on exposure 2–5 years later. They concluded that there is a strong correlation between low antibody levels after a single dose of vaccine and high susceptibility to infection with exposure.”

(Deseda-Tous et al. 1978)

Pediatrics Volume 101 • Issue 3 • March 1998

Acute Encephalopathy Followed by Permanent Brain Injury or Death Associated With Further Attenuated Measles Vaccines: A Review of Claims Submitted to the National Vaccine Injury Compensation Program

by Robert E. Weibel, Vito Caserta, David E. Benor, Geoffrey Evans

Abstract

Objective

To determine if there is evidence for a causal relationship between acute encephalopathy followed by permanent brain injury or death associated with the administration of further attenuated measles vaccines (Attenuvax or Lirugen, Hoechst Marion Roussel, Kansas City, MO), mumps vaccine (Mumpsvax, Merck and Co, Inc, West Point, PA), or rubella vaccines (Meruvax or Meruvax II, Merck and Co, Inc, West Point, PA), combined measles and rubella vaccine (M-R-Vax or M-R-Vax II, Merck and Co, Inc, West Point, PA), or combined measles, mumps, and rubella vaccine (M-M-R or M-M-R II, Merck and Co, Inc, West Point, PA), the lead author reviewed claims submitted to the National Vaccine Injury Compensation Program.

Methods

The medical records of children who met the inclusion criteria of receiving the first dose of these vaccines between 1970 and 1993 and who developed such an encephalopathy with no determined cause within 15 days were identified and analyzed.

Results

A total of 48 children, ages 10 to 49 months, met the inclusion criteria after receiving measles vaccine, alone or in combination. Eight children died, and the remainder had mental regression and retardation, chronic seizures, motor and sensory deficits, and movement disorders. The onset of neurologic signs or symptoms occurred with a nonrandom, statistically significant distribution of cases on days 8 and 9. No cases were identified after the administration of monovalent mumps or rubella vaccine.

Conclusions

This clustering suggests that a causal relationship between measles vaccine and encephalopathy may exist as a rare complication of measles immunization.

http://www.ncbi.nlm.nih.gov/pubmed/9481001

“A total of 48 children, ages 10 to 49 months, met the inclusion criteria after receiving measles vaccine, alone or in combination. Eight children died, and the remainder had mental regression and retardation, chronic seizures, motor and sensory deficits, and movement disorders. This clustering suggests that a causal relationship between measles vaccine and encephalopathy may exist as a rare complication of measles immunization.”

Biomedical And Environmental Science • March 1998

Detection of cytogenetic effects in peripheral lymphocytes of students exposed to formaldehyde with cytokinesis-blocked micronucleus assay

Author information

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Abstract

Cytokinesis-blocked micronucleus assay was applied as a biological dosimeter to detect abnormalities in human peripheral lymphocytes of thirteen students exposed to formaldehyde (FA) during a 12-week (10 h per week) anatomy class. Breathing-zone air samples collected during dissection procedures showed a mean concentration of 2.37 ppm (3.17 mg/m3). Ten students from the same school but without FA exposure served as controls. Chromosome aberrations (CA) and sister chromatid exchanges (SCE) were detected in both groups. The micronuclei (MN) rate (6.38 +/- 2.50 /1000) and CA rate (5.92 +/- 2.40%) in the FA-exposed group showed a significant increase ($P < 0.01$) when compared with those of the controls (3.15 +/- 1.46 /1000 and 3.40 +/- 1.57% respectively). A correlation between MN and CA in individuals was observed. SCE in the exposed group were also increased ($P < 0.05$), but not so greatly as MN or CA. The results indicated that FA might damage the chromosomes of human lymphocytes.

http://www.ncbi.nlm.nih.gov/pubmed/?term=9559107

“The results indicated that FA might damage the chromosomes of human lymphocytes.”

“The reader will notice an emerging clear picture that the majority (if not all) of these advances have been achieved from studies funded by independent or charity organizations rather than by the responsible authorities who are supposed and are duty bound to take on this task.”

Adverse Drug Reactions And Toxicological Reviews • March 1998

Gulf War syndrome— a model for the complexity of biological and environmental interaction with human health

Author information

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Abstract

Since the end of the Gulf War, tens of thousands of American, Canadian and British soldiers who participated in that war have claimed to be suffering from a variety of incapacitating symptoms which are generally termed as Gulf War Syndrome (GWS). The symptoms are multiple but mainly consist of excessive tiredness, muscle and joint pain, loss of balance, sensory symptoms, neurobehavioural manifestations, diarrhoea, bladder dysfunction, sweating disturbances, and respiratory, gastrointestinal, musculoskeletal and skin manifestations. These veterans have been exposed to a variety of damaging or potentially damaging risk factors including environmental adversities, pesticides such as organophosphate chemicals, skin insect repellents, medical agents such as pyridostigmine bromide (NAPS), possible low-levels of chemical warfare agents, multiple vaccinations in combinations, depleted uranium, and other factors. A large number of basic research findings, clinical epidemiological studies, and case control studies are reviewed to try and link them together to produce a coherent picture and to demonstrate the complexity of the interaction of biological systems, environmental and genetic factors, combinations of drugs and toxins with human health. The findings of these studies so far have demonstrated that many of the previous assumptions made about the ‘safety’ of certain drugs and toxic substances or vaccines must be radically reviewed. Many of the findings have far reaching implications not only in terms of explanation of what might have gone wrong during the Gulf War, but also have wider implications for many occupational groups who are exposed daily to some of these risk factors. More open-mindedness and much less prejudice are required concerning the basic biology of interactions of the above factors and their effects on cell functions and wider intelligent research is urgently required with high priority. This review highlights the importance of intelligent research for answers for a new phenomenon, and demonstrates the necessity for a combination of this approach with high quality epidemiological research. The reader will notice an emerging clear picture that the majority (if not all) of these advances have been achieved from studies funded by independent or charity organizations rather than by the responsible authorities who are supposed and are duty bound to take on this task.

http://www.ncbi.nlm.nih.gov/pubmed/9638279

Proceedings Of The National Academy Of Science USA • May 1998

Identification of rat susceptibility loci for adjuvant-oil-induced arthritis

Author information

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Abstract

One intradermal injection of incomplete Freund's adjuvant-oil induces a T cell-mediated inflammatory joint disease in DA rats. Susceptibility genes for oil-induced arthritis (OIA) are located both within and outside the major histocompatibility complex (MHC, Oia1). We have searched for disease-linked non-MHC loci in an F2 intercross between DA rats and MHC-identical but arthritis-resistant LEW.1AV1 rats. A genome-wide scan with microsatellite markers revealed two major chromosome regions that control disease incidence and severity: Oia2 on chromosome 4 (P = 4 x 10(-13)) and Oia3 on chromosome 10 (P = 1 x 10(-6)). All animals homozygous for DA alleles at both loci developed severe arthritis, whereas all those homozygous for LEW.1AV1 alleles were resistant. These results have general implications for situations where nonspecific activation of the immune system (e.g., incomplete Freund's adjuvant-oil) causes inflammation and disease, either alone or in conjunction with specific antigens. They may also provide clues to the etiology of inflammatory diseases in humans, including rheumatoid arthritis.

Full Report

http://www.ncbi.nlm.nih.gov/pmc/articles/PMC27729/

"These results have general implications for situations where nonspecific activation of the immune system (e.g., incomplete Freund's adjuvant-oil) causes inflammation and disease, either alone or in conjunction with specific antigens. They may also provide clues to the etiology of inflammatory diseases in humans, including rheumatoid arthritis."

Acta Virologica • June 1998

Neurologic complications associated with oral poliovirus vaccine and genomic variability of the vaccine strains after multiplication in humans

Author information

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Abstract

The oral poliovirus vaccine (OPV) has been effectively used in the reduction and control of poliomyelitis cases on the planet. Despite several advantages of using the attenuated OPV strains, the rare occurrence of vaccine-associated paralytic poliomyelitis (VAPP) cases in vaccine recipients and their susceptible contacts is a disadvantage. Molecular biology studies of polioviruses isolated from stool and central nervous system (CNS) of patients with VAPP have confirmed the vaccine origin of the isolates and demonstrated genomic modifications known or suspected to increase the neurovirulence. Similar genomic modifications have also been identified in OPV-derived strains isolated from healthy vaccinees and healthy contacts, suggesting that host factors are also involved in the establishment of poliomyelitis. Other neurologic complications such as meningitis, encephalitis, convulsions, transverse myelitis and Guillain-Barré syndrome have also been rarely associated with the use of this vaccine. The characterization of polioviruses isolated from such cases has demonstrated their OPV origin.

http://www.ncbi.nlm.nih.gov/pubmed/9842449

“Molecular biology studies of polioviruses isolated from stool and central nervous system (CNS) of patients with VAPP have confirmed the vaccine origin of the isolates and demonstrated genomic modifications known or suspected to increase the neurovirulence. Similar genomic modifications have also been identified in OPV-derived strains isolated from healthy vaccinees and healthy contacts, suggesting that host factors are also involved in the establishment of poliomyelitis. Other neurologic complications such as meningitis, encephalitis, convulsions, transverse myelitis and Guillain-Barré syndrome have also been rarely associated with the use of this vaccine.”

Lancet • August 1998

Macrophagic myofasciitis: an emerging entity

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Abstract

BACKGROUND
An unusual inflammatory myopathy characterised by an infiltration of non-epithelioid histiocytic cells has been recorded with increasing frequency in the past 5 years in France. We reassessed some of these cases.

METHODS
We did a retrospective analysis of 18 such cases seen in five myopathology centres between May, 1993, and December, 1997. The myopathological changes were reassessed at a clinopathology seminar.

FINDINGS
Detailed clinical information was available for 14 patients. The main presumptive diagnoses were polymyositis and polymyalgia rheumatica. Symptoms included myalgias in 12 patients, arthralgias in nine, muscle weakness in six, pronounced asthenia in five, and fever in four. Abnormal laboratory findings were occasionally observed, and included raised creatine kinase concentrations, increased erythrocyte sedimentation rate, and myopathic electromyography. Muscle biopsy showed infiltration of the subcutaneous tissue, epimysium, perimysium, and perifascicular endomysium by sheets of large macrophages, with a finely granular PAS-positive content. Also present were occasional CD8 T cells, and inconspicuous muscle-fibre damage. Epithelioid and giant cells, necrosis, and mitotic figures were not seen. The images were easily distinguishable from sarcoid myopathy and fasciitis-panniculitis syndromes. Whipple's disease, Mycobacterium avium intracellulare infection, and malakoplakia could not be confirmed. Ten patients were treated with various combinations of steroids and antibiotics; symptoms improved in eight patients, and stabilised in two.

INTERPRETATION
A new inflammatory muscle disorder of unknown cause, characterized by a distinctive pathological pattern of macrophagic myofasciitis, is emerging in France.

http://www.ncbi.nlm.nih.gov/pubmed/?term=9717921

"A new inflammatory muscle disorder of unknown cause, characterised by a distinctive pathological pattern of macrophagic myofasciitis, is emerging in France."

Clinical Immunology And Immunopathology • October 1998

Serological association of measles virus and human herpesvirus-6 with brain autoantibodies in autism

Author information

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Abstract

Considering an autoimmunity and autism connection, brain autoantibodies to myelin basic protein (anti-MBP) and neuron-axon filament protein (anti-NAFP) have been found in autistic children. In this current study, we examined associations between virus serology and autoantibody by simultaneous analysis of measles virus antibody (measles-IgG), human herpesvirus-6 antibody (HHV-6-IgG), anti-MBP, and anti-NAFP. We found that measles-IgG and HHV-6-IgG titers were moderately higher in autistic children but they did not significantly differ from normal controls. Moreover, we found that a vast majority of virus serology-positive autistic sera was also positive for brain autoantibody: (i) 90% of measles-IgG-positive autistic sera was also positive for anti-MBP; (ii) 73% of measles-IgG-positive autistic sera was also positive for anti-NAFP; (iii) 84% of HHV-6-IgG-positive autistic sera was also positive for anti-MBP; and (iv) 72% of HHV-6-IgG-positive autistic sera was also positive for anti-NAFP. This study is the first to report an association between virus serology and brain autoantibody in autism; it supports the hypothesis that a virus-induced autoimmune response may play a causal role in autism.

http://www.ncbi.nlm.nih.gov/pubmed/9756729

“This study is the first to report an association between virus serology and brain autoantibody in autism; it supports the hypothesis that a virus-induced autoimmune response may play a causal role in autism.”

Pediatrics • November 1998

Report of a US public health service workshop on hypotonic-hyporesponsive episode (HHE) after pertussis immunization

Author information

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Abstract

Hypotonic-hyporesponsive episode (HHE) is a term used to describe a somewhat heterogenous group of clinical disorders that have been reported primarily in association with whole-cell pertussis vaccination. A 1991 review by the Institute of Medicine determined that the evidence available was indeed consistent with a causal relation between whole-cell pertussis-diphtheria-tetanus immunization and HHE, but that the evidence was insufficient to indicate a causal relationship between HHE and the subsequent development of permanent neurologic damage. More recent data from clinical trials conducted in Europe suggest that HHE also occurs after vaccination with acellular pertussis vaccines. The US Food and Drug Administration, in collaboration with the US Public Health Service, sponsored a workshop on HHE in Rockville, Maryland, on June 19, 1997. The primary goals of the workshop were to develop a case definition of HHE and to evaluate the general design and feasibility of possible studies of HHE using the federal Vaccine Adverse Event Reporting System (VAERS), a national passive surveillance system. The goals of such studies would be to understand better the acute HHE event and to evaluate the possibility of long-term sequelae. Case Definition. There has been no generally accepted definition of HHE, and a standard definition would be useful for vaccine safety work and would potentially facilitate interstudy comparisons of the growing number of licensed vaccines containing acellular pertussis components. The workshop defined HHE as an event of sudden onset occurring within 48 hours of immunization, with duration of the episode ranging from 1 minute to 48 hours, in children younger than 10 years of age. All of the following must be present: 1) limpness or hypotonia, 2) reduced responsiveness or hyporesponsiveness, and 3) pallor or cyanosis or failure to observe or to recall skin coloration. HHE is not considered to have occurred if there is a known cause for these signs (eg, postictal), if urticaria is present during the event, if normal skin coloration is observed throughout the episode, or if the child is simply sleeping. This inclusive (sensitive) case definition will allow investigators, through the technique of stratification according to certain characteristics (eg, time from vaccination to onset of HHE), to attempt to hone the definition and make it more specific. Refinement of the definition of HHE has been hindered by the lack of information on its pathophysiology and by the lack of pathognomonic signs, symptoms, and diagnostic tests. Another hindrance is that by the time the child presents for medical evaluation, the signs of HHE often have normalized. Moreover, different mechanisms may be involved in different individuals whose events meet this workshop's HHE definition. Probably the most important question about HHE is whether it has any permanent sequelae. The workshop assessed the possible contribution VAERS-based studies could make to answering this question and found substantial methodologic problems; however, ongoing studies in Sweden and The Netherlands have the potential to provide useful information on this question. The most useful contribution of VAERS data would be in a descriptive study of HHE, with a possible case-control study of factors that may affect the risk of HHE after vaccination, rather than a study of possible permanent sequelae. The workshop participants felt that a detailed descriptive study of approximately 100 HHE events reported during a 1- to 2-year period could provide a more in-depth description of HHE cases in greater numbers than has been published previously, but the study would not address the issue of long-term sequelae of HHE. Better descriptive data may lead to new hypotheses concerning risk factors, etiology, and pathophysiology of HHE that might be evaluated further by studying subsequent cases and controls from VAERS or from other sources.

http://www.ncbi.nlm.nih.gov/pubmed/9794982

Journal Of Dental Research • November 1998

Toxicity of formaldehyde to human oral fibroblasts and epithelial cells: influences of culture conditions and role of thiol status

Author information

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Abstract

The toxicity of formaldehyde, a monomer released from certain polymeric dental materials, was studied in cultured human oral fibroblasts and epithelial cells. The influences of growth conditions were evaluated for both cell types, as well as the role of the internal and external thiol states. A one-hour exposure to formaldehyde decreased the colony-forming efficiency (CFE) of both cell types in a concentration-dependent manner, although the toxicity varied up to 100-fold with the conditions. Clearly, the presence of serum and the thiol cysteine counteracted the toxicity in fibroblasts. Similarly, pituitary extract and cysteine, or a mixture of amino acids and ethanolamines, counteracted the formaldehyde toxicity in serum-free cultures of epithelial cells. In contrast, a growth-promoting surface matrix of fibronectin and collagen did not influence the formaldehyde toxicity, as shown by both the CFE assay and a dye reduction assay. Further, a short-term change to the various growth media per se with or without the supplements serum or cysteine did not significantly alter the CFE. Analysis of the thiol state demonstrated significant differences between epithelial cells and fibroblasts, i.e., comparatively lower cellular levels of the free low-molecular-weight thiols glutathione and cysteine in fibroblasts. This result correlated to significantly higher formaldehyde toxicity in the fibroblasts than in the epithelial cells. Taken together, the results indicated the cytoprotective function of both intracellular and extracellular thiols toward formaldehyde, as well as the usefulness of thiol-free and chemically defined conditions for toxicity assessments in oral epithelial cells and fibroblasts. We conclude that the combined use of a controlled external milieu and the presumed target cell type may be advantageous in evaluations of oral toxicity mechanisms or the toxic potency of dental materials, particularly those which, like formaldehyde, may react with thiols or amines.

http://www.ncbi.nlm.nih.gov/pubmed/?term=9823728

“A one-hour exposure to formaldehyde decreased the colony-forming efficiency of both cell types in a concentration-dependent manner, although the toxicity varied up to 100-fold with the conditions.”

Scandinavian Journal Of Immunology • January 1999

Identification of arthritogenic adjuvants of self and foreign origin

Author information

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Abstract

The lack of defined triggers for human inflammatory joint diseases warrants efforts to identify candidate molecules. For this task, it may be an important lead that nonspecific activation of the immune system can precipitate arthritis in rats. Consequently, arthritis-prone rat strains were used to search for disease-triggering factors among molecules which initially induce innate defence reactions rather than specific immune responses. A variety of immunological adjuvants were investigated by intradermal injection into DA and LEW.1AV1 rats and monitoring of clinical signs for 30 days. Several arthritogenic cell-wall structures from yeast and bacteria were identified, such as beta-glucan, lipopolysaccharide and trehalosedimycolate. The test procedures also revealed arthritogens of chemical origin, such as dioctadecyldiammoniumbromide (DDA = C38H80NBr) and heptadecane (C17H36). Furthermore, it allowed the precise definition of arthritogenic determinants of lipids, since C16H34 induced arthritis, whereas the closely related linear hydrocarbons C16H32, C16H33Br and C15H32 did not. The observed pathogenicity of organic lipids raised the question of whether endogenous lipids can also precipitate arthritis. Indeed, this was true for the cholesterol precursor squalene (C30H50). In conclusion, this article describes the rational use of arthritis-prone rat strains to identify arthritogenic factors of both foreign and self origin. Although structurally unrelated, the pathogenic molecules defined here share the feature of being nonspecific triggers of the immune system. This consolidates a general principle for the induction of adjuvant arthritis which may provide clues to the aetiology of human arthritides, including rheumatoid arthritis.

http://www.ncbi.nlm.nih.gov/pubmed/?term=10023856

“The observed pathogenicity of organic lipids raised the question of whether endogenous lipids can also precipitate arthritis. Indeed, this was true for the cholesterol precursor squalene ...”

Archives Of Toxicology • February 1999

Effects of 2-phenoxyethanol on N-methyl-D-aspartate (NMDA) receptor-mediated ion currents

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Abstract

The actions were examined of 17 frequently used glycol ether compounds on the glutamate receptor-mediated ion currents. The receptors were expressed in Xenopus oocytes by injection of rat brain mRNA. Most of the 17 glycol ethers exerted no effects on the glutamate subreceptors activated by kainate and N-methyl-D-aspartate (NMDA), whereas 2-phenoxyethanol (ethylene glycol monophenyl ether) caused a considerable reduction of NMDA-induced membrane currents in a reversible and concentration-dependent manner. The threshold concentration of the ethylene glycol monophenyl ether effect was < 10 mumol/l. The concentration for a 50% inhibition (IC50) was approximately 360 mumol/l. The results indicate a neurotoxic potential for 2-phenoxyethanol.

http://www.ncbi.nlm.nih.gov/pubmed/?term=10207615

“The results indicate a neurotoxic potential for 2-phenoxyethanol.”

[2-phenoxyethanol is a vaccine ingredient]

Epidemiology • May 1999

Hepatitis B vaccine and liver problems in U.S. children less than 6 years old 1993 and 1994

Author information

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Abstract

Data to assess the benefits and risks of hepatitis B vaccine for the general population of U.S. children are sparse. This study addressed the problem of external validity found in previous studies of high risk populations by evaluating the benefit of hepatitis B vaccination for the general population of American children. We calculated the risk of liver problems among hepatitis B vaccinated and non-hepatitis B vaccinated children using logistic regression. Hepatitis B vaccinated children had an unadjusted odds ratio of 2.94 and age-adjusted odds ratio of 2.35 for liver problems compared with non-hepatitis B vaccinated children in the 1993 National Health Interview Survey. Hepatitis B vaccinated children had an unadjusted odds ratio of 2.57 and age-adjusted odds ratio of 1.53 for liver problems compared with non-hepatitis B vaccinated children in the 1994 National Health Interview Survey dataset.

http://www.ncbi.nlm.nih.gov/pubmed/10230847

“Hepatitis B vaccinated children had an unadjusted odds ratio of 2.94 and age-adjusted odds ratio of 2.35 for liver problems compared with non-hepatitis B vaccinated children in the 1993 National Health Interview Survey.”

Vaccine • July 1999

An overview of the vaccine adverse event reporting system (VAERS) as a surveillance system

VAERS Working Group

Author information

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Abstract

We evaluated the Vaccine Adverse Event Reporting System (VAERS), the spontaneous reporting system for vaccine-associated adverse events in the United States, as a public health surveillance system, using evaluation guidelines from the Centers for Disease Control and Prevention. We found that VAERS is simple for reporters to use, flexible by design and its data are available in a timely fashion. The predictive value positive for one severe event is known to be high, but for most events is unknown. The acceptability, sensitivity and representativeness of VAERS are unknown. The study of vaccine safety is complicated by underreporting, erroneous reporting, frequent multiple exposures and multiple outcomes.

http://www.ncbi.nlm.nih.gov/pubmed/?term=10438063

“The acceptability, sensitivity and representativeness of VAERS are unknown. The study of vaccine safety is complicated by underreporting, erroneous reporting, frequent multiple exposures and multiple outcomes.”

“... A non specific permeabilization of the Blood Brain Barrier ...”

Pharmaceutical Research • December 1999

Indirect evidence that drug brain targeting using polysorbate 80-coated polybutylcyanoacrylate nanoparticles is related to toxicity

Author information

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Abstract

PURPOSE
To investigate the mechanism underlying the entry of the analgesic peptide dalargin into brain using biodegradable polybutylcyanoacrylate (PBCA) nanoparticles (NP) overcoated with polysorbate 80.

METHODS
The investigations were carried out with PBCA NP and with non biodegradable polystyrene (PS) NP (200 nm diameter). Dalargin adsorption was assessed by HPLC. Its entry into the CNS in mice was evaluated using the tail-flick procedure. Locomotor activity measurements were performed to compare NP toxicities. BBB permeabilization by PBCA NP was studied in vitro using a coculture of bovine brain capillary endothelial cells and rat astrocytes.

RESULTS
Dalargin loading was 11.7 microg/mg on PBCA NP and 16.5 microg/ mg on PS NP. Adding polysorbate 80 to NP led to a complete desorption. Nevertheless, dalargin associated with PBCA NP and polysorbate 80 induced a potent and prolonged analgesia, which could not be obtained using PS NP in place of PBCA NP. Locomotor activity dramatically decreased in mice dosed with PBCA NP, but not with PS NP. PBCA NP also caused occasional mortality. In vitro, PBCA NP (10 microg/ml) induced a permeabilization of the BBB model.

CONCLUSIONS
A non specific permeabilization of the BBB, probably related to the toxicity of the carrier, may account for the CNS penetration of dalargin associated with PBCA NP and polysorbate 80.

http://www.ncbi.nlm.nih.gov/pubmed/10644071

Acta Paediatrica • January 2000

Gait disturbance interpreted as cerebellar ataxia after MMR vaccination at 15 months of age: a follow-up study

Author information

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Abstract

Measles, mumps and rubella (MMR) vaccination was included in the Danish childhood vaccination programme in 1987. During the following 10-y period, 550 notification records of adverse events after MMR vaccination at 15 mo of age have been registered, and a total of 41 notifications have included “gait disturbance”. This corresponds to a frequency of 8 per 100,000 doses of MMR vaccine used for 15-mo-old children. The symptoms and signs are characteristic of cerebellar ataxia. In 28 notifications, the descriptions by the doctors included only “gait disturbance”, while in 13 an additional interpretation was included. Thirty-two parents (78%) filled in a questionnaire and 26 (63%) agreed to participate in a clinical follow-up study. The gait disturbance symptoms mainly occurred 7-14 d after the vaccination, and the duration was median 1-2 wk (range 1 d to more than 4 mo). One-third of the children had symptoms lasting more than 2 wk. Significantly more children with long duration of symptoms had some kind of complaint or clinical signs at the follow-up in 1997. Gait disturbance registered after MMR vaccination seems to be more frequent than hitherto reported. Most cases are mild and short-lasting and a longer duration of symptoms seems to be predictive of late sequelae. A clinical diagnosis of cerebellar ataxia after MMR and the exact frequency of this adverse event remains to be tested in prospective studies.

http://www.ncbi.nlm.nih.gov/pubmed/10677059

“Gait disturbance registered after MMR vaccination seems to be more frequent than hitherto reported. Most cases are mild and short-lasting and a longer duration of symptoms seems to be predictive of late sequelae.”

Clinical And Experimental Rheumatology • January 2000

Immune-mediated pathology following hepatitis B vaccination. Two cases of polyarteritis nodosa and one case of pityriasis rosea-like drug eruption

Author information

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Abstract

The association of hepatitis B virus infection and vasculitis or other immune-mediated manifestations is well documented. Reports on such manifestations in relation to hepatitis B vaccination are scarce, however. We report 2 patients who developed polyarteritis nodosa following vaccination against hepatitis B. In one patient this resulted in an ischemic and necrotic digital ulcus, necessitating surgical amputation. The other patient presented with typical cutaneous polyarteritis nodosa which responded well to corticosteroid treatment. A third patient developed a severe pityrias rosea-like eruption. He was treated with topical steroids with healing of the lesions, leaving only post-inflammatory hyperpigmentation. The literature on these associations is reviewed.

http://www.ncbi.nlm.nih.gov/pubmed/10728450

“We report 2 patients who developed polyarteritis nodosa following vaccination against hepatitis B. In one patient this resulted in an ischemic and necrotic digital ulcus, necessitating surgical amputation. The other patient presented with typical cutaneous polyarteritis nodosa which responded well to corticosteroid treatment. A third patient developed a severe pityrias rosea-like eruption. He was treated with topical steroids with healing of the lesions, leaving only post-inflammatory hyperpigmentation.”

Journal Of Autoimmunity • February 2000

Vaccination and autoimmunity-
'vaccinosis': a dangerous liaison?

Author information

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Abstract

The question of a connection between vaccination and autoimmune illness (or phenomena) is surrounded by controversy. A heated debate is going on regarding the causality between vaccines, such as measles and anti-hepatitis B virus (HBV), and multiple sclerosis (MS). Brain antibodies as well as clinical symptoms have been found in patients vaccinated against those diseases. Other autoimmune illnesses have been associated with vaccinations. Tetanus toxoid, influenza vaccines, polio vaccine, and others, have been related to phenomena ranging from autoantibodies production to full-blown illness (such as rheumatoid arthritis (RA)). Conflicting data exists regarding also the connection between autism and vaccination with measles vaccine. So far only one controlled study of an experimental animal model has been published, in which the possible causal relation between vaccines and autoimmune findings has been examined: in healthy puppies immunized with a variety of commonly given vaccines, a variety of autoantibodies have been documented but no frank autoimmune illness was recorded. The findings could also represent a polyclonal activation (adjuvant reaction). The mechanism (or mechanisms) of autoimmune reactions following immunization has not yet been elucidated. One of the possibilities is molecular mimicry; when a structural similarity exists between some viral antigen (or other component of the vaccine) and a self-antigen. This similarity may be the trigger to the autoimmune reaction. Other possible mechanisms are discussed. Even though the data regarding the relation between vaccination and autoimmune disease is conflicting, it seems that some autoimmune phenomena are clearly related to immunization (e.g. Guillain-Barre syndrome). The issue of the risk of vaccination remains a philosophical one, since to date the advantages of this policy have not been refuted, while the risk for autoimmune disease has not been irrevocably proved. We discuss the pros and cons of this issue (although the temporal relationship (i.e. always 2-3 months following immunization) is impressive).

http://www.ncbi.nlm.nih.gov/pubmed/10648110

"Even though the data regarding
the relation between vaccination
and autoimmune disease is conflicting,
it seems that some autoimmune
phenomena are clearly related to
immunization (e.g. Guillain-Barre syndrome)."

Journal Of Manipulative And Physiological Therapeutics • February 2000

Effects of diphtheria-tetanus-pertussis or tetanus vaccination on allergies and allergy-related respiratory symptoms among children and adolescents in the United States

Author information

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Abstract

BACKGROUND

Findings from animal and human studies confirm that diphtheria and tetanus toxoids and pertussis (DTP) and tetanus vaccinations induce allergic responses; associations between childhood vaccinations and subsequent allergies have been reported recently.

OBJECTIVE

The association of DTP or tetanus vaccination with allergies and allergy-related respiratory symptoms among children and adolescents in the United States was assessed.

METHODS

Data were used from the Third National Health and Nutrition Examination Survey on infants aged 2 months through adolescents aged 16 years. DTP or tetanus vaccination, lifetime allergy history, and allergy symptoms in the past 12 months were based on parental or guardian recall. Logistic regression modeling was performed to estimate the effects of DTP or tetanus vaccination on each allergy.

RESULTS

The odds of having a history of asthma was twice as great among vaccinated subjects than among unvaccinated subjects (adjusted odds ratio, 2.00; 95% confidence interval, 0.59 to 6.74). The odds of having had any allergy-related respiratory symptom in the past 12 months was 63% greater among vaccinated subjects than unvaccinated subjects (adjusted odds ratio, 1.63; 95% confidence interval, 1.05 to 2.54). The associations between vaccination and subsequent allergies and symptoms were greatest among children aged 5 through 10 years.

CONCLUSIONS

DTP or tetanus vaccination appears to increase the risk of allergies and related respiratory symptoms in children and adolescents. Although it is unlikely that these results are entirely because of any sources of bias, the small number of unvaccinated subjects and the study design limit our ability to make firm causal inferences about the true magnitude of effect.

http://www.ncbi.nlm.nih.gov/pubmed/?term=10714532

“DTP or tetanus vaccination appears to increase the risk of allergies and related respiratory symptoms in children and adolescents.”

American Journal Of Epidemiology • March 2000

Outbreak of aseptic meningitis associated with mass vaccination with a urabe-containing measles-mumps-rubella vaccine: implications for immunization programs

Author information

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Abstract

A mass immunization campaign with a Urabe-containing measles-mumps-rubella vaccine was carried out in 1997 in the city of Salvador, northeastern Brazil, with a target population of children aged 1-11 years. There was an outbreak of aseptic meningitis following the mass campaign. Cases of aseptic meningitis were ascertained through data collected from the records of children admitted to the local referral hospital for infectious diseases between March and October of 1997, using previously defined eligibility criteria. Vaccination histories were obtained through home visits or telephone calls. Eighty-seven cases fulfilled the study criteria. Of those, 58 cases were diagnosed after the vaccination campaign. An elevated risk of aseptic meningitis was observed 3 weeks after Brazil's national vaccination day compared with the risk in the prevaccination period (relative risk = 14.3; 95% confidence interval: 7.9, 25.7). This result was confirmed by a case series analysis (relative risk = 30.4; 95% confidence interval: 11.5, 80.8). The estimated risk of aseptic meningitis was 1 in 14,000 doses. This study confirms a link between measles-mumps-rubella vaccination and aseptic meningitis. The authors discuss the implications of this for the organization and planning of mass immunization campaigns.

http://www.ncbi.nlm.nih.gov/pubmed/10707922

Full Report: http://aje.oxfordjournals.org/content/151/5/524.long

"An elevated risk of aseptic meningitis was observed 3 weeks after Brazil's national vaccination day compared with the risk in the prevaccination period (relative risk = 14.3; 95% confidence interval: 7.9, 25.7). This result was confirmed by a case series analysis (relative risk = 30.4; 95% confidence interval: 11.5, 80.8). The estimated risk of aseptic meningitis was 1 in 14,000 doses. This study confirms a link between measles-mumps-rubella vaccination and aseptic meningitis."

The Israel Medical Association Journal • March 2000

Gender differences in the reactogenicity of measles-mumps-rubella vaccine

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Abstract

BACKGROUND
In trials comparing different formulations of measles vaccine, excess non-specific mortality occurred in female children who received high titer vaccine. These findings suggest a gender-specific effect of measles vaccine.

OBJECTIVES
To determine whether gender differences exist in the rates of adverse reactions and morbidity in the month following immunization with measles-containing vaccine, and to evaluate whether there is a gender-specific association between the humoral immune response to measles vaccination and post-vaccination morbidity.

METHODS
Parents completed questionnaires on the health status of 755 infants aged 15-20 months, during the month preceding and the month following the measles-mumps-rubella vaccination. Blood samples were tested for measles antibody titers in a subsample of 237 infants.

RESULTS
After controlling background morbidity in the infants, the relative risk of fever and rash following vaccination was 2.35 in females and 1.36 in males. The geometric mean antibody titers against measles were similar in both sexes and there was no significant association between antibody titer and post-vaccination morbidity in either sex.

CONCLUSIONS
Our findings demonstrate higher rates of adverse effects in females following vaccination with MMR vaccine, irrespective of the humoral response. This study emphasizes the need to consider possible gender differences when evaluating new vaccines.

http://www.ncbi.nlm.nih.gov/pubmed/?term=10774264

Full Report: http://www.ima.org.il/FilesUpload/IMAJ/0/61/30887.pdf

“Our findings demonstrate higher rates of adverse effects in females following vaccination with MMR vaccine, irrespective of the humoral response. This study emphasizes the need to consider possible gender differences when evaluating new vaccines.”

Digestive Diseases And Science • April 2000

Detection and sequencing of measles virus from peripheral mononuclear cells from patients with inflammatory bowel disease and autism

Author information

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Abstract

It has been reported that measles virus may be present in the intestine of patients with Crohn's disease. Additionally, a new syndrome has been reported in children with autism who exhibited developmental regression and gastrointestinal symptoms (autistic enterocolitis), in some cases soon after MMR vaccine. It is not known whether the virus, if confirmed to be present in these patients, derives from either wild strains or vaccine strains. In order to characterize the strains that may be present, we have carried out the detection of measles genomic RNA in peripheral mononuclear cells (PBMC) in eight patients with Crohn's disease, three patients with ulcerative colitis, and nine children with autistic enterocolitis. As controls, we examined healthy children and patients with SSPE, SLE, HIV-1 (a total of eight cases). RNA was purified from PBMC by Ficoll-paque, followed by reverse transcription using AMV; cDNAs were subjected to nested PCR for detection of specific regions of the hemagglutinin (H) and fusion (F) gene regions. Positive samples were sequenced directly, in nucleotides 8393-8676 (H region) or 5325-5465 (from noncoding F to coding F region). One of eight patients with Crohn disease, one of three patients with ulcerative colitis, and three of nine children with autism, were positive. Controls were all negative. The sequences obtained from the patients with Crohn's disease shared the characteristics with wild-strain virus. The sequences obtained from the patients with ulcerative colitis and children with autism were consistent with being vaccine strains. The results were concordant with the exposure history of the patients. Persistence of measles virus was confirmed in PBMC in some patients with chronic intestinal inflammation.

http://www.ncbi.nlm.nih.gov/pubmed/10759242

"The sequences obtained from the patients with ulcerative colitis and children with autism were consistent with being vaccine strains. The results were concordant with the exposure history of the patients. Persistence of measles virus was confirmed in PBMC in some patients with chronic intestinal inflammation."

BMJ • May 2000

Role of vaccinations as risk factors for ill health in veterans of the Gulf war: cross sectional study

Author information

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Abstract

OBJECTIVES

To explore the relation between ill health after the Gulf war and vaccines received before or during the conflict. To test the hypothesis that such ill health is limited to military personnel who received multiple vaccines during deployment and that pesticide use modifies any effect.

DESIGN

Cross sectional study of Gulf war veterans followed for six to eight years after deployment.

SETTING

UK armed forces.

PARTICIPANTS

Military personnel who served in the Gulf and who still had their vaccine records.

MAIN OUTCOME MEASURES

Multisymptom illness as classified by the Centers for Disease Control and Prevention; fatigue; psychological distress; post-traumatic stress reaction; health perception; and physical functioning.

RESULTS

The response rate for the original survey was 70.4% (n=3284). Of these, 28% (923) had vaccine records. Receipt of multiple vaccines before deployment was associated with only one of the six health outcomes (post-traumatic stress reaction). By contrast five of the six outcomes (all but post-traumatic stress reaction) were associated with multiple vaccines received during deployment. The strongest association was for the multisymptom illness (odds ratio 5.0; 95% confidence interval 2.5 to 9.8).

CONCLUSION

Among veterans of the Gulf war there is a specific relation between multiple vaccinations given during deployment and later ill health. Multiple vaccinations in themselves do not seem to be harmful but combined with the "stress" of deployment they may be associated with adverse health outcomes. These results imply that every effort should be made to maintain routine vaccines during peacetime.

Full Report: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC27378/

"Among veterans of the Gulf war there is a specific relation between multiple vaccinations given during deployment and later ill health."

American Journal Of Pathology • June 2000

The Endogenous Adjuvant Squalene Can Induce a Chronic T-Cell-Mediated Arthritis in Rats

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Abstract

Squalene is a cholesterol precursor, which stimulates the immune system nonspecifically. We demonstrate that one intradermal injection of this adjuvant lipid can induce joint-specific inflammation in arthritis-prone DA rats. Histopathological and immunohistochemical analyses revealed erosion of bone and cartilage, and that development of polyarthritis coincided with infiltration of □□+ T cells. Depletion of these cells with anti-□□ TcR monoclonal antibody (R73) resulted in complete recovery, whereas anti-CD8 and anti-□□ TcR injections were ineffective. The apparent dependence on CD4+ T cells suggested a role for genes within the major histocompatibility complex (MHC), and this was concluded from comparative studies of MHC congenic rat strains, in which DA.1H rats were less susceptible than DA rats. Furthermore, LEW.1AV1 and PVG.1AV1 rats with MHC identical to DA rats were arthritis-resistant, demonstrating that non-MHC genes also determine susceptibility. Some of these genetic influences could be linked to previously described arthritis susceptibility loci in an F2 intercross between DA and LEW.1AV1 rats (ie, Cia3, Oia2 and Cia5). Interestingly, some F2 hybrid rats developed chronic arthritis, a phenotype not apparent in the parental inbred strains. Our demonstration that an autoadjuvant can trigger chronic, immune-mediated joint-specific inflammation may give clues to the pathogenesis of rheumatoid arthritis, and it raises new questions concerning the role of endogenous molecules with adjuvant properties in chronic inflammatory diseases.

In conclusion, arthritis induced with the cholesterol precursor squalene shares notable similarities with rheumatoid arthritis, and raises interesting questions concerning the role of endogenous molecules with adjuvant properties in chronic inflammatory diseases.

Full Report

http://www.ncbi.nlm.nih.gov/pmc/articles/PMC1850095/

“arthritis induced with the cholesterol precursor squalene shares notable similarities with rheumatoid arthritis, and raises interesting questions concerning the role of endogenous molecules with adjuvant properties in chronic inflammatory diseases.”

First International Conference on Metals & The Brain
September 20-23, 2000

From Neurochemistry to Neurodegeneration
University of Padova, Italy

Aluminum And Health

Recommendations

Aluminum is an environmentally abundant element to which we are all exposed. The neurotoxicity of this metal has been known for more than a century. More recently, it has been implicated as an etiological factor in some pathologies (including encephalopathy, bone disease, anemia) related to dialysis treatment . In addition, it has been hypothesized to be a cofactor in the etiopathogenesis of some neurodegenerative diseases, including Alzheimer's disease (AD), although, despite many studies in several laboratories in different countries, direct evidence is still, so far controversial. Thus, examples of aluminum neurotoxicity are well recognized-in experimental animals and in individuals with renal failure (consequent upon aging, intoxication or renal disease) - and there are grounds to link neurodegenerative disorders to aluminum exposure. Furthermore, an increased concentration of Al in infant formulas and in solutions for home parenteral nutrition has been associated with neurological consequences and metabolic bone disease, characterized by low-bone formation rate, respectively.

For all these reasons and on the basis of our many years of scientific experience in this field, we propose the following recommendations as guidelines to avoid risks due to aluminum accumulation and potential intoxication. These recommendations are not rigid and will be updated when relevant new scientific data is available.

General Recommendations

1. It would be valuable to define as completely as possible which patient groups are at risk for iatrogenic aluminum loading, and under which conditions aluminum represents a health hazard. The more complete knowledge we have for the clinical, iatrogenic setting, the better basis we will have to judge whether different types of aluminum exposure are hazardous to the general population or to susceptible subgroups.

2. A provisional list of patients groups at risk of iatrogenic aluminum loading should include, at least, people with impaired renal function, infants, old people and patients on total home parenteral nutrition. Where such exposure occurs, serum aluminum concentrations should be less than 30 µg/l and possibly lower. However, further studies are necessary.

3. Urinary aluminum is also an indicator of aluminum absorption, the excreted Al/retained Al ratio depends on the integrity of the renal function.

4. Al may enter human body by mouth, intravenous infusions and by environment. Specific controls have to be adopted in order to reduce each risk of exposure.

Oral Exposure

5. Aluminum in drinking water should be less than 50 µg L-1. Silicon is relevant to aluminum toxicity and, therefore, the water silicon concentrations should be monitored in parallel.

6. The aluminum content should be declared in all food preparations and pharmacological products.

7. Citrate-containing compounds appear to increase the bioavailability of ingested aluminum. Therefore, particular care should be taken to avoid these compounds in combination with Al-containing drugs. With citric acid, the enhanced gastrointestinal absorption may by compensated for by a parallel increase in urinary Al excretion, where there is good renal function. However, it is strongly suspected from recent simulation studies that other dietary acids (e.g., succinic and tartaric acids) also increase Al-bioavailability but do not cause any compensatory increase in urinary excretion. Ascorbate and lactate also significantly enhance gastrointestinal absorption of Al, as was recently demonstrated in animal studies.

8. It is recommended that acidic food, e.g., acid cabbage, tomato, etc. should not be cooked or stored in aluminum ware. In this connection, it has been demonstrated that in the juice of acidic cabbage, cooked in aluminum, the metal ion content is up to 20 mg/ L.

9. Individual susceptibility to aluminum has been reported by the scientific literature. Thus, special efforts should be taken to prevent contamination of food and beverages etc. with aluminum either directly or during preparation, with special regard to infants, old people or individuals with suboptimal renal functionality.

10. Magnesium depletion is considered a high risk for aluminum accumulation especially during pregnancy and in the neonate with possible consequent problems for normal development and growth. Magnesium depletion is also common with aging.

11. Iron depletion is considered a high risk for aluminium accumulation, as iron and Al share common carriers.

Parenteral Exposure

12. Aluminum in all intravenous (i.v.) fluids should be controlled monitored and labeled. There is a general consensus that the aluminum content of i.v. fluids used in children and adults with renal failure or undergoing dialysis, should be as low as possible and in any case no higher than 10 µg/L.

13. The use of parenteral nutrition fluids that are high in aluminum should be eliminated or significantly reduced.

This document will be published in relevant scientific journals, and will be sent to all Health Ministers of the European Community as well as to other Public Health Authorities. (FDA, WHO etc.). For further information, please contact Prof. P. Zatta: zatta@civ.bio.unipd.it

BMJ • December 2000

Routine vaccinations and child survival: follow up study in Guinea-Bissau, West Africa

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Contributors: IK supervised the last year of data collection and wrote the first draft of the paper. HJ supervised data control and carried out the statistical analyses. PA initiated the study, supervised data collection, carried out the first analyses, and wrote the final version of the paper. HJ and PA will act as guarantors.

Abstract

Objective
To examine the association between routine childhood vaccinations and survival among infants in Guinea-Bissau.

Design
Follow up study.

Participants
15 351 women and their children born during 1990 and 1996.

Setting
Rural Guinea-Bissau.

Main Outcome Measures
Infant mortality over six months (between age 0-6 months and 7-13 months for BCG, diphtheria, tetanus, and pertussis, and polio vaccines and between 7-13 months and 14-20 months for measles vaccine).

Results
Mortality was lower in the group vaccinated with any vaccine compared with those not vaccinated, the mortality ratio being 0.74 (95% confidence interval 0.53 to 1.03). After cluster, age, and other vaccines were adjusted for, BCG was associated with significantly lower mortality (0.55 (0.36 to 0.85)). However, recipients of one dose of diphtheria, tetanus, and pertussis or polio vaccines had higher mortality than children who had received none of these vaccines (1.84 (1.10 to 3.10) for diphtheria, tetanus, and pertussis). Recipients of measles vaccine had a mortality ratio of 0.48 (0.27 to 0.87). When deaths from measles were excluded from the analysis the mortality ratio was 0.51 (0.28 to 0.95). Estimates were unchanged by controls for background factors.

Conclusions
These trends are unlikely to be explained exclusively by selection biases since different vaccines were associated with opposite tendencies. Measles and BCG vaccines may have beneficial effects in addition to protection against measles and tuberculosis. Diphtheria, tetanus, and pertussis and polio vaccines were associated with higher infant mortality.

Full Report:
http://www.ncbi.nlm.nih.gov/pmc/articles/PMC27544/

“Diphtheria, tetanus, and pertussis and polio vaccines were associated with higher infant mortality.”

"... in rats, the pertussis component of DTPoP

acts on the cardiovascular system and disturbs its circadian rhythm."

Laboratory Animals • 2000

Disturbance of cardiovascular circadian rhythms by pertussis vaccine in freely-moving rats

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Summary

Vaccination of young children with diphtheria, tetanus, poliomyelitis and pertussis (DTPoP) vaccine is effective in preventing outbreaks of whooping cough but adverse events sometimes occur. This pilot study shows that in freely-moving rats, multiple treatment with DTPoP (at day 0 and day 5, 6 ml/kg i.v.) increased heart rate (HR) for 5 days after the first treatment and decreased diastolic blood pressure (DBP)for at least 26 days after the first treatment and inhibited the circadian rhythm of HR and DBP for at least 10 days. DTPo vaccine, containing no pertussis vaccine, was free of such effects. Thus, in rats, the pertussis component of DTPoP acts on the cardiovascular system and disturbs its circadian rhythm. The contribution of these findings to clinical adverse effects is as yet unknown and needs further research.

http://lan.sagepub.com/content/34/4/399.long

Veterinary Pathology • March 2001

Feline vaccine-associated fibrosarcoma: an ultrastructural study of 20 tumors 1996-1999

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Abstract

Twenty feline vaccine-associated sarcomas were examined by transmission electron microscopy. Tumors contained pleomorphic spindle cells, histiocytoid cells, and giant cells. Most tumors contained myofibroblasts, which had morphologic features similar to those of fibroblasts. These cells were further distinguished by subplasmalemmal dense plaques and thin cytoplasmic actin myofilaments organized as elongated bundles concentrated at irregular intervals forming characteristic dense bodies. Intracellular crystalline particulate material was found in 5 of the 20 tumors. Energy dispersive X-ray spectroscopy was used to identify the crystalline material within one tumor as aluminum-based. One tumor from a feline leukemia virus-infected cat contained budding and immature retroviral particles.

In one of the first reports of feline vaccine-associated sarcomas, dense crystalline material was recognized by electron microscopy within macrophages surrounding tumor cells.9 Subsequent electron-probe microanalytical studies demonstrated aluminum in the cytoplasm of the macrophages within these sarcomas, suggesting the role of aluminum-containing adjuvant as irritant in the pathogenesis of vaccine-associated sarcomas.9 The role of vaccine adjuvant in the etiopathogenesis of these tumors remains unclear. The most prevalent adjuvants used in licensed veterinary vaccines are aluminum salts and oil emulsions; all of these formulations are considered to act as depots for injected vaccines.1 Aluminum hydroxide adjuvants are used in many human and veterinary vaccines, presumably because of their safety and low cost. Aluminum has been detected at the site of subcutaneous injections for up to 1 year in animals.3 That the tissues collected in this study represented tumors that developed months to years after vaccination when the precise site of vaccination was unknown and that most tumors were several centimeters in diameter or greater at the time of excision suggest that a large amount of aluminum, indeed, was contained within these adjuvanted vaccines to allow its detection in randomly selected ultrathin (60–90 nm thick) tissue sections examined in the electron microscope.

The results of this study support previous morphologic observations of feline vaccine-associated sarcomas. The role of the myofibroblast in vaccine-associated sarcomas is unclear but perhaps reflects a continuum of the inflammatory response that characterizes, in part, these unique neoplasms. The role of adjuvant, similarly, in these tumors is unknown.

Full Report: http://vet.sagepub.com/content/38/2/196.long

“The results of this study support previous morphologic observations of feline vaccine-associated sarcomas. The role of the myofibroblast in vaccine-associated sarcomas is unclear but perhaps reflects a continuum of the inflammatory response that characterizes, in part, these unique neoplasms. The role of adjuvant, similarly, in these tumors is unknown.”

Brain • May 2001

Central nervous system disease in patients with macrophagic myofasciitis

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Abstract

Macrophagic myofasciitis (MMF), a condition newly recognized in France, is manifested by diffuse myalgias and characterized by highly specific myopathological alterations which have recently been shown to represent an unusually persistent local reaction to intramuscular injections of aluminium-containing vaccines. Among 92 MMF patients recognized so far, eight of them, which included the seven patients reported here, had a symptomatic demyelinating CNS disorder. CNS manifestations included hemisensory or sensorimotor symptoms (four out of seven), bilateral pyramidal signs (six out of seven), cerebellar signs (four out of seven), visual loss (two out of seven), cognitive and behavioural disorders (one out of seven) and bladder dysfunction (one out of seven). Brain T(2)-weighted MRI showed single (two out of seven) or multiple (four out of seven) supratentorial white matter hyperintense signals and corpus callosum atrophy (one out of seven). Evoked potentials were abnormal in four out of six patients and CSF in four out of seven. According to Poser's criteria for multiple sclerosis, the diagnosis was clinically definite (five out of seven) or clinically probable multiple sclerosis (two out of seven). Six out of seven patients had diffuse myalgias. Deltoid muscle biopsy showed stereotypical accumulations of PAS (periodic acid-Schiff)-positive macrophages, sparse CD8+ T cells and minimal myofibre damage. Aluminium-containing vaccines had been administered 3-78 months (median = 33 months) before muscle biopsy (hepatitis B virus: four out of seven, tetanus toxoid: one out of seven, both hepatitis B virus and tetanus toxoid: two out of seven). The association between MMF and multiple sclerosis-like disorders may give new insights into the controversial issues surrounding vaccinations and demyelinating CNS disorders. Deltoid muscle biopsy searching for myopathological alterations of MMF should be performed in multiple sclerosis patients with diffuse myalgias.

Full Report

http://brain.oxfordjournals.org/content/124/5/974

"Macrophagic myofasciitis (MMF), a condition newly recognized in France, is manifested by diffuse myalgias and characterized by highly specific myopathological alterations which have recently been shown to represent an unusually persistent local reaction to intramuscular injections of aluminium-containing vaccines. Among 92 MMF patients recognized so far, eight of them, which included the seven patients reported here, had a symptomatic demyelinating Central Nervous System disorder."

Current Atherosclerosis Reports • July 2001

Antiphospholipid syndrome, antiphospholipid antibodies, and atherosclerosis

Author information

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Abstract

The antiphospholipid syndrome is characterized by arterial and venous thrombosis, as well as pregnancy morbidity, in the presence of elevated levels of antiphospholipid antibodies. These autoantibodies have procoagulant activity, as they affect platelets, humoral coagulation factors, and endothelial cells. In addition, they are proatherogenic, as demonstrated by animal models and by the increased prevalence of cardiovascular diseases in patients with systemic lupus erythematosus and antiphospholipid syndrome. Moreover, antiphospholipid antibodies, including anticardiolipin, anti-b2-glycoprotein-I, and anti-oxidized low-density lipoprotein, are associated with atherosclerosis and its consequences in the general population as well. This autoimmune aspect of atherosclerosis in the presence or absence of an autoimmune disease suggests benefit from development of immunomodulating therapies.

http://www.ncbi.nlm.nih.gov/pubmed/?term=11389799

“The antiphospholipid syndrome is characterized by arterial and venous thrombosis, as well as pregnancy morbidity, in the presence of elevated levels of antiphospholipid antibodies.”

“Vaccine-related cardiorespiratory events are relatively common in preterm babies.”

Acta Paediatrica • August 2001

Adverse events following vaccination in premature infants

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Abstract

The aims of this study were to study the frequency, severity and types of adverse reactions following DPT/Hib (diphtheria and tetanus toxoids and pertussisHaemophilus influenzae type B conjugate) immunization in very preterm infants and to identify possible risk factors. Case notes of 45 preterm babies vaccinated in the neonatal intensive care unit between January 1993 and December 1998 were studied retrospectively. Birthweight, gestational age, duration of ventilation, oxygen dependency, timing of vaccination, weight, corrected gestation at vaccination and apparent adverse effects were noted. Apparent adverse events were noted in 17 of 45 (37.8%) babies: 9 (20%) had major events, i.e. apnoea, bradycardia or desaturations, and 8 (17.8%) had minor events, i.e. increased oxygen requirements, temperature instability, poor handling and feed intolerance. Babies with major events were significantly younger ($p<0.05$), had a lower postmenstrual age ($p < 0.05$) and weighed less ($p< 0.05$) at the time of vaccination compared with babies without major events. No differences in the mean birthweight, gestational age, duration of ventilation or oxygen dependency were found between the two groups. Age at vaccination of 70 days or less was significantly associated with increased risk ($p < 0.01$). Of 27 babies vaccinated at 70 days or less, 9 (33.3%) developed major events compared with none when vaccinated over 70d.

Conclusion

Vaccine-related cardiorespiratory events are relatively common in preterm babies. Problems were much more common if vaccine is administered at or before 70 d. These babies should therefore be monitored postvaccination. Further prospective studies are needed to clarify whether delaying vaccination offers protection against these adverse events.

http://onlinelibrary.wiley.com/doi/10.1111/j.1651-2227.2001.tb02457.x/abstract

Archives Of Virology • August 2001

Comparative analysis of host responses related to immunosuppression between measles patients and vaccine recipients with live attenuated measles vaccines

Author information

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Abstract

Measles virus infection induces a profound immunosuppression. We analyzed in a time-dependent manner peripheral bloods of one to two-year-old children immunized with live attenuated measles vaccines, compared with age-matched measles patients, for immunosuppression. In contrast to transient severe lymphopenia with measles patients, primarily due to extensive apoptosis of a broad spectrum of uninfected lymphocytes, neither apoptosis nor lymphopenia occurred with measles vaccine recipients. Increase in number and activation of NK cells, which might compensate for the lymphopenia in measles patients, were not found with the vaccinees. While cell surface expression of apoptosis-related molecules such as TNF-related apoptosis-inducing ligand (TRAIL), TRAIL-receptors, CD95(Fas) and Fas-ligand, and plasma interferon-gamma were increased for measles patients, they remained unchanged after vaccination. Plasma interleukin (IL)-18, which is responsible for inducing apoptosis in several infectious diseases, was increased predominantly with measles patients, whereas the increase remained marginal with the vaccinees. IL-10 was elevated transiently in both measles patients and vaccinees. Decrease in plasma IL-12, which is often correlated with T cell suppression, was not found for both cases. Serum IgM and IgG antibodies to measles virus were induced at lower titers in the vaccinees than measles patients. These results indicate that in contrast to wild-type measles virus, live measles vaccines hardly provoked host cytokine responses that lead to apoptotic cytolysis of uninfected lymphocytes, lymphopenia and immunosuppression, and thereby induced weaker immune responses to the virus.

http://www.ncbi.nlm.nih.gov/pubmed/?term=11448026

“These results indicate that in contrast to wild-type measles virus, live measles vaccines hardly provoked host cytokine responses that lead to apoptotic cytolysis of uninfected lymphocytes, lymphopenia and immunosuppression, and thereby induced weaker immune responses to the virus.”

Acta Paediatrica • August 2001

Adverse events following vaccination in premature infants

Author information

Sen S1, Cloete Y, Hassan K, Buss P.

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Abstract

The aims of this study were to study the frequency, severity and types of adverse reactions following DPT/Hib (diphtheria and tetanus toxoids and pertussis/Haemophilus influenzae type B conjugate) immunization in very preterm infants and to identify possible risk factors. Case notes of 45 preterm babies vaccinated in the neonatal intensive care unit between January 1993 and December 1998 were studied retrospectively. Birthweight, gestational age, duration of ventilation, oxygen dependency, timing of vaccination, weight, corrected gestation at vaccination and apparent adverse effects were noted. Apparent adverse events were noted in 17 of 45 (37.8%) babies: 9 (20%) had major events, i.e. apnoea, bradycardia or desaturations, and 8 (17.8%) had minor events, i.e. increased oxygen requirements, temperature instability, poor handling and feed intolerance. Babies with major events were significantly younger ($p < 0.05$), had a lower postmenstrual age ($p < 0.05$) and weighed less ($p < 0.05$) at the time of vaccination compared with babies without major events. No differences in the mean birthweight, gestational age, duration of ventilation or oxygen dependency were found between the two groups. Age at vaccination of 70 days or less was significantly associated with increased risk ($p < 0.01$). Of 27 babies vaccinated at 70 days or less, 9 (33.3%) developed major events compared with none when vaccinated over 70 days.

CONCLUSION:

Vaccine-related cardiorespiratory events are relatively common in preterm babies. Problems were much more common if vaccine is administered at or before 70 d. These babies should therefore be monitored postvaccination. Further prospective studies are needed to clarify whether delaying vaccination offers protection against these adverse events.

http://www.ncbi.nlm.nih.gov/pubmed/?term=11529542

“Vaccine-related cardiorespiratory events are relatively common in preterm babies. Problems were much more common if vaccine is administered at or before 70 days.”

Clinical Immunology • September 2001

Infection of human B lymphocytes with MMR vaccine induces IgE class switching

Author information

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Abstract

Circulating immunoglobulin E (IgE) is one of the characteristics of human allergic diseases including allergic asthma. We recently showed that infection of human B cells with rhinovirus or measles virus could lead to the initial steps of IgE class switching. Since many viral vaccines are live viruses, we speculated that live virus vaccines may also induce IgE class switching in human B cells. To examine this possibility, we selected the commonly used live attenuated measles mumps rubella (MMR) vaccine. Here, we show that infection of a human IgM(+) B cell line with MMR resulted in the expression of germline epsilon transcript. In addition, infection of freshly prepared human PBLs with this vaccine resulted in the expression of mature IgE mRNA transcript. Our data suggest that a potential side effect of vaccination with live attenuated viruses may be an increase in the expression of IgE.

http://www.ncbi.nlm.nih.gov/pubmed/11513549

"Circulating immunoglobulin E (IgE) is one of the characteristics of human allergic diseases including allergic asthma. We recently showed that infection of human B cells with rhinovirus or measles virus could lead to the initial steps of IgE class switching. Our data suggest that a potential side effect of vaccination with live attenuated viruses may be an increase in the expression of IgE."

[Based on these findings, the authors concluded that viral vaccines might be playing a role in the increasing incidence of asthma and other allergic diseases]

“From October 1998 to December 1999, 112 cases of intussusception were reported.”

Vaccine • September 2001

Data mining in the US Vaccine Adverse Event Reporting System (VAERS): early detection of intussusception and other events after rotavirus vaccination

Author Information

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Abstract

The Vaccine Adverse Event Reporting System (VAERS) is the US passive surveillance system monitoring vaccine safety. A major limitation of VAERS is the lack of denominator data (number of doses of administered vaccine), an element necessary for calculating reporting rates. Empirical Bayesian data mining, a data analysis method, utilizes the number of events reported for each vaccine and statistically screens the database for higher than expected vaccine-event combinations signaling a potential vaccine-associated event. This is the first study of data mining in VAERS designed to test the utility of this method to detect retrospectively a known side effect of vaccination–intussusception following rotavirus (RV) vaccine. From October 1998 to December 1999, 112 cases of intussusception were reported. The data mining method was able to detect a signal for RV-intussusception in February 1999 when only four cases were reported. These results demonstrate the utility of data mining to detect significant vaccine-associated events at early date. Data mining appears to be an efficient and effective computer-based program that may enhance early detection of adverse events in passive surveillance systems.

http://www.sciencedirect.com/science/article/pii/S0264410X01002377

Emerging Infectious Diseases • September 2001

Adaptation of Bordetella pertussis to vaccination: a cause for its reemergence?

Author information

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Abstract

In the Netherlands, as in many other western countries, pertussis vaccines have been used extensively for more than 40 years. Therefore, it is conceivable that vaccine-induced immunity has affected the evolution of Bordetella pertussis. Consistent with this notion, pertussis has reemerged in the Netherlands, despite high vaccination coverage. Further, a notable change in the population structure of B. pertussis was observed in the Netherlands subsequent to the introduction of vaccination in the 1950s. Finally, we observed antigenic divergence between clinical isolates and vaccine strains, in particular with respect to the surface-associated proteins pertactin and pertussis toxin. Adaptation may have allowed B. pertussis to remain endemic despite widespread vaccination and may have contributed to the reemergence of pertussis in the Netherlands.

Full Report

http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2631860/

“Adaptation may have allowed B. pertussis to remain endemic despite widespread vaccination and may have contributed to the reemergence of pertussis in the Netherlands.”

European Journal Of Immunology • October 2001

Immunization with the adjuvant MF59 induces macrophage trafficking and apoptosis

Author information

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Abstract

The mechanisms associated with the immunostimulatory activity of vaccine adjuvants are still poorly understood. We have undertaken a study to determine whether antigen-presenting cell trafficking is modified by administration of the submicron emulsion adjuvant MF59. We investigated the fate of inflammatory macrophages after intramuscular injection of the antigen herpes simplex virus gD2 with fluorescence-labeled MF59. A homogeneous population of macrophages infiltrated the muscle, internalized adjuvant and expressed markers characteristic of mature macrophages over a 48-h period. Macrophage influx to the injection site was reduced by 70% in mice deficient for the chemokine receptor 2 (CCR2). Two distinct cell populations were shown to contain fluorescence-labeled MF59 in the draining lymph node at 48 h post injection. The first population had a round morphology, exhibited bright fluorescence, was located in the subcapsular sinus, and was apoptotic. The second population had a dendritic morphology, was weakly fluorescent, and was located in the T cell area where adjuvant-containing apoptotic bodies identified by TUNEL labeling were present. We propose that lymph node-resident dendritic cells can acquire antigen and MF59 after intramuscular immunization by uptake of the apoptotic macrophages.

http://www.ncbi.nlm.nih.gov/pubmed/11592066

“We propose that lymph node-resident dendritic cells can acquire antigen and MF59 [squalene] after intramuscular immunization by uptake of the apoptotic macrophages.”

“There are significantly elevated risks

of febrile seizures after receipt of DTP vaccine or MMR vaccine ...”

CDC New England Journal Of Medicine • 2001

The Risk of Seizures after Receipt of Whole-Cell Pertussis or Measles, Mumps, and Rubella Vaccine

William E. Barlow, Ph.D., Robert L. Davis, M.D., M.P.H., John W. Glasser, Ph.D., M.P.H., Phillip H. Rhodes, Ph.D., Robert S. Thompson, M.D., John P. Mullooly, Ph.D., Steven B. Black, M.D., Henry R. Shinefield, M.D., Joel I. Ward, M.D., S. Michael Marcy, M.D., Frank DeStefano, M.D., Virginia Immanuel, M.P.H., John A. Pearson, M.D., Constance M. Vadheim, Ph.D., Viviana Rebolledo, B.S., Dimitri Christakis, M.D., M.P.H., Patti J. Benson, M.P.H., Ned Lewis, M.P.H., and Robert T. Chen, M.D.
for the Centers for Disease Control and Prevention Vaccine Safety Datalink Working Group

BACKGROUND

The administration of the diphtheria and tetanus toxoids and whole-cell pertussis (DTP) vaccine and measles, mumps, and rubella (MMR) vaccine has been associated with seizures. We studied the relation between these vaccinations and the risk of a first seizure, subsequent seizures, and neurodevelopmental disability in children.

METHODS

This cohort study was conducted at four large health maintenance organizations and included reviews of the medical records of children with seizures. We calculated the relative risks of febrile and nonfebrile seizures among 679,942 children after 340,386 vaccinations with DTP vaccine, 137,457 vaccinations with MMR vaccine, or no recent vaccination. Children who had febrile seizures after vaccination were followed to identify the risk of subsequent seizures and other neurologic disabilities.

RESULTS

Receipt of DTP vaccine was associated with an increased risk of febrile seizures only on the day of vaccination (adjusted relative risk, 5.70; 95 percent confidence interval, 1.98 to 16.42). Receipt of MMR vaccine was associated with an increased risk of febrile seizures 8 to 14 days after vaccination (relative risk, 2.83; 95 percent confidence interval, 1.44 to 5.55). Neither vaccination was associated with an increased risk of nonfebrile seizures. The number of febrile seizures attributable to the administration of DTP and MMR vaccines was estimated to be 6 to 9 and 25 to 34 per 100,000 children, respectively. As compared with other children with febrile seizures that were not associated with vaccination, the children who had febrile seizures after vaccination were not found to be at higher risk for subsequent seizures or neurodevelopmental disabilities.

CONCLUSIONS

There are significantly elevated risks of febrile seizures after receipt of DTP vaccine or MMR vaccine, but these risks do not appear to be associated with any long-term, adverse consequences.

http://www.nejm.org/doi/full/10.1056/NEJMoa003077

Toxicology In Vitro • February 2002

Formaldehyde cytotoxicity in three human cell types assessed in three different assays

Author information

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Abstract

International standards for preclinical screening of the cytotoxicity of dental materials so far recommend the use of established cell lines. The aim of this study was to assess the relative susceptibility of human dental pulp fibroblasts (HPF), human buccal epithelial cells (HBE) and HeLa cervix cancer cells exposed to identical cytotoxic challenges. Formaldehyde, which may be released from dental materials such as dental composites, glassionomer cements, and endodontic sealers, was used as test chemical. Cytotoxicity data including dose-response relations and TC(50) values were assessed in three different assays: BrdU incorporation, neutral red uptake and MTT assays. HBE and HPF demonstrated statistically significant lower TC(50) values in both the neutral red and the BrdU assay in comparison to HeLa cells. In the MTT assay no statistically significant differences were observed between the cell types. In the two target-tissue cell types (HPF and HBE) the Neutral Red assay revealed lower TC(50) values in comparison to the BrdU assay. In HeLa cells no statistically significant differences were observed between the assays. In conclusion, the present study confirms that cytotoxicity data obtained by cell culture studies are influenced by both cell culture model and choice of assay. Under identical experimental conditions, human target tissue cells appeared to be more sensitive to formaldehyde toxicity than human HeLa cancer cells.

http://www.ncbi.nlm.nih.gov/pubmed/?term=11812641

“Under identical experimental conditions, human target tissue cells appeared to be more sensitive to formaldehyde toxicity than human HeLa cancer cells.”

“antivaccination activists use: highly emotive content,

conspiratorial claims and privately published material and newspapers articles ...”

[the reason for the publication of this eBook]

Archives Of Disease In Childhood • March 2002

Antivaccination activists on the world wide web

Author Information

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Abstract

Aims

To determine the likelihood of finding an antivaccination site on the world wide web and to characterise their explicit claims and rhetorical appeals.

Methods

Using “vaccination” and “immunisation”, examining the first 10 sites displayed on seven leading search engines. Detailed examination of content of 100 antivaccination sites found on Google.

Results

43% of websites were antivaccination (all of the first 10 on Google). Main rhetorical appeals involve themes of the scientific veracity of antivaccination argument; rapport with parents seeking to protect their children from harm; and alleged collusion between doctors, the pharmaceutical industry, and government to deny vaccine harm.

Conclusions

There is a high probability that parents will encounter elaborate antivaccination material on the world wide web. Factual refutational strategies alone are unlikely to counter the highly rhetorical appeals that shape these sites.Campaigns by those opposed to immunisation have been followed by falling immunisation rates and outbreaks of vaccine preventable disease.1 The internet has provided antivaccinationists with unprecedented opportunities for exposure. In the USA, 55% of adults with internet access use it to seek health related information.2 For all its benefits, the internet has great potential to disseminate health information that is incorrect and potentially dangerous.3 To date, all studies on health information on the internet have assessed content against a priori standards of evidence, and have not considered the rhetorical subtexts and wider social discourses in which this information is embedded.4,5 We examined the content of 100 antivaccination websites, considering not only the explicit claims made about vaccination, but also the ways these claims are framed to maximise their appeal and influence.

Response to the problem

To defuse conspiratorial claims the public should be made aware of efforts to address the issue of vaccine safety through more active surveillance of adverse events and studies investigating hypothesised links between vaccination and serious chronic diseases.9,10 Since antivaccination websites share many of the characteristics we have described, the themes identified in this article might act as a tool for parents to discern whether the source is trustworthy. The checklist might include:

- Highly emotive content
- Conspiratorial claims
- Privately published material, newspapers articles, etc., given as sources of information
- Claims to have privileged information unknown to medical authorities

Where refuting antivaccination arguments on the basis of fact alone is insufficient, it may be possible to use similarly emotive tactics to promote immunisation. Emphasis could be given to images and stories of children harmed by vaccine preventable illnesses (see, for example, http://www.immunize.org/stories/unprot.htm).

Full Report: http://adc.bmj.com/content/87/1/22.full

“Several recent epidemiological studies have shown that vaccinations against biological warfare using pertussis as an adjuvant were associated with the Gulf war syndrome.”

Medical Hypotheses • April 2002

Gulf war syndrome: could it be triggered by biological warfare-vaccines using pertussis as an adjuvant?

Author information

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Abstract

Several recent epidemiological studies have shown that vaccinations against biological warfare using pertussis as an adjuvant were associated with the Gulf war syndrome. If such epidemiological findings are confirmed, we propose that the use of pertussis as an adjuvant could trigger neurodegeneration through induction of interleukin-1beta secretion in the brain. In turn, neuronal lesions may be sustained by stress or neurotoxic chemical combinations. Particular susceptibility for IL-1beta secretion and potential distant neuronal damage could provide an explanation for the diversity of the symptoms observed on veterans.

http://www.ncbi.nlm.nih.gov/pubmed/12027522

The Journal of Infection • May 2002

The effect of vaccination on the epidemiology of varicella zoster virus

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Abstract

Varicella zoster virus (VZV) causes chickenpox (varicella) on primary exposure and can reactivate later in life to cause shingles (zoster). As primary infection is more serious in adults than children, and exposure to the virus might boost the immune response to both chickenpox and shingles, there are two main concerns regarding infant VZV vaccination: that it could lead to an increase in adult disease; and/or that it could lead to a temporary increase in the incidence of shingles. This paper reviews the evidence for such outcomes. The consensus view of mathematical modelling studies is that the overall varicella associated burden is likely to decrease in the long term, regardless of the level of vaccine coverage. On the other hand, recent evidence suggests that an increase in zoster incidence appears likely, and the more effective vaccination is at preventing varicella, the larger the increase in zoster incidence. Targeted vaccination of susceptible adolescents and/or the contacts of high-risk individuals can be effective at preventing disease in these individuals with minimal risk to the community. However, targeted strategies would not prevent most disease (including most severe disease), and will not lead to a long-term reduction in the incidence of zoster. Understanding the mechanisms for maintaining immunity against varicella and zoster is critical for predicting the long-term effects of vaccination. Meanwhile sensitive surveillance of both chickenpox and shingles is essential in countries that have implemented, or are about to implement, varicella vaccination.

http://www.ncbi.nlm.nih.gov/pubmed/12099726

“... recent evidence suggests that an increase in zoster [shingles] incidence appears likely, and the more effective vaccination is at preventing varicella, the larger the increase in zoster incidence.”

[varicella is chicken pox]

Current Opinions In Neurology • June 2002

Neurological adverse events associated with vaccination

Author information

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Abstract

Public tolerance to adverse reactions is minimal. Several reporting systems have been established to monitor adverse events following immunization. The present review summarizes data on neurologic complications following vaccination, and provides evidence that indicates whether they were directly associated with the vaccines. These complications include autism (measles vaccine), multiple sclerosis (hepatitis B vaccine), meningoencephalitis (Japanese encephalitis vaccine), Guillain-Barré syndrome and giant cell arteritis (influenza vaccine), and reactions after exposure to animal rabies vaccine. Seizures and hypotonic/hyporesponsive episodes following pertussis vaccination and potential risks associated with varicella vaccination, as well as vaccine-associated paralytic poliomyelitis following oral poliovirus vaccination, are also described. In addition, claims that complications are caused by adjuvants, preservatives and contaminants [i.e. macrophagic myofasciitis (aluminium), neurotoxicity (thimerosal), and new variant Creutzfeldt-Jakob disease (bovine-derived materials)] are discussed.

http://www.ncbi.nlm.nih.gov/pubmed/?term=12045734

“These complications include autism (measles vaccine), multiple sclerosis (hepatitis B vaccine), meningoencephalitis (Japanese encephalitis vaccine), Guillain-Barré syndrome and giant cell arteritis (influenza vaccine), and reactions after exposure to animal rabies vaccine. Seizures and hypotonic/hyporesponsive episodes following pertussis vaccination and potential risks associated with varicella vaccination, as well as vaccine-associated paralytic poliomyelitis following oral poliovirus vaccination, are also described.”

“The present review summarizes data on neurologic complications following vaccination ...”

Current Opinion in Neurology • June 2002

Neurological adverse events associated with vaccination

Piyasirisilp, Sucheepa; Hemachudha, Thiravatb

Abstract

Public tolerance to adverse reactions is minimal. Several reporting systems have been established to monitor adverse events following immunization. The present review summarizes data on neurologic complications following vaccination, and provides evidence that indicates whether they were directly associated with the vaccines. These complications include autism (measles vaccine), multiple sclerosis (hepatitis B vaccine), meningoencephalitis (Japanese encephalitis vaccine), Guillain-Barré syndrome and giant cell arteritis (influenza vaccine), and reactions after exposure to animal rabies vaccine. Seizures and hypotonic/hyporesponsive episodes following pertussis vaccination and potential risks associated with varicella vaccination, as well as vaccine-associated paralytic poliomyelitis following oral poliovirus vaccination, are also described. In addition, claims that complications are caused by adjuvants, preservatives and contaminants [i.e. macrophagic myofasciitis (aluminium), neurotoxicity (thimerosal), and new variant Creutzfeldt-Jakob disease (bovine-derived materials)] are discussed.

http://www.ncbi.nlm.nih.gov/pubmed/12045734

Journal Of Biomedical Science • July 2002

Abnormal measles-mumps-rubella antibodies and CNS autoimmunity in children with autism

Author information

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Abstract

Autoimmunity to the central nervous system (CNS), especially to myelin basic protein (MBP), may play a causal role in autism, a neurodevelopmental disorder. Because many autistic children harbor elevated levels of measles antibodies, we conducted a serological study of measles-mumps-rubella (MMR) and MBP autoantibodies. Using serum samples of 125 autistic children and 92 control children, antibodies were assayed by ELISA or immunoblotting methods. ELISA analysis showed a significant increase in the level of MMR antibodies in autistic children. Immunoblotting analysis revealed the presence of an unusual MMR antibody in 75 of 125 (60%) autistic sera but not in control sera. This antibody specifically detected a protein of 73-75 kD of MMR. This protein band, as analyzed with monoclonal antibodies, was immunopositive for measles hemagglutinin (HA) protein but not for measles nucleoprotein and rubella or mumps viral proteins. Thus the MMR antibody in autistic sera detected measles HA protein, which is unique to the measles subunit of the vaccine. Furthermore, over 90% of MMR antibody-positive autistic sera were also positive for MBP autoantibodies, suggesting a strong association between MMR and CNS autoimmunity in autism. Stemming from this evidence, we suggest that an inappropriate antibody response to MMR, specifically the measles component thereof, might be related to pathogenesis of autism.

http://www.ncbi.nlm.nih.gov/pubmed/12145534

“... over 90% of MMR antibody-positive autistic sera were also positive for MBP autoantibodies, suggesting a strong association between MMR and CNS autoimmunity in autism. Stemming from this evidence, we suggest that an inappropriate antibody response to MMR, specifically the measles component thereof, might be related to pathogenesis of autism.”

“The results indicated that whole-cell DTP vaccine contained high levels of endotoxin and was statistically significantly more reactogenic than acellular DTaP vaccine.”

Pediatric Rehabilitation • July 2002

Serious neurological conditions following pertussis immunization: an analysis of endotoxin levels, the vaccine adverse events reporting system (VAERS) database and literature review

Author information

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Abstract

The purpose of this study was to determine the potential risks for the development and outcome of serious neurological illnesses following whole-cell DTP vaccination and also to determine if the switch to using acellular DTaP vaccine in the US has had any effect on the incidence rate of serious neurological illnesses following vaccination. This study used the Limulus amebocyte lysate (LAL) endotoxin assay to determine the levels of endotoxin in various commercially available whole-cell and acellular DTaP vaccines, analysed the Vaccine Adverse Events Reporting System (VAERS) database to determine the clinical effects of the use of whole-cell DTP and acellular DTaP vaccines in the US and reviewed recently published pertinent studies that analysed the incidence rates of serious neurological illness following whole-cell DTP and acellular DTaP vaccines. The results indicated that whole-cell DTP vaccine contained high levels of endotoxin and was statistically significantly more reactogenic than acellular DTaP vaccine. The presence of bias in the VAERS database was not borne-out. The recommendation by the American Academy of Paediatrics to use acellular DTaP vaccine for the entire childhood vaccination schedule beginning in 1996 and the absence of the availability of whole-cell DTP in the US beginning in 2001 seems well justified based upon the results of this study.

http://www.ncbi.nlm.nih.gov/pubmed/12587565

Experimental And Molecular Pathology • August 2002

Antibodies to squalene in recipients of anthrax vaccine

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Abstract

We previously reported that antibodies to squalene, an experimental vaccine adjuvant, are present in persons with symptoms consistent with Gulf War Syndrome (GWS) (P. B. Asa et al., Exp. Mol. Pathol 68, 196-197, 2000). The United States Department of Defense initiated the Anthrax Vaccine Immunization Program (AVIP) in 1997 to immunize 2.4 million military personnel. Because adverse reactions in vaccinated personnel were similar to symptoms of GWS, we tested AVIP participants for anti-squalene antibodies (ASA). In a pilot study, 6 of 6 vaccine recipients with GWS-like symptoms were positive for ASA. In a larger blinded study, only 32% (8/25) of AVIP personnel compared to 15.7% (3/19) of controls were positive ($P > 0.05$). Further analysis revealed that ASA were associated with specific lots of vaccine. The incidence of ASA in personnel in the blinded study receiving these lots was 47% (8/17) compared to an incidence of 0% (0/8; $P < 0.025$) of the AVIP participants receiving other lots of vaccine. Analysis of additional personnel revealed that in all but one case (19/20; 95%), ASA were restricted to personnel immunized with lots of vaccine known to contain squalene. Except for one symptomatic individual, positive clinical findings in 17 ASA-negative personnel were restricted to 4 individuals receiving vaccine from lots containing squalene. ASA were not present prior to vaccination in preimmunization sera available from 4 AVIP personnel. Three of these individuals became ASA positive after vaccination. These results suggest that the production of ASA in GWS patients is linked to the presence of squalene in certain lots of anthrax vaccine.

http://www.ncbi.nlm.nih.gov/pubmed/12127050

“Three of these individuals became anti-squalene antibody positive after vaccination. These results suggest that the production of anti-squalene antibody in Gulf War Syndrome patients is linked to the presence of squalene in certain lots of anthrax vaccine.”

Laboratory Medicine • September 2002

Vaccines and Autism

by Bernard Rimland, PhD, Woody McGinnis, MD

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Abstract

Autism research is characterized by diverse findings. There is no consensus about the biological determinants of autism. This paper examines the autistic immune profile and the possible role of vaccines in autism.

Vaccinations may be one of the triggers for autism. Substantial data demonstrate immune abnormality in many autistic children consistent with impaired resistance to infection, activation of inflammatory response, and autoimmunity. Impaired resistance may predispose to vaccine injury in autism.

A mercurial preservative in childhood vaccines, thimerosal, may cause direct neurotoxic, immunodepressive, and autoimmune injury and contribute to early-onset and regressed autism. Live viruses in measles, mumps, and rubella (MMR) may result in chronic infection of the gut and trigger regressed autism. Thimerosal injection may potentiate MMR injury.

Consideration of vaccine etiology must include recognition of compromised gut and nutrition in most autistic children. An integrated view of the underlying biological problems in autistic children serves our understanding of the possible role of vaccines. Development of screening methods for deferral of vaccines in at-risk children is a worthy goal.

http://labmed.oxfordjournals.org/content/labmed/33/9/708.full.pdf

“Vaccinations may be one of the triggers for autism. Substantial data demonstrate immune abnormality in many autistic children consistent with impaired resistance to infection, activation of inflammatory response, and autoimmunity. Impaired resistance may predispose to vaccine injury in autism.

A mercurial preservative in childhood vaccines, thimerosal, may cause direct neurotoxic, immunodepressive, and autoimmune injury and contribute to early-onset and regressed autism. Live viruses in measles, mumps, and rubella (MMR) may result in chronic infection of the gut and trigger regressed autism. Thimerosal injection may potentiate MMR injury.”

Journal Of Pharmaceutical Sciences • October 2002

Peroxide formation in polysorbate 80 and protein stability

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Abstract

Nonionic surfactants are widely used in the development of protein pharmaceuticals. However, the low level of residual peroxides in surfactants can potentially affect the stability of oxidation-sensitive proteins. In this report, we examined the peroxide formation in polysorbate 80 under a variety of storage conditions and tested the potential of peroxides in polysorbate 80 to oxidize a model protein, IL-2 mutein. For the first time, we demonstrated that peroxides can be easily generated in neat polysorbate 80 in the presence of air during incubation at elevated temperatures. Polysorbate 80 in aqueous solution exhibited a faster rate of peroxide formation and a greater amount of peroxides during incubation, which is further promoted/catalyzed by light. Peroxide formation can be greatly inhibited by preventing any contact with air/oxygen during storage. IL-2 mutein can be easily oxidized both in liquid and solid states. A lower level of peroxides in polysorbate 80 did not change the rate of IL-2 mutein oxidation in liquid state but significantly accelerated its oxidation in solid state under air. A higher level of peroxides in polysorbate 80 caused a significant increase in IL-2 mutein oxidation both in liquid and solid states, and glutathione can significantly inhibit the peroxide-induced oxidation of IL-2 mutein in a lyophilized formulation. In addition, a higher level of peroxides in polysorbate 80 caused immediate IL-2 mutein oxidation during annealing in lyophilization, suggesting that implementation of an annealing step needs to be carefully evaluated in the development of a lyophilization process for oxidation-sensitive proteins in the presence of polysorbate.

http://www.ncbi.nlm.nih.gov/pubmed/?term=12226852

“For the first time,

we demonstrated that

peroxides can be easily generated

in neat polysorbate 80 ...”

Vaccine • November 2002

Routine vaccinations and child survival in a war situation with high mortality: effect of gender

Author information

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Abstract

Non-specific effects of vaccination may be different for boys and girls. Due to the sequential administration of vaccines, it is difficult to separate the effect of different vaccines. We tested sex-specific effects of diphtheria, tetanus, pertussis (DTP) and polio vaccines and measles vaccines during the recent war (1998) in Guinea-Bissau when there was no functioning immunisation programme in the country. The study included 1491 children aged 1-17 months in four urban districts in Bissau. Vaccination status had been assessed in the study area in the 3 months before the war. The effect of DTP and polio vaccines was assessed for children who had not received measles vaccine. The effect of measles vaccine was evaluated for children aged 6-17 months. Compared with measles-unvaccinated children, measles-vaccinated children had lower mortality (mortality ratio (MR)=0.44 (95% CI 0.20-1.00)), the difference being marked for girls (0.25 (0.09-0.71)) but not for boys (0.84 (0.26-2.75)) (test of homogeneity, P=0.095). If measles cases were censored in the analysis, the mortality ratio for vaccinated and unvaccinated children was 0.38 (0.16-0.89). DTP and polio-vaccinated children did not have lower mortality than unvaccinated children. The female-male mortality ratio for DTP and polio-vaccinated children was 3.08 (1.11-8.56) and 0.63 (0.28-1.40) for measles-vaccinated children, a significant inversion of the ratios (test of homogeneity, P=0.013). The divergent female-male mortality ratios are unlikely to be explained by a selection bias going in different directions for different vaccines. The reduction associated with measles vaccination was unrelated to prevention against measles infection. Non-specific effects of vaccination should be assessed separately for boys and girls. Taking these effects into consideration may have implications for child mortality patterns in developing countries.

http://www.ncbi.nlm.nih.gov/pubmed/12443658

“The divergent female-male mortality ratios are unlikely to be explained by a selection bias going in different directions for different vaccines. Non-specific effects of vaccination should be assessed separately for boys and girls.”

Diabetes • December 2002

The rise of childhood type 1 diabetes in the 20th century

Author information

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Abstract

The incidence of childhood type 1 diabetes increased worldwide in the closing decades of the 20th century, but the origins of this increase are poorly documented. A search through the early literature revealed a number of useful but neglected sources, particularly in Scandinavia. While these do not meet the exacting standards of more recent surveys, tentative conclusions can be drawn concerning long-term changes in the demography of the disease. Childhood type 1 diabetes was rare but well recognized before the introduction of insulin. Low incidence and prevalence rates were recorded in several countries over the period 1920-1950, and one carefully performed study showed no change in childhood incidence over the period 1925-1955. An almost simultaneous upturn was documented in several countries around the mid-century. The overall pattern since then is one of linear increase, with evidence of a plateau in some high-incidence populations and of a catch-up phenomenon in some low-incidence areas. Steep rises in the age-group under 5 years have been recorded recently. The disease process underlying type 1 diabetes has changed over time and continues to evolve. Understanding why and how this produced the pandemic of childhood diabetes would be an important step toward reversing it.

http://www.ncbi.nlm.nih.gov/pubmed/12453886

“Understanding why and how this produced the pandemic of childhood diabetes would be an important step toward reversing it.”

"... probably because the pertussis component of most currently available acellular DPT vaccines contains toxoided pertussis toxin that has a significant rate of reversion to active toxin."

Toxicology Mechanisms And Methods • 2002

An analysis of the occurrence of convulsions and death after childhood vaccination

Author information

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Abstract

The association between the whole-cell diphtheria, tetanus, and pertussis (DTP) vaccine and the occurrence of convulsions and death has long been debated by the medical and scientific communities. A certified copy of the Vaccine Adverse Events Reporting System database was obtained from the Centers for Disease Control, and the data were analyzed using the Microsoft Access program. The results of this analysis reveal a statistically ($p < .01$) higher rate of occurrence of convulsions and death after whole-cell DTP vaccination than after acellular DTP and DT vaccination, showing, as do the previous findings of many other scientists, that acellular DTP vaccine is much less reactogenic than is whole-cell DTP vaccine. This study helps to validate the decision by American vaccine manufactures and the Food and Drug Administration to use only acellular DTP for the American childhood vaccination schedule. However, acellular DTP vaccine is still more reactogenic than is DT vaccine, probably because the pertussis component of most currently available acellular DPT vaccines contains toxoided pertussis toxin that has a significant rate of reversion to active toxin. This suggests the need to use the newer acellular pertussis vaccines, which are of higher purity and in which the reversion of the pertussis toxin is prevented.

http://www.ncbi.nlm.nih.gov/pubmed/20597817

“DTP and MMR vaccine are associated with a transiently increased risk of febrile seizures ...”

Paediatric Drugs • 2003

Placing the risk of seizures with pediatric vaccines in a clinical context

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Abstract

In this review we discuss the relationship between commonly administered childhood vaccines such as diphtheria-tetanus-whole cell pertussis (DTP) and measles-mumps-rubella (MMR), and the risk of nonfebrile and febrile seizure. We summarize data from the Vaccine Safety Datalink Study and other studies that suggest that DTP and MMR vaccine are associated with a transiently increased risk of febrile seizures, and cause between 5-9 and 25-34 additional extra febrile seizures per 100 000 immunized children, respectively. DTP and MMR do not appear to increase the risk of nonfebrile seizures. We discuss some methodologic challenges in studies of vaccines and seizures. Because there is no adequate comparison group that would allow for the study of seizures long after vaccination, studies of seizures are limited to acute events shortly following vaccination. Additionally, while seizures following vaccination are worrisome to parents and physicians alike, observational studies of the neurodevelopmental outcomes of these children are particularly problematic. We discuss how such studies are confounded by the natural history of predisposition to febrile seizures and by the increased diagnostic scrutiny that children with febrile seizures might undergo. Nevertheless, current data suggest that children with febrile seizures do not experience long-term negative effects. Finally, we discuss the creation of new clinics designed specifically to assist physicians in managing the vaccination of children with a personal or family history of seizures. Data from these clinics suggest that vaccination is safe for children with a personal or family history of seizures, but statistical power has been limited. We conclude by discussing the introduction of new vaccines, and note that, even with widespread use, it will take many years before we can be knowledgeable about the risk of rare events with these newly licensed products.

http://www.ncbi.nlm.nih.gov/pubmed/?term=14580221

International Pediatrics • Vol. 18 • No. 2 • 2003

by Mark R. Geier, MD, PhD; David A Geier

Pediatric MMR Vaccination Safety

Abstract

Measles, mumps and rubella are viral infections that have the potential to result in globally destructive disorders. Measles, mumps and rubella (MMR) vaccine has helped to dramatically reduce the number of cases of measles, mumps and rubella infection, as well as to reduce the amount of pain and suffering associated with each of these natural infections. The purpose of this study was to analyze the incidence of serious neurologic disorders in a comparative examination between MMR vaccine and a vaccine control group. The Vaccine Adverse Events Reporting System (VAERS) database was analyzed for the incidence rate of permanent brain damage, cerebellar ataxia, autism and mental retardation reported following MMR vaccine and diphtheria, tetanus and whole-cell pertussis (DTwcP) containing-vaccines from 1994 through 2000 in the US.

Statistically significant increases in the incidence of serious neurologic disorders following pediatric MMR vaccine in comparison to DTwcP vaccine were found. The potentially globally destructive effects of natural measles, mumps and rubella infections means that continued vaccination is necessary, but improvements in MMR vaccines are needed to improve its safety.

These results show that primary pediatric MMR vaccination in children is associated with a marked increase in serious neurologic disorders in comparison to DTwcP vaccination. The increase is statistically significant for cerebellar ataxia, autism, mental retardation and permanent brain damage following primary pediatric MMR vaccination in comparison to DTwcP vaccination. These results are remarkable considering that DTwcP vaccination has been found by the scientific and medical communities to be responsible for permanent neurologic sequellae in children.

Another study found 18 cases of neurological complications following live measles vaccine administered between 1971 to 1978 in Hamburg, Germany. A causal connection was assumed by the author in 14 of the cases, resulting in an incidence of 1 per 2,500 vaccinees. The author observed an incidence of 1 per 17,650 vaccinees of abortive encephalopathy following live measles vaccination.

In conclusion, this study showed a highly statistically significant increase in serious neurologic conditions following primary pediatric MMR vaccination in comparison to a DTwcP vaccine control group. This finding confirms and extends a number of previous studies showing that patients are at increased risk for developing serious neurologic disorders for about 5-10 days following pediatric MMR vaccination. The pathogenesis of these reactions appears to follow a similar course as in the natural viral infections. In order to alleviate the potential for serious neurologic disorders following primary pediatric MMR vaccination, we recommend that killed MMR vaccine be made available. If live MMR vaccine is to be used, parents should have the option to have each viral component of MMR vaccine administered separately.

http://www.tested.net/vaccine/MMRresearch.pdf

“These results show that primary pediatric MMR vaccination in children is associated with a marked increase in serious neurologic disorders in comparison to DTwcP vaccination. The increase is statistically significant for cerebellar ataxia, autism, mental retardation and permanent brain damage following primary pediatric MMR vaccination in comparison to DTwcP vaccination. These results are remarkable considering that DTwcP vaccination has been found by the scientific and medical communities to be responsible for permanent neurologic sequellae in children.”

Revue Neurologique, Paris • February 2003

Lessons from macrophagic myofasciitis: towards definition of a vaccine adjuvant-related syndrome

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Abstract

Macrophagic myofasciitis is a condition first reported in 1998, which cause remained obscure until 2001. Over 200 definite cases have been identified in France, and isolated cases have been recorded in other countries. The condition manifests by diffuse myalgias and chronic fatigue, forming a syndrome that meets both Center for Disease Control and Oxford criteria for the so-called chronic fatigue syndrome in about half of patients. One third of patients develop an autoimmune disease, such as multiple sclerosis. Even in the absence of overt autoimmune disease they commonly show subtle signs of chronic immune stimulation, and most of them are of the HLADRB1*01 group, a phenotype at risk to develop polymyalgia rheumatica and rheumatoid arthritis. Macrophagic myofasciitis is characterized by a stereotyped and immunologically active lesion at deltoid muscle biopsy. Electron microscopy, microanalytical studies, experimental procedures, and an epidemiological study recently demonstrated that the lesion is due to persistence for years at site of injection of an aluminum adjuvant used in vaccines against hepatitis B virus, hepatitis A virus, and tetanus toxoid. Aluminum hydroxide is known to potently stimulate the immune system and to shift immune responses towards a Th-2 profile. It is plausible that persistent systemic immune activation that fails to switch off represents the pathophysiologic basis of chronic fatigue syndrome associated with macrophagic myofasciitis, similarly to what happens in patients with post-infectious chronic fatigue and possibly idiopathic chronic fatigue syndrome. Therefore, the WHO recommended an epidemiological survey, currently conducted by the French agency AFSSAPS, aimed at substantiating the possible link between the focal macrophagic myofasciitis lesion (or previous immunization with aluminium-containing vaccines) and systemic symptoms. Interestingly, special emphasis has been put on Th-2 biased immune responses as a possible explanation of chronic fatigue and associated manifestations known as the Gulf war syndrome. Results concerning macrophagic myofasciitis may well open new avenues for etiologic investigation of this syndrome. Indeed, both type and structure of symptoms are strikingly similar in Gulf war veterans and patients with macrophagic myofasciitis. Multiple vaccinations performed over a short period of time in the Persian gulf area have been recognized as the main risk factor for Gulf War syndrome. Moreover, the war vaccine against anthrax, which is administered in a 6-shot regimen and seems to be crucially involved, is adjuvanted by aluminium hydroxide and, possibly, squalene, another Th-2 adjuvant. If safety concerns about long-term effects of aluminium hydroxide are confirmed it will become mandatory to propose novel and alternative vaccine adjuvants to rescue vaccine-based strategies and the enormous benefit for public health they provide worldwide.

http://www.ncbi.nlm.nih.gov/pubmed/12660567

“Macrophagic myofasciitis is a condition first reported in 1998, which cause remained obscure until 2001. Over 200 definite cases have been identified in France, and isolated cases have been recorded in other countries [many thousands of cases have since been identified]. Electron microscopy, microanalytical studies, experimental procedures, and an epidemiological study recently demonstrated that the lesion is due to persistence for years at site of injection of an aluminum adjuvant used in vaccines against hepatitis B virus, hepatitis A virus, and tetanus toxoid ... If safety concerns about long-term effects of aluminium hydroxide are confirmed it will become mandatory to propose novel and alternative vaccine adjuvants to *rescue* vaccine-based strategies ...”

Arthritis & Rheumatism • February 2003

Chronic fatigue syndrome in patients with macrophagic myofasciitis

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Julien Champey MD, Irène Drogou MD, Michèle Coquet MD andRomain K. Gherardi MD

Abstract

Macrophagic myofasciitis (MMF), a condition first reported in France in 1998, is defined by the presence of a stereotyped and immunologically active lesion at deltoid muscle biopsy (1, 2). It was recently demonstrated that this lesion is an indicator of long-term persistence of the immunologic adjuvant aluminum hydroxide within the cytoplasm of macrophages at the site of previous intramuscular (IM) injection (2). MMF is typically detected in patients with diffuse arthromyalgias that have appeared subsequent to aluminum hydroxide administration in the absence of a clearly defined anatomic substratum (2). Patients also report unexplained chronic fatigue (1). These manifestations are reminiscent of the so-called chronic fatigue syndrome (CFS), a poorly understood condition manifesting as disabling fatigue, musculoskeletal pain, sleep disturbance, impaired concentration, and headaches (3). The present study was conducted to determine the proportion of MMF patients fulfilling international criteria for CFS.

Thirty unselected consecutive patients with biopsy-proven MMF identified in Créteil and Bordeaux were retrospectively included, regardless of symptoms that led to indication of muscle biopsy. As previously described (2), MMF was assessed by 1) well-circumscribed sheets of densely-packed, large, nonepithelioid macrophages with a finely granular, periodic acid–Schiff–positive content, in the connective structures of deltoid muscle; 2) lymphocytic infiltrates intermingled with macrophages and forming microvascular cuffs; and 3) absence of significant muscle fiber injury (see Figure 1). In each patient, we determined, through both chart review and either direct patient questioning or telephone interview, 1) the presence of chronic fatigue of >6 months' duration, 2) the alleged severity of fatigue, and 3) the presence of CFS according to Centers for Disease Control and Prevention (CDC) criteria (1994) (4) or Oxford criteria (1991) (5). In addition, in 20 patients, we retrospectively evaluated history of immunization as well as prevalence of fever and neurologic features suggestive of central nervous system demyelinating disease; laboratory findings, including erythrocyte sedimentation rate, creatine kinase levels, and 67Ga scintigraphy; and responsiveness to steroids.

Figure 1. Deltoid muscle biopsy samples from patients with macrophagic myofasciitis (MMF). A, Tightly packed, large, basophilic macrophages intermingled with lymphocytes in perifascicular endomysium (frozen section, hematoxylin and eosin stained; original magnification ×400). B, MMF lesion in perimuscular adipose tissue showing immunolocalization of the macrophage marker CD68 (paraffin section, immunoperoxidase procedure; original magnification ×400). C, Adjacent section of the same biopsy sample showing immunolocalization of the T cell marker CD3 (paraffin section, immunoperoxidase procedure; original magnification ×400).

The male:female ratio was 1:2. The mean age of patients was 52 years (range 12–78 years). Chronic fatigue was found in 28 of 30 patients (93%) and was considered disabling in 26 of 30 patients (87%). Sixteen patients (53%) fulfilled CFS criteria from either the CDC (14 of 30 patients, 47%) or Oxford (12 of 30 patients, 40%), 11 of 30 patients (37%) fulfilled both CDC and Oxford criteria. Other symptoms, laboratory findings, and steroid responsiveness are detailed in Table 1. 67Ga scintigraphy was performed in 5 patients and showed increased levels of 67Ga uptake in muscle and para-articular areas, mainly in lower limbs. A history of vaccination was available for 19 of 20 patients. All 19 patients had received IM administration of aluminum-containing vaccine prior to the onset of CFS symptoms, and the delay from the last vaccination to the first manifestations ranged from 1 month to 72 months (median 12 months).

We have previously determined that myalgias are a major symptom in patients with MMF. The prevalence of myalgias was much higher in such patients than in other patients who had undergone deltoid muscle biopsies at the same time in the same centers (85% versus 45%; $P < 0.0001$ by Fisher's exact test) (2). We show now that chronic disabling fatigue is a symptom as frequent as diffuse myalgias in patients with MMF (87%), a finding also noted in the French Institut de Veille Sanitaire exploratory investigation report (6). More than half of the patients also reported other manifestations of CFS. Therefore, MMF should be alternatively considered as a cause of CFS or as an additional exclusion criterion, along with rheumatoid arthritis, lupus, and other diseases, for the diagnosis of idiopathic CFS (4). Consequently, we suggest that patients with CFS should be carefully checked for a history of IM administration of aluminum hydroxide, and, if there is consistent chronology, a muscle biopsy to search for MMF at the site of injection should be considered, even many years after onset of symptoms.

Pathophysiology of CFS is still fiercely debated by psychologists, neuroendocrinologists, and immunologists. Chronic immune stimulation that fails to switch off has been previously reported as a possible cause of CFS (7–9), and such a situation may very well result from persistence of the immunologic adjuvant aluminum hydroxide within antigen-presenting cells (2, 10). Therefore, MMF may well represent a paradigm for CFS of immunologic origin. We believe that clarification of MMF pathophysiology would significantly contribute to the understanding of the whole spectrum of chronic fatigue and its syndromes.

Full Report: http://onlinelibrary.wiley.com/doi/10.1002/art.10740/full

PDF: http://onlinelibrary.wiley.com/doi/10.1002/art.10740/epdf

Expert Opinion On Drug Safety • March 2003

A review of hepatitis B vaccination

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Abstract

Hepatitis B is one of the most important infectious causes of acute and chronic liver disease both in the US and worldwide. In order to combat the life-threatening effects of hepatitis B infection, recombinant hepatitis B vaccines have been developed. The medical and scientific communities have generally accepted that recombinant hepatitis B vaccine - a highly purified, genetically engineered, single antigen vaccine - is a safe vaccine. Information is presented showing that hepatitis B vaccine contains yeast, aluminium, thimerosal and hepatitis B surface antigen epitopes, which may result in hepatitis B vaccine being associated with autoimmune diseases among susceptible adult vaccine recipients. There is little doubt that the benefits of this vaccine overall far outweigh its risks. Physicians and patients should evaluate the risks and benefits of hepatitis B vaccination and, together, make an informed consent decision as to whether to undergo vaccination. Individuals who experience an adverse reaction to hepatitis B vaccination should report it to the Vaccine Adverse Event Reporting System database and be advised that they may be eligible for compensation from the no-fault National Vaccine Injury Compensation Program, administered by the US Court of Claims. The authors strongly urge that additional research be conducted into the molecular basis of adverse events following hepatitis B vaccine administration, so that further recommendations may be made on how to improve their safety profiles.

http://www.ncbi.nlm.nih.gov/pubmed/12904111

“Information is presented showing that hepatitis B vaccine contains yeast, aluminium, thimerosal and hepatitis B surface antigen epitopes, which may result in hepatitis B vaccine being associated with autoimmune diseases among susceptible adult vaccine recipients.”

Pediatric Neurology • April 2003

Elevated levels of measles antibodies in children with autism

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Abstract

Virus-induced autoimmunity may play a causal role in autism. To examine the etiologic link of viruses in this brain disorder, we conducted a serologic study of measles virus, mumps virus, and rubella virus. Viral antibodies were measured by enzyme-linked immunosorbent assay in the serum of autistic children, normal children, and siblings of autistic children. The level of measles antibody, but not mumps or rubella antibodies, was significantly higher in autistic children as compared with normal children (P = 0.003) or siblings of autistic children (P <or= 0.0001). Furthermore, immunoblotting of measles vaccine virus revealed that the antibody was directed against a protein of approximately 74 kd molecular weight. The antibody to this antigen was found in 83% of autistic children but not in normal children or siblings of autistic children. Thus autistic children have a hyperimmune response to measles virus, which in the absence of a wild type of measles infection might be a sign of an abnormal immune reaction to the vaccine strain or virus reactivation.

http://www.ncbi.nlm.nih.gov/pubmed/?term=12849883

“Thus autistic children have a hyperimmune response to measles virus, which in the absence of a wild type of measles infection might be a sign of an abnormal immune reaction to the vaccine strain or virus reactivation.”

Clinical Immunology • May 2003

Influenza vaccination and Guillain Barre syndrome

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Abstract

Acute and severe Guillain Barre Syndrome (GBS) cases reported following influenza vaccine to the Vaccine Adverse Events Reporting System (VAERS) database from 1991 through 1999 were examined. Endotoxin concentrations were measured using the Limulus amebocyte lysate assay in influenza vaccines. There were a total of 382 cases of GBS reported to the VAERS database following influenza vaccination (male/female ratio, 1.2). The median onset of GBS following influenza vaccine was 12 days (interquartile range, 7 days to 21 days). There was an increased risk of acute GBS (relative risk, 4.3; 95% confidence interval, 3.0 to 6.4) and severe GBS (relative risk, 8.5; 95% confidence interval, 3.7 to 18.9) in comparison to an adult tetanus-diphtheria (Td) vaccine control group. There were maximums in the incidence of GBS following influenza vaccine that occurred approximately every third year (1993, 1996, and 1998) and statistically significant variation in the incidence of GBS among different influenza manufacturers. Influenza vaccines contained from a 125- to a 1250-fold increase in endotoxin concentrations in comparison to an adult Td vaccine control and endotoxin concentrations varied up to 10-fold among different lots and manufacturers of influenza vaccine. The biologic mechanism for GBS following influenza vaccine may involve the synergistic effects of endotoxin and vaccine-induced autoimmunity. There were minimal potential reporting biases in the data reported to the VAERS database in this study. Patients should make an informed consent decision on whether to take this optional vaccine based upon its safety and efficacy and physicians should vigilantly report GBS following influenza vaccination to the VAERS in the United States so that continued evaluation of the safety of influenza vaccine may be undertaken.

http://www.ncbi.nlm.nih.gov/pubmed/?term=12763480

“from 1991 through 1999 ...

There were a total of 382 cases of

Guillain-Barre Syndrome reported to

the VAERS database following influenza vaccination ...”

Mediators Of Inflammation • August 2003

Cytokine profile after rubella vaccine inoculation: evidence of the immunosuppressive effect of vaccination

Author information

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Abstract

BACKGROUND AND AIM:
Immunization with live virus vaccines may cause an immunosuppression with lymphopaenia, impaired cytokine production and defective lymphocyte response to mitogenes. These abnormalities were described in subjects vaccinated against measles. This study was performed to analyse the host immune response related to immunosuppression in subjects vaccinated with live attenuated rubella vaccine.

METHODS:
Eighteen schoolgirls, aged 11-13 years, were vaccinated with live attenuated rubella vaccine Rudivax. Before immunization, and 7 and 30 days after, peripheral blood was collected. Cellular fractions were subjected to flow cytometric analysis, and the lymphocyte response to phytohaemagglutinin was investigated. Plasma samples were analysed for cytokines (interleukin (IL)-4, IL-10, tumour necrosis factor-alpha, and interferon-gamma) by enzyme-linked immunosorbent assay techniques.

RESULTS:
On day 7 after vaccination, the number of each lymphocyte subset was decreased; however, only for CD3 and CD4 lymphocytes has a significant reduction been shown. On the contrary, tumour necrosis factor-alpha and IL-10 levels markedly increased and amounted to its maximum on day 30. Simultaneously, a significant reduction in plasma interferon-gamma and a profound decrease of the lymphocyte response to phytohaemagglutinin were shown. The changes were accompanied with marked elevation of plasma IL-4.

CONCLUSIONS:
Our data indicate that the vaccination with live attenuated rubella vaccine results in moderate but sustained immune disturbance. The signs of immunosuppression, including defective lymphocyte response to mitogene and impaired cytokine production, may persist for at least 1 month after vaccination.

http://www.ncbi.nlm.nih.gov/pubmed/?term=14514470

“Immunization with live virus vaccines may cause an immunosuppression with lymphopaenia, impaired cytokine production and defective lymphocyte response to mitogenes. These abnormalities were described in subjects vaccinated against measles. Our data indicate that the vaccination with live attenuated rubella vaccine results in moderate but sustained immune disturbance.”

“The potential to induce autoimmunity may complicate the use of oil adjuvants in human and veterinary vaccines.”

Journal Of Autoimmunity • August 2003

Induction of lupus autoantibodies by adjuvants

Author information

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Abstract

Exposure to the hydrocarbon oil pristane induces lupus specific autoantibodies in non-autoimmune mice. We investigated whether the capacity to induce lupus-like autoimmunity is a unique property of pristane or is shared by other adjuvant oils. Seven groups of 3-month-old female BALB/cJ mice received a single intraperitoneal injection of pristane, squalene (used in the adjuvant MF59), incomplete Freund’s adjuvant (IFA), three different medicinal mineral oils, or saline, respectively. Serum autoantibodies and peritoneal cytokine production were measured. In addition to pristane, the mineral oil Bayol F (IFA) and the endogenous hydrocarbon squalene both induced anti-nRNP/Sm and -Su autoantibodies (20% and 25% of mice, respectively). All of these hydrocarbons had prolonged effects on cytokine production by peritoneal APCs. However, high levels of IL-6, IL-12, and TNFalpha production 2-3 months after intraperitoneal injection appeared to be associated with the ability to induce lupus autoantibodies. The ability to induce lupus autoantibodies is shared by several hydrocarbons and is not unique to pristane. It correlates with stimulation of the production of IL-12 and other cytokines, suggesting a relationship with a hydrocarbon’s adjuvanticity. The potential to induce autoimmunity may complicate the use of oil adjuvants in human and veterinary vaccines.

http://www.ncbi.nlm.nih.gov/pubmed/?term=12892730

Neurology • September 2003

Excess incidence of ALS in young Gulf War veterans

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Abstract

BACKGROUND
Reported cases of ALS in young veterans of the 1991 Gulf War have suggested excess incidence.

OBJECTIVE
To compare observed and expected incidence of ALS in Gulf War veterans diagnosed before age 45 years (young veterans).

METHODS
Cases of ALS diagnosed from 1991 through 1998 were collected from military registries and a publicity campaign in late 1998. Diagnoses were established from neurologists' medical records using El Escorial criteria. Expected incidence was estimated from the age distribution of the Gulf War veteran population, weighted by age-specific death rates of the US population. Secular changes in nationwide ALS rates were assessed using calculations of the age-specific US population death rates from vital statistics data of 1979 to 1998.

RESULTS
During 8 postwar years, 20 ALS cases were confirmed in approximately 690,000 Gulf War veterans, and 17 were diagnosed before age 45 years. All developed bulbar and spinal involvement, and 11 have died. In young veterans, the expected incidence increased from 0.93 cases/year in 1991 to 1.57 cases/year in 1998, but the observed incidence increased from 1 to 5 cases/year. The observed incidence was 0.94 (95% CI, 0.26 to 2.41) times that expected in the baseline period from 1991 to 1994 (4 vs 4.25 cases; $p = 0.6$); it increased to 2.27 (95% CI, 1.27 to 3.88) times that expected during the 4-year period from 1995 to 1998 (13 vs 5.72 cases; $p = 0.006$); and it peaked at 3.19 (95% CI, 1.03 to 7.43) times that expected in 1998 (5 vs 1.57 cases; $p = 0.02$). The magnitude of the excess of ALS cases over the expected incidence increased during the 8-year period (Poisson trend test, $p = 0.05$), and the increase was not explained by a change in the interval from onset to diagnosis or by a change in the US population death rate of ALS in those aged <45 years.

CONCLUSIONS
The observed incidence of ALS in young Gulf War veterans exceeded the expected, suggesting a war-related environmental trigger.

http://www.ncbi.nlm.nih.gov/pubmed/?term=14504316

"The observed incidence of Amyotrophic Lateral Sclerosis in young Gulf War veterans exceeded the expected ..."

Neuroscience And Biobehavioral Reviews • October 2003

Analysis of neurological disease in four dimensions: insight from ALS-PDC epidemiology and animal models

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Abstract

The causal factor(s) responsible for sporadic neurological diseases are unknown and the stages of disease progression remain undefined and poorly understood. We have developed an animal model of amyotrophic lateral sclerosis-parkinsonism dementia complex which mimics all the essential features of the disease with the initial neurological insult arising from neurotoxins contained in washed cycad seeds. Animals fed washed cycad develop deficits in motor, cognitive, and sensory behaviors that correlate with the loss of neurons in specific regions of the central nervous system. The ability to recreate the disease by exposure to cycad allows us to extend the model in multiple dimensions by analyzing behavioral, cellular, and biochemical changes over time. In addition, the ability to induce toxin-based neurodegeneration allows us to probe the interactions between genetic and epigenetic factors. Our results show that the impact of both genetic causal and susceptibility factors with the cycad neurotoxins are complex. The article describes the features of the model and suggests ways that our understanding of cycad-induced neurodegeneration can be used to decipher and identify the early events in various human neurological diseases.

http://www.ncbi.nlm.nih.gov/pubmed/?term=14599431

“... causal factor(s) responsible for sporadic neurological diseases are unknown and the stages of disease progression remain undefined and poorly understood.”

Immunology And Allergy Clinics Of North America • November 2003

Aluminum inclusion macrophagic myofasciitis: a recently identified condition

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Abstract

The authors conclude that the persistence of aluminum hydroxide at the site of intramuscular injection is a novel finding which has an exact significance that remains to be established fully. It seems mandatory to evaluate possible long-term adverse effects induced by this compound, because this issue has not been addressed (in the past, aluminum hydroxide was believed to be cleared quickly from the body). If safety concerns about the long-term effects of aluminum hydroxide are confirmed, novel and alternative vaccine adjuvants to rescue vaccine-based strategies should be proposed to ensure the enormous benefit for public health that these vaccines provide worldwide.

http://www.ncbi.nlm.nih.gov/pubmed/?term=14753387

“The authors conclude that the persistence of aluminum hydroxide at the site of intramuscular injection is a novel finding which has an exact significance that remains to be established fully.”

"... it has become apparent over the past 20 years, and most notably during the past 10 years, that an array of metabolic machinery is also expressed in this organ ..."

Drug Metabolism & Disposition • December 2003

The Small Intestine As A Xenobiotic-Metabolizing Organ

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Abstract

The mammalian small intestine serves principally as the site for absorption of nutrients, water, and both beneficial and potentially harmful xenobiotics. However, it has become apparent over the past 20 years, and most notably during the past 10 years, that an array of metabolic machinery is also expressed in this organ (Kaminsky and Fasco, 1992; Lin et al., 1999; Doherty and Charman, 2002; Ding and Kaminsky, 2003). Both phase I and phase II metabolic enzymes are expressed, together with associated transporters. In this minireview we discuss some of the most prominent phase I and II enzymes in the metabolic systems in the small intestine. The transporters, despite their importance for the fate of enterocyte- absorbed xenobiotics, are beyond the scope of this minireview (Suzuki and Sugiyama, 2000).

http://dmd.aspetjournals.org/content/31/12/1520.long

[vaccines are xenobiotics]

Pediatrics • December 2003

Addressing parents' concerns: do vaccines contain harmful preservatives, adjuvants, additives, or residuals?

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Abstract

Vaccines often contain preservatives, adjuvants, additives, or manufacturing residuals in addition to pathogen-specific immunogens. Some parents, alerted by stories in the news media or information contained on the World Wide Web, are concerned that some of the substances contained in vaccines might harm their children. We reviewed data on thimerosal, aluminum, gelatin, human serum albumin, formaldehyde, antibiotics, egg proteins, and yeast proteins. Both gelatin and egg proteins are contained in vaccines in quantities sufficient to induce rare instances of severe, immediate-type hypersensitivity reactions. However, quantities of mercury, aluminum, formaldehyde, human serum albumin, antibiotics, and yeast proteins in vaccines have not been found to be harmful in humans or experimental animals.

http://www.ncbi.nlm.nih.gov/pubmed/14654615

[Dr. Offit, pro-vaccine media pundit, discusses vaccine safety with parents]

Alternative Medicine Reviews • 2003

Th1/Th2 Balance: The Hypothesis, its Limitations, and Implications for Health and Disease

Parris Kidd, PhD

Abstract

One theory of immune regulation involves homeostasis between T-helper 1 (Th1) and T- helper 2 (Th2) activity. The Th1/Th2 hypothesis arose from 1986 research suggesting mouse T-helper cells expressed differing cytokine patterns. This hypothesis was adapted to human immunity, with Th1- and Th2-helper cells directing different immune response pathways. Th1 cells drive the type-1 pathway ("cellular immunity") to fight viruses and other intracellular pathogens, eliminate cancerous cells, and stimulate delayed-type hypersensitivity (DTH) skin reactions. Th2 cells drive the type-2 pathway ("humoral immunity") and up-regulate antibody production to fight extracellular organisms; type 2 dominance is credited with tolerance of xenografts and of the fetus during pregnancy. Overactivation of either pattern can cause disease, and either pathway can down-regulate the other. But the hypothesis has major inconsistencies; human cytokine activities rarely fall into exclusive pro- Th1 or -Th2 patterns. The non-helper regulatory T cells, or the antigen-presenting cells (APC), likely influence immunity in a manner comparable to Th1 and Th2 cells. Many diseases previously classified as Th1 or Th2 dominant fail to meet the set criteria. Experimentally, Th1 polarization is readily transformed to Th2 dominance through depletion of intracellular glutathione, and vice versa. Mercury depletes glutathione and polarizes toward Th2 dominance. Several nutrients and hormones measurably influence Th1/Th2 balance, including plant sterols/sterolins, melatonin, probiotics, progesterone, and the minerals selenium and zinc. The long- chain omega-3 fatty acids EPA (eicosapentaenoic acid) and DHA (docosahexaenoic acid) significantly benefit diverse inflammatory and autoimmune conditions without any specific Th1/Th2 effect. Th1/Th2-based immunotherapies, e.g., T-cell receptor (TCR) peptides and interleukin-4 (IL- 4) injections, have produced mixed results to date.

Conclusion

In managing immune hypofunction or other dysfunction, it is crucial to manage all forms of stress. Rooks reported diverse stressors, includ- ing sleep deprivation, calorie restriction, excessive exercise, examination stress, and cardiopul- monary bypass surgery, down-regulate Th1 and up-regulate Th2 activity.95 These effects are mediated mainly by glucocorticoids, but also by the catecholamine hormones epinephrine and norepi- nephrine.92 As heroic efforts to tailor technological immune therapies go forward, the best immune intervention tools continue to be lifestyle modification, vitamins, minerals, orthomolecules, and selected nontoxic phytotherapies.

http://www.altmedrev.com/publications/8/3/223.pdf

"As heroic efforts to tailor technological immune therapies go forward, the best immune intervention tools continue to be lifestyle modification, vitamins, minerals, orthomolecules, and selected nontoxic phytotherapies."

Brain Pathology • January 2004

The July 2003 Case of the Month (COM)
62-year-old female with progressive muscular weakness

Author information

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Abstract

The July 2003 Case of the Month (COM). A 62-year-old female patient experienced progressive muscular weakness over the last ten years, involving shoulder and pelvic girdle muscles, paraspinal and facial muscles. A biopsy was taken from the left deltoid muscle where hepatitis vaccination had taken place 4 weeks previously. The specimen revealed macrophagic myofasciitis due to the injection of aluminium-bound vaccines. The finding can be reproduced experimentally by injecting vaccines in rats. The pathomechanism is supposed to involve immune stimulation due to long term persistence of the adjuvant. Macrophagic myofasciitis has been suggested to occasionally cause myopathy but is supposed to be unrelated to the underlying myopathy in our patient.

http://www.ncbi.nlm.nih.gov/pubmed/?term=14997943

“The specimen revealed
macrophagic myofasciitis due to
the injection of aluminium-bound vaccines.”

"When mass vaccination programs encompass billions of lives, even relatively rare toxicity events cannot be tolerated."

Presentation to the Vaccine Safety Committee of the Institute of Medicine
The National Academies of Science • February 9, 2004

Jeff Bradstreet MD, ICDRC 321-953-0278

Biological Evidence of Significant Vaccine Related Side-effects Resulting in Neurodevelopmental Disorders

Hypothesis

Evident for many individuals experienced with these issues, is the data supporting unprecedented levels of neurodevelopmental and immune disorders within the last two decades. The prevalence has risen to the point that many believe it has reached epidemic proportions. Our group of researchers and clinicians, have hypothesized that a subset of neurodevelopmental and medical disorders including: encephalopathy with autistic features, a unique inflammatory bowel disease, along with speech, learning and sensorimotor dysfunction, represent the manifestations of injuries related to vaccine components, especially mercury in the form of Thimerosal and measles virus from the MMR. Part of this hypothesis has been the existence of specific genetic vulnerability or environmental susceptibility cofactors. Our group represents researchers and clinicians with heterogeneous experience and expertise, that when taken together, provide the substance for a broad understanding of this phenomena.

Thesis

It must be recognized I am defining the data of a subgroup of children and in no way making estimates about autism or autism spectrum disorders in general. These terms will be discussed further in a moment. For what is often referred to as the broader autism phenotype, numerous candidate genes have been presented in the literature which I will not discuss here. To my knowledge, none of these genes would serve as susceptibility genes for measles viral persistence, mercury toxicity or autoimmunity of the type we will describe in this presentation, with the exception of the haplotype B44-SC30-DR4. Within this population, specific vulnerability factors, i.e. single nucleotide polymorphisms (SNP) within genes for enzymes regulating the methionine transulfuration and glutathione systems, occur at statistically significant greater frequency than within the general or control populations. The biochemical defects predicted by these SNP are all present as well. These include: low methionine, thiol deficiencies, heavy metal (particularly mercury) accumulation, immunological disorders including autoimmunity and neurotransmitter malregulation, and the probability of viral persistence. Proteomic studies are presently underway and will help to further define and confirm these associations. Other environmental factors include oxidative stress, which has broad implications on chemistry, and in utero exposure to mercury (methylmercury from fish and Thimerosal in anti-Rho immunoglobulin preparations). In all endpoint issues, the findings have been reproduced by at least two independent laboratories, and as in the case of SNP identification and low thiols, by multiple laboratories using various methodologies. These data will be presented in summary form to the committee during the brief time allotted, but will be presented in toto in written form with supporting literature.

Vaccine Contribution to Public Health

The well-accepted benefits of vaccinations to prevention of many childhood and serious illnesses are without question. All the data presented herein are intended to improve vaccine safety and long-term public confidence in vaccines. When mass vaccination programs encompass billions of lives, even relatively rare toxicity events cannot be tolerated. While others may debate the frequency of specific adverse events and the appropriate detection and surveillance methodologies, medicine remains governed by the foundational tenet, primum non nocere. Where options exist, as is the case with Thimerosal, there is no acceptable rationale for continued use of a known, suspected or plausible neurotoxin in vaccines for developing children. Safe vaccine policy can now completely eliminate any concern of mercury for every age-group. This way, none of us need to fear even subtle potential effects of mercury.

The sixth month cut-off, which seems to be in practice (whereby children over 6 months are routinely advised to take vaccines with 25 mcg of ethylmercury, e.g. influenza vaccine) is equally untenable. As has been eloquently demonstrated by Landing et al, (full paper submitted: Pediatric Pathology and Molecular Medicine 21: 321^342, 2002) the organization of the six layers of the human neocortex undergoes repeated and dynamic changes during the exact time when a known neurotoxicant (ethylmercury) has been and is continuing to be administered. Strides to reduce Thimerosal in vaccines have been partially successful in the youngest children, but incompletely understood potential risks remain in older children who are still being exposed through Diptheria Tetanus boosters, Influenza and other vaccines. Since no market-ready alternative for MMR exists in the US, this is a more challenging issue until new options emerge. I did receive notice from Secretary Tommy Thompson that a nasal measles vaccine was in development and expected within 2-3 years. No safety data is available, nor will be available for some time. Researchers at Johns Hopkins are working on a DNA MV vaccine. The concept is designed to further improve safety, but I have serious reservation regarding those within the population at risk for DNA hypomethylation, i.e. the same individuals with deficient methionine production secondary to folate deficiency, MTHFR defects or other factors. Methylation of viral DNA is a critical pathway to viral replication regulation/suppression. A discussion of this is beyond the scope of this paper. Below are two graphs from the Landing paper, presented here to allow easier understanding of the timing issue on neocortical development.

http://www.vaccinationnews.org/DailyNews/2004/February/IOMBradstreet14.htm

Full Report: http://iom.nationalacademies.org/~/media/4B8DAC4AD18F432283E67D91DB81F49B.ashx

Neuromuscular Disorders • February 2004

Macrophagic myofasciitis: an infantile Italian case

Author information

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Abstract

Macrophagic myofasciitis is a recently identified inflammatory myopathy mostly described in adult French patients complaining of arthro-myalgias and fatigue. It is probably due to intramuscular injection of aluminium-containing vaccines and is characterized by a typical muscular infiltrate of large macrophages with aluminium inclusions. We report a 1-year-old Italian child presenting irritability, delayed motor development, hyperCKemia (up to 10 times the normal value), and typical features of macrophagic myofasciitis on muscle biopsy. The child recovered fully after steroid therapy. Macrophagic myofasciitis is a new treatable cause of motor retardation and hyperCKemia in children, and is probably more common than reported. Diagnosis requires a high index of suspicion and can be missed if biopsy is performed outside the vaccination site.

http://www.ncbi.nlm.nih.gov/pubmed/?term=14733966

"It is probably due to intramuscular injection of aluminium-containing vaccines and is characterized by a typical muscular infiltrate of large macrophages with aluminium inclusions."

Pediatrics • April 2004

An analysis of rotavirus vaccine reports to the vaccine adverse event reporting system: more than intussusception alone?

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Abstract

BACKGROUND

The rhesus-human rotavirus reassortant-tetravalent vaccine (RRV-TV) was licensed on August, 31, 1998, and subsequently recommended for routine infant immunizations in the United States. After approximately 1 million doses had been administered, an increase in acute risk of intussusception in vaccinees led to the suspension of the use of RRV-TV and its withdrawal from the market. These postmarketing safety studies focused on a single adverse event (intussusception) and, to minimize the risk of a false-positive finding, accepted only cases that met a strict case definition. Safer rotavirus vaccines are needed to prevent the substantial global morbidity and mortality caused by rotavirus infections; their development and future use may benefit from a better understanding of the postmarketing safety profile of RRV-TV beyond intussusception.

OBJECTIVE

To characterize more completely the postmarketing surveillance safety profile of RRV-TV more completely by review and analysis of Vaccine Adverse Event Reporting System (VAERS) case reports to better understand 1) whether severe adverse events other than intussusception may have occurred after RRV-TV and 2) the likely scope of gastrointestinal illnesses, of which the previously identified, highly specific intussusception cases may account for just a fraction.

SETTING AND PARTICIPANTS

Infants vaccinated with RRV-TV and other vaccines in the United States and for whom a report was submitted to VAERS during September 1, 1998, to December 31, 1999.

METHODOLOGY

To detect adverse events of interest other than intussusception, we used proportional morbidity analysis to compare the adverse event profile of VAERS reports among infants who received routine vaccines including RRV-TV (after excluding confirmed and suspected intussusception reports) with infants who received identical vaccine combinations but without RRV-TV. Next, to better capture all described diagnoses, signs, and symptoms associated with the suspected adverse events, a set of new codes was developed and assigned to each VAERS report. All 448 nonfatal RRV-TV-associated reports (including intussusception) were recoded manually from the clinical description on the VAERS report and categorized into clinical groups to better describe a spectrum of reported illnesses after the vaccine. Each report was assigned to one of the following hierarchical and mutually exclusive clinical groups: 1) diagnosed intussusception; 2) suspected intussusception; 3) illness consistent with either gastroenteritis or intussusception; 4) gastroenteritis; 5) other gastrointestinal diagnoses (ie, not consistent with intussusception or rotavirus-like gastroenteritis); and 6) nongastrointestinal diagnoses.

RESULTS

Even after excluding intussusception cases, a higher proportion of RRV-TV reports than non-RRV-TV reports included fever and various gastrointestinal symptoms, most notably bloody stool but also vomiting, diarrhea, abdominal pain, gastroenteritis, abnormal stool, and dehydration. Distribution of RRV-TV reports by clinical groups was as follows: diagnosed intussusception (109 [24%], suspected intussusception (36 [8%]), and illness consistent with gastroenteritis or intussusception (33 [7%]), gastroenteritis (101 [22%]), other gastrointestinal diagnoses (10 [2%]), and nongastrointestinal outcomes (159 [35%]). The median time interval between vaccination and illness onset decreased incrementally among the first 4 clinical groups: from 7 days for diagnosed intussusceptions to 3 days for gastroenteritis.

CONCLUSIONS

Intussusception and gastroenteritis were the most commonly reported outcomes; however, a substantial number of reports indicate signs and symptoms consistent with either illness, possibly suggestive of a spectrum of gastrointestinal illness(es) related to RRV-TV. Although VAERS data have recognized limitations such as underreporting (that may differ by vaccine) and are nearly always insufficient to prove causality between a vaccine and an adverse event, this safety profile of RRV-TV may aid better understanding of the pathophysiology of intussusception as well as development of future safer rotavirus vaccines.

http://www.ncbi.nlm.nih.gov/pubmed/15060267

“Intussusception and gastroenteritis were the most commonly reported outcomes; however, a substantial number of reports indicate signs and symptoms consistent with either illness, possibly suggestive of a spectrum of gastrointestinal illness(es) related to RRV-TV.”

“Induction of autoantibodies by mineral oils considered nontoxic

also may have pathogenetic implications in human autoimmune diseases.”

Toxicology Science • April 2004

Distinctive patterns of autoimmune response induced by different types of mineral oil

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Abstract

Although mineral oils are generally considered nontoxic and have a long history of use in humans, the mineral oil Bayol F (incomplete Freund’s adjuvant, IFA) and certain mineral oil components (squalene and n-hexadecane) induce lupus-related anti-nRNP/Sm or -Su autoantibodies in nonautoimmune mice. In the present study, we investigated whether medicinal mineral oils can induce other types of autoantibodies and whether structural features of hydrocarbons influence autoantibody specificity. Female 3-month-old BALB/c (16-45/group) mice each received an i.p. injection of pristane (C19), squalene (C30), IFA, three medicinal mineral oils (MO-F, MO-HT, MO-S), or PBS. Sera were tested for autoantibodies and immunoglobulin levels. Hydrocarbons were analyzed by gas chromatography/mass spectrometry. IFA contained mainly C15-C25 hydrocarbons, whereas MO-HT and MO-S contained C20-C40, and MO-F contained C15-C40. Pristane and n-hexadecane were found in IFA (0.17% and 0.10% w/v, respectively) and MOs (0.0026-0.027%). At 3 months, pristane and IFA induced mainly IgG2a, squalene IgG1, and MOs IgG3 and IgM in sera. Anti-cytoplasmic antibodies were common in mice treated with MO-F, as well as those treated with pristane, squalene, and IFA. Anti-ssDNA and -chromatin antibodies were higher in MO-F and MO-S than in untreated/PBS, squalene-, or IFA-treated mice, suggesting that there is variability in the induction of anti-nRNP/Sm versus -chromatin/DNA antibodies. The preferential induction of anti-chromatin/ssDNA antibodies without anti-nRNP/Sm/Su by MO-S and MO-F is consistent with the idea that different types of autoantibodies are regulated differently. Induction of autoantibodies by mineral oils considered nontoxic also may have pathogenetic implications in human autoimmune diseases.

Full Report

http://toxsci.oxfordjournals.org/content/78/2/222.long

Journal Of American Physicians And Surgeons • Summer 2004

Chronic Microglial Activation and Excitotoxicity Secondary to Excessive Immune Stimulation: Possible Factors in Gulf War Syndrome and Autism

Russell L. Blaylock, M.D.

Abstract

There is considerable and growing evidence that chronic microglial activation plays a major role in numerous neurological conditions including Alzheimer's dementia, Parkinson's disease, ALS, strokes, and inflammatory brain diseases. The release of toxic elements from activated microglia, such as cytokines and excitotoxins, is known to produce neurodegeneration. Peripheral immune stimulation has been shown to activate CNS microglia, and when excessive can lead to neurodegeneration and cognitive defects commonly associated with both the Gulf War Syndrome (GWS) and autism. This paper summarizes the mechanism linking these two disorders with excessive immune stimulation secondary to overvaccination.

The Role of Vaccines

As stated above, peripheral immune stimulation readily activates the brain's immune system. In most instances this is short- lived, and neuron damage is minimal. Chronic activation of microglia, however, can lead to substantial disruption of neuronal function and even neurodegeneration.

Two basic processes seem to be responsible for the chronic stimulation of brain immunity: repeated, closely spaced inoculation without allowing brain recovery, and inoculation with live viruses or contaminant organisms that persist in the brain. Gulf War veterans were given some 17 inoculations very close together. Children are often given as many as five to seven inoculations during one visit to the pediatrician's office, several as combined vaccines, such as measles-mumps-rubella (MMR).

Of particular concern is the use of live organisms and contaminant organisms. Garth Nicolson and co-workers have demonstrated polymerase chain reaction (PCR) evidence of mycoplasma species in the blood samples of Gulf War veterans suffering from ALS, the incidence of which was found to be increased by 200 percent in this population.40 Nicolson et al. found that 83 percent of veterans with ALS had positive tests, whereas positives were rarely seen in controls. It is hypothesized that the vaccines were contaminated primarily with Mycoplasma fermentens. Numerous activated microglia are found in the spinal cord of affected veterans. The involvement of live M. fermentens could also explain the appearance of similar illnesses in other household members.

Excitotoxins contribute to the damage in central nervous system infections. Cerebrospinal fluid glutamate levels rise in bacterial meningitis, and levels are directly correlated with prognosis. Extracellular glutamate levels are elevated in all cases of viral encephalopathies, including that of the acquired immunodeficiency syndrome (AIDS). Glutamate and aspartate levels in the plasma were also found to be elevated in 11 of 14 autistic children.41 There is also evidence that viruses can enhance the toxicity of glutamate.42

Injection of the immune adjuvant lipopolysaccharide (LPS) closely resembles the vaccination process. In one study, it was shown for the first time that peripherally administered LPS decreased learning in mice.43 The dose used did not produce observable injury to the neurons, but significantly impaired the animals' completing the Morris water maze and spontaneous alternation Y-maze, which tests spatial learning requiring a functional hippocampus. Associative learning was affected most. Memory retention was spared. LPS injection, by elevating IL-1 levels, has been shown to alter hippocampal norepinephrine and serotonin levels, as well as increasing glutamate levels.44 Elevated serotonin levels have been described in autism.45

Long-term persistent immune activation and low-grade brain inflammation have been described in three children who recovered from Herpex simplex encephalitis before age two.46 The children all demonstrated abundant activated microglia at brain biopsy and continued to deteriorate after viral treatment, indicating continued microgial activation. Viral fragments, without active infection, can produce this phenomenon.

Not all persistent viral infections are associated with obvious inflammatory responses. Using a hamster neurotrophic strain of measles, it was found that a noninflammatory encephalopathy could occur with destruction of the CA1 and CA3 segments of the hippocampus.47 This could more closely resemble the situation in autistic child and some cases of GWS, since obvious clinical and laboratory signs of inflammation would be absent. Neurodegeneration caused by this neurotrophic measles virus was blocked using the NMDA receptor antagonist, MK-801, indicating an excitotoxic mechanism. (The NMDA receptor is the postsynaptic receptor for L- glutamate that can be activated by the drug N-methyl-D-aspartate.)

The smallpox vaccine is associated with postvaccinal encephalitis at a rate of 1 in 110,000 vaccinations. This includes only obvious cases of encephalitis; more chronic, subtle cases involving ill-defined neurological symptoms remote from the vaccination would be overlooked. Most vaccine follow-up studies do not extend beyond two weeks. It is obvious from the above studies that this follow-up period is far too short. More persistent neurotropic viruses now being discovered appear to be related to chronic neurodegeneration. These include HSV-1, coronavirus, measles virus, and human herpes viruses 6 and 7 (HHV-6 and HHV- 7). A postvaccinal encephalopathy has been described in children under age two years following the smallpox vaccine.48 Most of these occur as chronic conditions.

Toxicology • July 2004

Flow-cytometric analysis on adverse effects of polysorbate 80 in rat thymocytes

Author information

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Abstract

The effects of polysorbate 80, a non-ionic surfactant widely used in pharmaceutical products, on rat thymocytes were examined to reveal its toxic property at the cellular level. Polysorbate 80 at concentrations of 1-100 microg/ml did not significantly affect the cell viability. This surfactant at 30 microg/ml or more augmented the intensity of fluo-3 fluorescence, indicating the increase in intracellular Ca(2+) concentration. Such an augmentation of fluo-3 fluorescence by polysorbate 80 was not seen under the Ca(2+)-free condition, suggesting that polysorbate 80 increased membrane Ca(2+) permeability. The concentration-dependent polysorbate 80 at 10 microg/ml or more attenuated the intensity of 5-chloromethylfluorescein, indicating a decrease in cellular content of glutathione by polysorbate 80. Furthermore, the agent at 1 microg/ml or more attenuated the intensity of bis-(1,3-dibutylbarbituric acid) trimethine oxonol fluorescence, being independent from the changes in membrane potential. This phenomenon indicates that polysorbate 80 at 1 microg/ml or more may attenuate the incorporation of anionic compounds into the membranes. It can be suggested that polysorbate 80 modifies some of membranes and intracellular physiological parameters without affecting the cell viability.

http://www.ncbi.nlm.nih.gov/pubmed/15147788

“ It can be suggested that polysorbate 80 modifies some of membranes and intracellular physiological parameters without affecting the cell viability.”

JAMA • July 2004

MMR vaccination and febrile seizures: evaluation of susceptible subgroups and long-term prognosis

Author information

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Abstract

CONTEXT

The rate of febrile seizures increases following measles, mumps, and rubella (MMR) vaccination but it is unknown whether the rate varies according to personal or family history of seizures, perinatal factors, or socioeconomic status. Furthermore, little is known about the long-term outcome of febrile seizures following vaccination.

OBJECTIVES

To estimate incidence rate ratios (RRs) and risk differences of febrile seizures following MMR vaccination within subgroups of children and to evaluate the clinical outcome of febrile seizures following vaccination.

DESIGN, SETTING, AND PARTICIPANTS

A population-based cohort study of all children born in Denmark between January 1, 1991, and December 31, 1998, who were alive at 3 months; 537,171 children were followed up until December 31, 1999, by using data from the Danish Civil Registration System and 4 other national registries.

MAIN OUTCOME MEASURES

Incidence of first febrile seizure, recurrent febrile seizures, and subsequent epilepsy.

RESULTS

A total of 439,251 children (82%) received MMR vaccination and 17,986 children developed febrile seizures at least once; 973 of these febrile seizures occurred within 2 weeks of MMR vaccination. The RR of febrile seizures increased during the 2 weeks following MMR vaccination (2.75; 95% confidence interval [CI], 2.55-2.97), and thereafter was close to the observed RR for nonvaccinated children. The RR did not vary significantly in the subgroups of children that had been defined by their family history of seizures, perinatal factors, or socioeconomic status. At 15 to 17 months, the risk difference of febrile seizures within 2 weeks following MMR vaccination was 1.56 per 1000 children overall (95% CI, 1.44-1.68), 3.97 per 1000 (95% CI, 2.90-5.40) for siblings of children with a history of febrile seizures, and 19.47 per 1000 (95% CI, 16.05-23.55) for children with a personal history of febrile seizures. Children with febrile seizures following MMR vaccinations had a slightly increased rate of recurrent febrile seizures (RR, 1.19; 95% CI, 1.01-1.41) but no increased rate of epilepsy (RR, 0.70; 95% CI, 0.33-1.50) compared with children who were nonvaccinated at the time of their first febrile seizure.

CONCLUSIONS

MMR vaccination was associated with a transient increased rate of febrile seizures but the risk difference was small even in high-risk children. The long-term rate of epilepsy was not increased in children who had febrile seizures following vaccination compared with children who had febrile seizures of a different etiology.

http://www.ncbi.nlm.nih.gov/pubmed/15265850

“439,251 children received MMR vaccination and 17,986 children developed febrile seizures at least once ...”

Brain Development • August 2004

An evaluation of serious neurological disorders following immunization: a comparison of whole-cell pertussis and acellular pertussis vaccines

Author information

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Abstract

Serious neurological disorders reported following whole-cell pertussis in comparison to acellular pertussis vaccines were evaluated. The Vaccine Adverse Events Reporting System (VAERS) was analyzed for Emergency Department (ED) visits, life-threatening reactions, hospitalizations, disabilities, deaths, seizures, infantile spasms, encephalitis/encephalopathy, autism, Sudden Infant Death Syndrome (SIDS) and speech disorders reported with an initial onset of symptoms within 3 days following whole-cell pertussis and acellular pertussis vaccines among those residing in the US from 1997 to 1999. Controls were employed to evaluate potential biases in VAERS. Evaluations as to whether whole-cell and acellular vaccines were administered to populations of similar age and sex were undertaken because these factors might influence the study's results. Statistical increases were observed for all events examined following whole-cell pertussis vaccination in comparison to acellular pertussis vaccination, excepting cerebellar ataxia. Reporting biases were minimal in VAERS, and whole-cell and acellular pertussis vaccines were administered to populations of similar age and sex. Biologic mechanisms for the increased reactogenicity of whole-cell pertussis vaccines may stem from the fact that whole-cell pertussis vaccines contain 3,000 different proteins, whereas DTaP contains two to five proteins. Whole-cell pertussis vaccine contains known neurotoxins including: endotoxin, pertussis toxin and adenylate cyclase. Our results, and conclusions by the US Institute of Medicine, suggest an association between serious neurological disorders and whole-cell pertussis immunization. In light of the presence of a safer and at least equally efficacious acellular pertussis vaccine alternative, the Japanese and US switch to using acellular pertussis vaccine seems well justified. Other countries using whole-cell pertussis-containing vaccines should consider following suite in the near future.

http://www.ncbi.nlm.nih.gov/pubmed/15165669

"... results, and conclusions by the US Institute of Medicine, suggest an association between serious neurological disorders and whole-cell pertussis immunization."

Annals Of Dermatology And Venereology • August 2004

Granuloma with lymphocytic hyperplasia following vaccination: 10 cases Presence of aluminium in the biopsies

Author information

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Abstract

BACKGROUND
Few cases of cutaneous lymphocytic hyperplasia secondary to vaccination have been published, although such lesions are not rare.

PATIENTS AND METHODS
We report a series of 10 cases registered between 1993 and 2003.

RESULTS
Mean age was 25. The clinical aspect was solitary or multiple subcutaneous nodules, located on the arm, developing after a delay of 1 to 18 months after vaccination. Histologic examination showed a lymphocytic infiltration of the subcutaneous fat, with diffuse and/or follicular pattern, without nuclear atypia, the morphological and immunohistochemical analysis of which revealed the benign nature. In all cases, there was fibrosis and granuloma composed of lymphocytes, plasma cells, eosinophils and macrophages with basophilic cytoplasm. Morin stain showed intralesional aluminium in the 6 investigated cases. Evolution was always benign, with no relapse following exeresis.

DISCUSSION
Cutaneous lymphocytic hyperplasia secondary to vaccination has to be suspected in a young patient with subcutaneous nodules appearing at a vaccination site. Evidence of aluminium in the lesions supports the diagnosis and the hypothesis that aluminium in the vaccine excipient might have a role in the onset of such lesions.

http://www.ncbi.nlm.nih.gov/pubmed/?term=15505542

“Cutaneous lymphocytic hyperplasia secondary to vaccination has to be suspected in a young patient with subcutaneous nodules appearing at a vaccination site. Evidence of aluminium in the lesions supports the diagnosis ...”

American Journal Of Therapeutics • September 2004

Urinary tract diseases revealed after DTP vaccination in infants and young children: cytokine irregularities and down-regulation of cytochrome P-450 enzymes induced by the vaccine may uncover latent diseases in genetically predisposed subjects

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Abstract

Prophylactic vaccinations may sometimes shorten the incubation period of some illnesses and/or convert a latent infection/inflammation into a clinically apparent disease. Cytokines play a major role in mediating the inflammatory process in various clinical entities and represent a potential source of tissue damage if their production is not sufficiently well controlled. It seems that irregularities in production of proinflammatory cytokines may be responsible for the abnormalities associated with full-blown clinical symptoms of various urinary tract diseases observed after DTP vaccination in 13 infants and young children hospitalized over the past 24 years. On admission, upper respiratory tract diseases, atopic dermatitis, and/or latent urinary tract infection/inflammation were found in these children. It is suggested that the whole-cell pertussis present in DTP vaccine, acting as an excessive stimulus in these patients, produced symptoms reminiscent of biologic responses to circulating proinflammatory monokines such as IL-1beta, TNF-alpha, and IL-6 because earlier it was reported that in vitro the whole-cell vaccine induced significantly more such cytokine production than did the acellular pertussis or diphtheria-tetanus-only vaccine. Analysis of the cellular immune disturbances previously reported in urinary tract infection/inflammation (increased serum and/or urinary IL-1alpha, IL-1 receptor antagonist, IL-6 and IL-8), steroid-sensitive nephrotic syndrome (increased IL-2, IFN-gamma, TNF-alpha, and decreased or increased IL-4, depending on the cells studied), and atopic dermatitis (decreased IFN-gamma and increased IL-4 production), may suggest that similar subclinical chronic cytokine-mediated abnormalities produced in the course of latent diseases revealed in our patients, combined with those caused by DTP vaccination stimulus, were responsible for the pathomechanism of these clinical entities. This speculation is in agreement with the reports on the long-lasting induction of cytokine release and down-regulation of hepatic cytochrome P-450 isoenzyme activities after administration of DTP vaccine to mice and may be supported by the fact that TH1 phenotype is associated with the up-regulation of intercellular adhesion molecule-1 and RANTES, whereas TH2 phenotype is associated with the up-regulation of the vascular cell adhesion molecule and P-selectin, which are key players in the migration into inflamed tissues and localization of lymphocytes and other allergic effector and inflammatory cells. Because several inflammatory cytokines down-regulate gene expression of major cytochrome P-450 and/or other enzymes with the specific effects on mRNA levels, protein expression, and enzyme activity, thus affecting the metabolism of several endogenous lipophilic substances such as steroids, lipid-soluble vitamins, prostaglandins, leukotrienes, thromboxanes, and exogenous substances, their irregularities in the body may eventually lead to the flare of latent diseases in some predisposed subjects. Also, interleukin genetic polymorphisms, especially the constellation of TNF-alpha and IL-6 genetic variants, might predispose some infants with infection to a more than usually intense inflammatory response in the kidneys after vaccination. It seems that the aforementioned pathomechanism may also be responsible for some cases of sudden infant death syndrome, which is often preceded by infection/inflammation.

http://www.ncbi.nlm.nih.gov/pubmed/15356430

“It seems that the aforementioned pathomechanism may also be responsible for some cases of sudden infant death syndrome, which is often preceded by infection/inflammation.”

Neurology • September 2004

Recombinant hepatitis B vaccine and the risk of multiple sclerosis: a prospective study

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Abstract

BACKGROUND
A potential link between the recombinant hepatitis B vaccine and an increased risk of multiple sclerosis (MS) has been evaluated in several studies, but some of them have substantial methodologic limitations.

METHODS
The authors conducted a nested case-control study within the General Practice Research Database (GPRD) in the United Kingdom. The authors identified patients who had a first MS diagnosis recorded in the GPRD between January 1993 and December 2000. Cases were patients with a diagnosis of MS confirmed through examination of medical records, and with at least 3 years of continuous recording in the GPRD before their date of first symptoms (index date). Up to 10 controls per case were randomly selected, matched on age, sex, practice, and date of joining the practice. Information on receipt of immunizations was obtained from the computer records.

RESULTS
The analyses include 163 cases of MS and 1,604 controls. The OR of MS for vaccination within 3 years before the index date compared to no vaccination was 3.1 (95% CI 1.5, 6.3). No increased risk of MS was associated with tetanus and influenza vaccinations.

CONCLUSIONS
These findings are consistent with the hypothesis that immunization with the recombinant hepatitis B vaccine is associated with an increased risk of MS, and challenge the idea that the relation between hepatitis B vaccination and risk of MS is well understood.

http://www.ncbi.nlm.nih.gov/pubmed/?term=15365133

“These findings are consistent with the hypothesis that immunization with the recombinant hepatitis B vaccine is associated with an increased risk of MS, and challenge the idea that the relation between hepatitis B vaccination and risk of MS is well understood.”

“In this review, we discuss recent articles and controversies pertaining to vaccine-associated adverse events.”

Current Allergy And Asthma Reports • November 2004

Update on side effects from common vaccines

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Abstract

Vaccines have had a tremendous impact on public health by reducing morbidity and mortality from a variety of virulent pathogens. However, unintended side effects continue to pose a potential risk that may outweigh the vaccine’s protective attributes. In this review, we discuss recent articles and controversies pertaining to vaccine-associated adverse events. Included in the discussion are influenza, hepatitis B, measles-mumps-rubella, diphtheria-tetanus-pertussis, polio, Haemophilus influenzae type b, and rotavirus vaccines. The importance and contribution of vaccine constituents (such as thimerosal) to side effects is also reviewed.

http://www.ncbi.nlm.nih.gov/pubmed/15462710

JAMA • November 2004

Guillain-Barré syndrome following influenza vaccination

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Abstract

CONTEXT
An unexplained increase in the risk of Guillain-Barre syndrome (GBS) occurred among recipients of the swine influenza vaccine in 1976-1977. Guillain-Barre syndrome remains the most frequent neurological condition reported after influenza vaccination to the Vaccine Adverse Events Reporting System (VAERS) since its inception in 1990.

OBJECTIVE
To evaluate trends of reports to VAERS of GBS following influenza vaccination in adults.

DESIGN, SETTING, AND PARTICIPANTS
VAERS is the US national spontaneous reporting system for adverse events following vaccination. Reports of GBS in persons 18 years or older following influenza vaccination were evaluated for each influenza season from July 1, 1990, through June 30, 2003. The number of people vaccinated was estimated from the National Health Interview Survey and US census data. Beginning in 1994, active follow-up was conducted to verify GBS diagnosis and obtain other clinical details.

MAIN OUTCOME MEASURE
Reporting rates of GBS following influenza vaccination over time.

RESULTS
From July 1990 through June 2003, VAERS received 501 reports of GBS following influenza vaccination in adults. The median onset interval (13 days) was longer than that of non-GBS reports of adverse events after influenza vaccine (1 day) (P<.001). The annual reporting rate decreased 4-fold from a high of 0.17 per 100,000 vaccinees in 1993-1994 to 0.04 in 2002-2003 (P<.001). A GBS diagnosis was confirmed in 82% of reports. Preceding illness within 4 weeks of vaccination was identified in 24% of reported cases.

CONCLUSIONS
From 1990 to 2003, VAERS reporting rates of GBS after influenza vaccination decreased. The long onset interval and low prevalence of other preexisting illnesses are consistent with a possible causal association between GBS and influenza vaccine. These findings require additional research, which can lead to a fuller understanding of the causes of GBS and its possible relationship with influenza vaccine.

http://www.ncbi.nlm.nih.gov/pubmed/?term=15562126

“An unexplained increase in the risk of Guillain-Barre syndrome (GBS) occurred among recipients of the swine influenza vaccine in 1976-1977. Guillain-Barre syndrome remains the most frequent neurological condition reported after influenza vaccination to the Vaccine Adverse Events Reporting System (VAERS) since its inception in 1990.”

“... the whole cell vaccine may lead to the acute encephalopathy, fever seizures, hypotonic-hyporeactive episodes, inconsolable crying or anaphylactic reactions.”

Przeglad Epidemiologiczny • 2004

Prevention of pertussis and high expectations concerning vaccines

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Abstract

The basic vaccine used in the prevention of pertussis is the combined vaccine including a whole cell pertussis component and tetanus and diphtheria toxoids. Although this type of vaccine has been used more than 50 years in USA and more than 40 years in Poland it is still effective what can be evidenced by the decreased number of pertussis cases since the vaccine has been implemented. There are however some evidences that the whole cell vaccine may lead to the acute encephalopathy, fever seizures, hypotonic-hyporeactive episodes, inconsolable crying or anaphylactic reactions. But still is a lack of convincing evidences that the vaccine may be a cause of persistent brain damage. It was also shown that the longer is the period after the last dose of the vaccine the lower effectiveness was observed. Improving the safety of the pertussis vaccine was the reason of introducing the acellular vaccines in the eightieth. All these products contain pertussis toxoid and some of them contain also filamentous hemagglutinin, pertactin and fimbrial agglutinogens. Some published studies have shown that the effectiveness of these vaccines is similar to the whole cells vaccines and that the incidence of some adverse events especially seizures, hypotonic-hyporeactive episodes and inconsolable crying is lower.

http://www.ncbi.nlm.nih.gov/pubmed/15807156

Archives de Pediatrie • January 2005

Vaccine adjuvants and macrophagic myofasciitis

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Abstract

Aluminium-based adjuvants have been used throughout the world since 1926, and their safety profile is such that they have long been the sole adjuvants registered for clinical use. Their safety has nevertheless been questioned in France over the last few years following the demonstration that aluminium could persist for prolonged periods at the injection site, within macrophages gathered around the muscular fibres and forming a microscopic histological lesion called “macrophagic myofasciitis (MMF)”. This image has been observed in patients undergoing a deltoid muscular biopsy for diagnostic purposes of various symptoms essentially including muscular pain and fatigue, in association with a large panel of various symptoms and diseases, including those of an autoimmune nature. Studies of the clinical, biological and epidemiological characteristics undertaken to identify a possible association between the MMF histological image and a systematic disease have remained negative. As of today, available evidence indicates that although vaccine aluminium may persist at the site of injection for years (“vaccine tattoo”), this does not reflect the existence of a diffuse inflammatory muscular disease and is not associated with a specific clinical disease. The existence of sampling bias inherent to the complexity of the clinical and pathological diagnoses remains the most likely hypothesis.

http://www.ncbi.nlm.nih.gov/pubmed/15653065

“Aluminium-based adjuvants have been used throughout the world since 1926, and their safety profile is such that they have long been the sole adjuvants registered for clinical use. Their safety has nevertheless been questioned in France over the last few years following the demonstration that aluminium could persist for prolonged periods at the injection site, within macrophages gathered around the muscular fibres and forming a microscopic histological lesion called “macrophagic myofasciitis (MMF)”.”

Danish Medical Journal • January 2005

Combining vitamin A and vaccines: convenience or conflict?

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Abstract

The present thesis is based on 11 papers from 1995-2010. The studies have mainly taken place at the Bandim Health Project in Guinea-Bissau, West Africa, but a reanalysis of a randomised trial from Ghana is also included. My research has explored the consequences of combining high-dose vitamin A supplementation and childhood vaccines. Vitamin A deficiency is associated with increased mortality. To protect against the consequences of vitamin A deficiency the World Health Organization recommends that high-dose vitamin A supplements be given together with routine vaccines to children between 6 months and 5 years of age in more than 100 low-income countries. The recommendation is based on logistical considerations. The consequences of combining vitamin A and vaccines were not investigated in randomised trials prior to the implementation of this policy - it was assumed that the interventions were independent. My first project aimed to study the effect on the immune response to measles of providing vitamin A together with measles vaccine. We found that the two interventions were not independent. Vitamin A enhanced the antibody response to measles vaccine given at 9 months of age significantly, especially in boys. The effects were sustained over time; the children who had received vitamin A with their measles vaccine were more protected against measles at 6-8 years of age. Though vitamin A supplementation had a beneficial effect on the immune response to measles vaccine, it intrigued me that the effect of vitamin A supplementation on overall mortality was not always beneficial. While vitamin A was beneficial when given after 6 months of age, and two studies had shown a beneficial effect when given at birth, all studies testing the effect between 1-5 months of age had found no effect. These time windows are dominated by three different childhood vaccines: BCG vaccine given at birth, diphtheria-tetanus-pertussis (DTP) vaccine given between 1-5 months of age, and measles vaccine given at 9 months of age. These vaccines have been shown to have strong effects on mortality from infectious diseases in general, so-called non-specific effects. The live BCG and measles vaccine protects against more mortality than can be ascribed to the prevention of tuberculosis and measles, respectively. The inactivated DTP vaccine worryingly has been associated with increased mortality from other infectious diseases. Both positive and negative effects are strongest for girls. I proposed the hypothesis that vitamin A amplifies not only the specific vaccine effects, as we saw for measles vaccine, but also the non-specific effects of vaccines on mortality from other infectious diseases. According to my hypothesis, vitamin A would enhance the non-specific beneficial effects on mortality of BCG and measles vaccine, but also the negative effects of DTP vaccine. Hence, the hypothesis offered an explanation for the mortality-age pattern after vitamin A supplementation. Since it was formulated, I have aimed to test this hypothesis. Since it is associated with ethical problems to randomise children above 6 months of age to vitamin A supplementation, and to randomise children in general to recommended vaccines, we have had to be pragmatic when designing the trials. Hence, our studies have taken many different forms. We conducted an observational study during a vitamin A campaign in which missing vaccines were also provided, and a randomised trial testing the effect of two different doses of vitamin A during another campaign; we tested the effect of providing vitamin A with BCG at birth in two randomised trials, and we reanalysed data from one of the original randomised trials of vitamin A supplementation from the perspective of vaccination status. In all studies the main outcome was mortality. The results document that vitamin A supplements do more than protect against vitamin A deficiency. They support the hypothesis that vitamin A supplements interact with vaccines with important consequences for mortality. First, a smaller dose of vitamin A was more beneficial than a larger dose for girls. Second, the effect of vitamin A given with DTP vaccine was significantly different from the effect of vitamin A given with measles vaccine, and children, who received vitamin A with DTP vaccine, had higher mortality than children, who had received vitamin A alone, or who did not receive anything. Third, vitamin A given with BCG at birth interacted negatively with subsequent DTP vaccines in girls. Fourth, the effect of vitamin A to older children in Ghana depended on vaccination status, being beneficial in boys, but harmful in girls who received DTP vaccine during follow-up. The results also show that boys and girls respond differently to vitamin A and vaccines. It is a common assumption within public health in low-income countries that interventions can be combined without producing unexpected consequences. The work presented in this thesis confronts this assumption; the results show that vitamin A and vaccines should be seen not only as specific interventions with specific and independent effects, but as immuno-modulators, which can interact with important consequences for overall mortality. Combining interventions can be convenient and lead to synergistic health benefits, but we documented several examples, where it also leads to unexpectedly increased mortality. Thus, to optimise the child health intervention policy in low-income countries a shift in paradigm is needed. Health interventions should no longer be seen as merely specific and independent, and the policy should probably not be the same for boys and girls. Though more complex, it is necessary to evaluate all health interventions in terms of their effect on overall mortality - and their potential interactions with other health interventions and potential sex-differential effects should always be investigated. Only in this way can we assure that the children in the poorest countries get the best possible treatment and avoid using large amounts of money and resources on interventions which may, in worst case, kill them.

http://www.ncbi.nlm.nih.gov/pubmed/22239846

“In all studies the main outcome was mortality. The results document that vitamin A supplements do more than protect against vitamin A deficiency. They support the hypothesis that vitamin A supplements interact with vaccines with important consequences for mortality. First, a smaller dose of vitamin A was more beneficial than a larger dose for girls. Second, the effect of vitamin A given with DTP vaccine was significantly different from the effect of vitamin A given with measles vaccine, and children, who received vitamin A with DTP vaccine, had higher mortality than children, who had received vitamin A alone, or who did not receive anything. Third, vitamin A given with BCG at birth interacted negatively with subsequent DTP vaccines in girls. Fourth, the effect of vitamin A to older children in Ghana depended on vaccination status, being beneficial in boys, but harmful in girls who received DTP vaccine during follow-up. The results also show that boys and girls respond differently to vitamin A and vaccines. It is a common assumption within public health in low-income countries that interventions can be combined without producing unexpected consequences. The work presented in this thesis confronts this assumption; the results show that vitamin A and vaccines should be seen not only as specific interventions with specific and independent effects, but as immuno-modulators, which can interact with important consequences for overall mortality. Combining interventions can be convenient and lead to synergistic health benefits, but we documented several examples, where it also leads to unexpectedly increased mortality.”

Vaccine • January 2005

Routine vaccinations associated with divergent effects on female and male mortality at the paediatric ward in Bissau, Guinea-Bissau

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Abstract

Several studies have suggested that routine childhood immunisations may have non-specific effects on mortality. To examine which disease categories might be affected, we investigated whether immunisation status had an impact on the case fatality for hospitalised children. Between 1990 and 1996, the Bandim Health Project maintained a register of all children from the study area hospitalised at the paediatric ward of the central hospital in Bissau, Guinea-Bissau. The study included 2079 hospitalised children aged 1.5-17 months coming from the Bandim study area. Among children whose vaccination card had been seen at admission, the case fatality ratio for measles-vaccinated children versus measles-unvaccinated children was 0.51 (0.27-0.98), the beneficial effect being significantly stronger for girls than for boys (test of interaction, p=0.050). The protective effect of measles vaccine remained unchanged when hospitalised measles cases were excluded from the analysis (0.49 (0.26-0.94)). The effect of measles vaccine was strongest for children with pneumonia (MR=0.28 (0.07-0.91)) and presumptive malaria (MR=0.40 (0.13-1.18)). For measles-vaccinated children, the female to male case fatality ratio was 0.54 (0.28-0.97). Among children having received diphtheria-tetanus-pertussis (DTP) and oral polio (OPV) as the last vaccines, girls had higher case fatality than boys, the mortality ratio being 1.63 (1.03-2.59). The female to male ratios were significantly inversed for DTP and OPV versus measles vaccine (test of interaction, p=0.003). These results remained unchanged if 1-month post-discharge deaths were included in the analysis, and in multivariate analyses controlling for determinants of mortality. In conclusion, measles vaccine was associated with reduced mortality from diseases other than measles, the beneficial effect being stronger for girls than for boys. On the other hand, DTP and OPV vaccine were associated with higher case fatality for girls than for boys. Understanding the divergent non-specific effects of common vaccines may contribute to better child survival in developing countries.

http://www.ncbi.nlm.nih.gov/pubmed/15629363

“Diphtheria-Tetanus-Pertussis and Oral Polio Vaccine were associated with higher case fatality for girls than for boys.”

Reviews In Medical Virology • January 2005

Viruses as adjuvants for autoimmunity: evidence from Coxsackievirus-induced myocarditis

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Abstract

Adjuvants historically are considered to stimulate immune responses 'non-specifically'. Recently, a renewed understanding of the critical role of innate immunity in influencing the development of an adaptive immune response has led researchers to a better understanding of 'the adjuvant effect'. Although innate immune cells do not respond to specific antigenic epitopes on pathogens, they do produce restricted responses to particular classes of pathogens via pattern recognition receptors such as Toll-like receptors (TLR). Coxsackievirus infection was found to upregulate TLR4 on mast cells and macrophages immediately following infection. Although both susceptible and resistant mice produce a mixture of Th1 and Th2 cytokines, susceptible mice have increased levels of key proinflammatory cytokines, increased numbers of mast cells, and go on to develop chronic autoimmune heart disease. TLR4 signalling also increases acute myocarditis and proinflammatory cytokines in the heart. Many similarities are described in the pathogenesis of Coxsackievirus and the adjuvant-induced model of myocarditis including upregulation of particular TLRs and cytokines soon after inoculation. Recent findings suggest that mast cell activation by viruses or adjuvants may be important in initiating autoimmune disease.

http://www.ncbi.nlm.nih.gov/pubmed/15386590

"... mast cell activation by viruses or adjuvants may be important in initiating autoimmune disease."

Autoimmunity Reviews • February 2005

Autoimmune hazards of hepatitis B vaccine

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Abstract

According to Hippocratic tradition, the safety level of a preventive medicine must be very high, as it is aimed at protecting people against diseases that they may not contract. This paper points out that information on the safety of hepatitis B vaccine (HBV) is biased as compared to classical requirements of evidence-based medicine (EBM), as exemplified by a documented selectivity in the presentation or even publication of available clinical or epidemiological data. Then, a review is made of data suggesting that HBV is remarkable by the frequency, the severity and the variety of its complications, some of them probably related to a mechanism of molecular mimicry leading to demyelinating diseases, and the others reproducing the spectrum of non-hepatic manifestations of natural hepatitis B. To be explained, this unusual spectrum of toxicity requires additional investigations based upon complete release of available data.

http://www.ncbi.nlm.nih.gov/pubmed/15722255

“... a review is made of data suggesting that Hepatitus B Vaccine is remarkable by the frequency, the severity and the variety of its complications, some of them probably related to a mechanism of molecular mimicry leading to demyelinating diseases, and the others reproducing the spectrum of non-hepatic manifestations of natural hepatitis B.”

“Result suggests that polysorbate 80 (at clinically-relevant concentrations) may increase the susceptibility of cells to oxidative stress.”

Toxicology • February 2005

Polysorbate 80 increases the susceptibility to oxidative stress in rat thymocytes

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Abstract

Effect of simultaneous application of polysorbate 80, a nonionic surfactant widely used in pharmaceutical products, and hydrogen peroxide on rat thymocytes was examined to see if polysorbate 80 increases the susceptibility to oxidative stress because this surfactant decreases the cellular content of glutathione. Polysorbate 80 at clinically-relevant concentrations increases the cytotoxicity of hydrogen peroxide under the in vitro condition. Result suggests that polysorbate 80 may increase the susceptibility of cells to oxidative stress.

http://www.ncbi.nlm.nih.gov/pubmed/15590117

Journal Of The American Academy Of Dermatology • April 2005

Vaccination-induced cutaneous pseudolymphoma

Author information

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Abstract

BACKGROUND
Although mild early cutaneous transient reactions to vaccinations are common, late-onset chronic lesions have been scarcely reported. We report herein a series of 9 patients presenting with cutaneous and subcutaneous pseudolymphoma.

OBSERVATIONS
Nine patients presenting with late-onset, chronic skin lesions occurring at the site of antihepatitis B (8 cases) and antihepatitis A (one case) vaccination were reported. Histopathologic and immunohistochemic studies, and molecular analysis of clonality of skin biopsy specimens, were performed. Furthermore, the presence of vaccine products was investigated in skin lesions by using histochemical, microanalytic, and electronic microscopy techniques.

RESULTS
Histopathologic studies showed dermal and hypodermal lymphocytic follicular infiltrates with germinal center formation. The center of follicles was mostly composed of B cells without atypia, whereas CD4+ T cells were predominant at the periphery. Molecular analysis of clonality revealed a polyclonal pattern of B-cell and T-cell subsets. Aluminium deposits were evidenced in all cases by using histochemical staining in all cases, and by microanalysis and ultrastructural studies in one case. Associated manifestations were vitiligo (one case) and chronic fatigue with myalgia (two cases).

CONCLUSION
Cutaneous lymphoid hyperplasia is a potential adverse effect of vaccinations including aluminium hydroxide as an adjuvant. Further prospective studies are warranted to evaluate the incidence of this complication in the immunized population.

http://www.ncbi.nlm.nih.gov/pubmed/?term=15793512

“Cutaneous lymphoid hyperplasia is a potential adverse effect of vaccinations including aluminium hydroxide as an adjuvant.”

Autoimmunity • May 2005

Infection, vaccines and other environmental triggers of autoimmunity

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Abstract

The etiology of autoimmune diseases is still not clear but genetic, immunological, hormonal and environmental factors are considered to be important triggers. Most often autoimmunity is not followed by clinical symptoms unless an additional event such as an environmental factor favors an overt expression. Many environmental factors are known to affect the immune system and may play a role as triggers of the autoimmune mosaic.Infections: bacterial, viral and parasitic infections are known to induce and exacerbate autoimmune diseases, mainly by the mechanism of molecular mimicry. This was studied for some syndromes as for the association between SLE and EBV infection, pediatric autoimmune neuropsychiatric disorders associated with streptococcal infection and more. Vaccines, in several reports were found to be temporally followed by a new onset of autoimmune diseases. The same mechanisms that act in infectious invasion of the host, apply equally to the host response to vaccination. It has been accepted for diphtheria and tetanus toxoid, polio and measles vaccines and GBS. Also this theory has been accepted for MMR vaccination and development of autoimmune thrombocytopenia, MS has been associated with HBV vaccination. Occupational and other chemical exposures are considered as triggers for autoimmunity. A debate still exists about the role of silicone implants in induction of scleroderma like disease.Not only foreign chemicals and agents have been associated with induction of autoimmunity, but also an intrinsic hormonal exposure, such as estrogens. This might explain the sexual dimorphism in autoimmunity. Better understanding of these environmental risk factors will likely lead to explanation of the mechanisms of onset and progression of autoimmune diseases and may lead to effective preventive involvement in specific high-risk groups. So by diagnosing a new patient with autoimmune disease a wide anamnesis work should be done.

http://www.ncbi.nlm.nih.gov/pubmed/16126512

“The same mechanisms
that act in infectious invasion of the host,
apply equally to the host response to vaccination.

It has been accepted for diphtheria and tetanus toxoid,
polio and measles vaccines and Guillain Barre Syndrome.

Also this theory has been accepted for MMR vaccination
and development of autoimmune thrombocytopenia,
Multiple Sclerosis has been associated with HBV vaccination.”

Neurologic Clinics • May 2005

Neurodegenerative memory disorders: a potential role of environmental toxins

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Abstract

The hypothesis that neurotoxins may play a role in neurodegenerative disorders remains an elusive one, given that epidemiologic studies often provide conflicting results. Although these conflicting results may result from methodological differences within and between studies, the complexity of chemical disruption of the central nervous system cannot be ignored in attempts to evaluate this hypothesis in different neurodegenerative disorders. Spencer provides a detailed review of the complex processes involved in defining the neurotoxic potential of naturally occurring and synthetic agents. Even concepts such as exposure and dose, as often reported in studies attempting to evaluate the risk imparted by a potential compound, can be deceptive. For example, although dose reflects "that amount of chemical transferred to the exposed subject", factors such as time and concentration in the organism, the ability to access the central nervous system, and how a compound reaches the central nervous system (routes of administration) or secondarily affects other organ systems leading to central nervous system disruption are clearly important to the concept of neurotoxic risk in neurodegenerative disorders. These factors would appear to explain the observed disagreements between studies using animal or neuronal models of neurotoxicity and population-based studies in humans. The importance of these factors and how a potential neurotoxin is investigated are clearly seen in the data on AD and aluminum. In contrast, the impact of MTPT on the central nervous system is more direct and compelling. Added complexity in the study of neurotoxins in human neurodegeneration is derived from data showing that agents may have additive, potentiating, synergistic, or antagonistic effects. Therefore, data from studies evaluating EMF risks could be readily confounded by the presence or absence of heavy metals (eg, arc welding). Other factors that may conceal neurotoxic causes for a given disorder focus on additional features such as genetic predispositions, physiologic changes that occur in aging, and even nutritional status that can support or hinder the affect of a given agent on the central nervous system. Finally, many studies that investigate exposure risk do not readily incorporate the five criteria proposed by Schaumburg for establishing causation. For example, if we apply Schaumburg's first criterion, epidemiologic studies often determines the presence of an agent through history, yet they cannot readily confirm exposure based on environmental or clinical chemical analyses to fulfill this criterion for causation. Additional limitations in research design along with the populations and methods that are sued to study neurotoxins in human neurodegenerative disorders often fail to meet other criteria such as linking the severity and onset with duration and exposure level. Therefore, although studies of agents such as MTPT provide compelling models of neurotoxins and neurodegeneration in humans, disorders such as ALS, PD, and particularly AD will require additional effort if research is to determine the contribution (presence or absence) of neurotoxins to these neurologic disorders.

http://www.ncbi.nlm.nih.gov/pubmed/15757794

"Added complexity in the study of neurotoxins in human neurodegeneration is derived from data showing that agents may have additive, potentiating, synergistic, or antagonistic effects."

Journal Of Neurochemistry • May 2005

Vaccination alone or in combination with pyridostigmine promotes and prolongs activation of stress-activated kinases induced by stress in the mouse brain

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Abstract

Gulf war illnesses (GWI) are currently affecting thousands of veterans. To date, the molecular mechanisms underlying the pathogenesis of these illnesses remain unknown. During Gulf war I, military personnel were exposed to multiple stressors, one or more vaccines, pyridostigmine (PY), and other chemicals. In our previous studies, we found that stress induces activation of mitogen activated protein-kinase kinase 4 (MKK4) and c-Jun-N-terminal kinase (JNK) in the mouse brain (Liu et al. 2004). Our working hypothesis is that stress, vaccination, and PY may synergistically induce activation of MKK4 and JNK in the brain, leading to over-activation of these kinases and neurological injuries. To test our hypothesis, we examined the effect of keyhole limpet hemocyanin (KLH) immunization alone or in combination with PY on activation of MKK4 and JNK induced by stress. We found that KLH immunization alone had a small effect on MKK4 or JNK activity but it significantly enhanced and prolonged activation of these kinases induced by stress, from a few hours to several days. Additionally, KLH immunization caused activation of p38MAPK. PY treatment further enhanced and prolonged activation of these kinases induced by stress in combination with KLH immunization and triggered activation of caspase-3. Our current studies suggest that stress, vaccination, and PY may synergistically act on multiple stress-activated kinases in the brain to cause neurological impairments in GWI.

http://www.ncbi.nlm.nih.gov/pubmed/?term=15857404

“Our current studies suggest that stress, vaccination, and pyridostigmine may synergistically act on multiple stress-activated kinases in the brain to cause neurological impairments in Gulf War Illness.”

Journal Of Hygiene Research • May 2005

Effect of formaldehyde on energy metabolism in postnatal rat cortex neurons in culture

Author information

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Abstract

OBJECTIVE:
The mechanism of the effect of formaldehyde on CNS which is much concerned to formaldehyde poisoning was studied.

METHODS:
In the present study, incubation of postnatal rat cortex neurons in culture with formaldehyde at 1, 2, 4, 8 mg/L (medium) was carried out to evaluate the effect of formaldehyde on energy metabolism.

RESULTS:
The result of cytochemistry showed a significant down-regulation of cytochrome oxidase activity after consecutive formaldehyde treatment for 4 hours compared with the control ($P < 0.01$), the significant dosage-response relationship was also observed (R value is - 0.92, $P < 0.01$).

CONCLUSION:
The result demonstrates that excessive exposure of formaldehyde can decrease cytochrome oxidase activity in cortex neurons which indicates energy metabolism will be decreased and therefore normal physiology function would be damaged.

http://www.ncbi.nlm.nih.gov/pubmed/?term=16111027

“The result demonstrates that excessive exposure of formaldehyde can decrease cytochrome oxidase activity in cortex neurons which indicates energy metabolism will be decreased and therefore normal physiology function would be damaged.”

Autoimmunity • June 2005

A case-control study of serious autoimmune adverse events following hepatitis B immunization

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Abstract

Hepatitis B infection is one of the most important causes of acute and chronic liver disease. During the 1980s, genetically engineered hepatitis B vaccines (HBVs) were introduced in the United States. A large-series of serious autoimmune conditions have been reported following HBVs, despite the fact that HBVs have been reported to be "generally well-tolerated." A case-control epidemiological study was conducted to evaluate serious autoimmune adverse events prospectively reported to the vaccine adverse events reporting system (VAERS) database following HBVs, in comparison to an age, sex, and vaccine year matched unexposed tetanus-containing vaccine (TCV) group for conditions that have been previously identified on an a priori basis from case-reports. Adults receiving HBV had significantly increased odds ratios (OR) for multiple sclerosis (OR = 5.2, $p < 0.0003$, 95% Confidence Interval (CI) = 1.9 - 20), optic neuritis (OR = 14, $p < 0.0002$, 95% CI = 2.3 - 560), vasculitis (OR = 2.6, $p < 0.04$, 95% CI = 1.03 - 8.7), arthritis (OR = 2.01, $p < 0.0003$, 95% CI = 1.3 - 3.1), alopecia (OR = 7.2, $p < 0.0001$, 95% CI = 3.2 - 20), lupus erythematosus (OR = 9.1, $p < 0.0001$, 95% CI = 2.3 - 76), rheumatoid arthritis (OR = 18, $p < 0.0001$, 95% CI = 3.1 - 740), and thrombocytopenia (OR = 2.3, $p < 0.04$, 95% CI = 1.02 - 6.2) in comparison to the TCV group. Minimal confounding or systematic error was observed. Despite the negative findings of the present study regarding the rare serious adverse effects of HBVs, it is clear that HBV does, indeed, offer significant benefits, but it is also clear that chances of exposure to hepatitis B virus in adults is largely life-style dependent. Adults should make an informed consent decision, weighing the risks and benefits of HBV, as to whether or not to be immunized.

http://www.ncbi.nlm.nih.gov/pubmed/?term=16206512

"Adults receiving Hepatitus B Vaccine had significantly increased odds ratios (OR) for multiple sclerosis ... optic neuritis ... vasculitis ... arthritis ... alopecia ... lupus erythematosus ... rheumatoid arthritis and thrombocytopenia"

Environmental Health Perspectives • September 2005

Meeting report: summary of IARC monographs on formaldehyde, 2-butoxyethanol, and 1-tert-butoxy-2-propanol

Author information

Cogliano VJ1, Grosse Y, Baan RA, Straif K, Secretan MB, El Ghissassi F; Working Group for Volume 88

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Abstract

An international, interdisciplinary working group of expert scientists met in June 2004 to develop IARC Monographs on the Evaluation of the Carcinogenic Risk of Chemicals to Humans (IARC Monographs) on formaldehyde, 2-butoxyethanol, and 1-tert-butoxy-2-propanol. Each IARC Monograph includes a critical review of the pertinent scientific literature and an evaluation of an agent's potential to cause cancer in humans. After a thorough discussion of the epidemiologic, experimental, and other relevant data, the working group concluded that formaldehyde is carcinogenic to humans, based on sufficient evidence in humans and in experimental animals. In the epidemiologic studies, there was sufficient evidence that formaldehyde causes nasopharyngeal cancer, "strong but not sufficient" evidence of leukemia, and limited evidence of sinonasal cancer. The working group also concluded that 2-butoxyethanol and 1-tert-butoxy-2-propanol are not classifiable as to their carcinogenicity to humans, each having limited evidence in experimental animals and inadequate evidence in humans. These three evaluations and the supporting data will be published as Volume 88 of the IARC Monographs.

http://www.ncbi.nlm.nih.gov/pubmed/?term=16140628

"there was sufficient evidence that formaldehyde causes nasopharyngeal cancer, "strong but not sufficient" evidence of leukemia, and limited evidence of sinonasal cancer."

Cochrane Database Systematic Review • October 2005

Vaccines for measles, mumps and rubella in children

Author information

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Abstract

BACKGROUND

Public debate over the safety of the trivalent measles, mumps and rubella (MMR) vaccine, and the resultant drop in vaccination rates in several countries, persists despite its almost universal use and accepted effectiveness.

OBJECTIVES

We carried out a systematic review to assess the evidence of effectiveness and unintended effects associated with MMR.

SEARCH STRATEGY

We searched the Cochrane Central Register of Controlled Trials (CENTRAL) (The Cochrane Library Issue 4, 2004), MEDLINE (1966 to December 2004), EMBASE (1974 to December 2004), Biological Abstracts (from 1985 to December 2004), and Science Citation Index (from 1980 to December 2004). Results from reviews, handsearching and from the consultation of manufacturers and authors were also used.

SELECTION CRITERIA

Eligible studies were comparative prospective or retrospective trials testing the effects of MMR compared to placebo, do-nothing or a combination of measles, mumps and rubella antigens on healthy individuals up to 15 years of age. These studies were carried out or published by 2004.

DATA COLLECTION AND ANALYSIS

We identified 139 articles possibly satisfying our inclusion criteria and included 31 in the review.

MAIN RESULTS

MMR was associated with a lower incidence of upper respiratory tract infections, a higher incidence of irritability, and similar incidence of other adverse effects compared to placebo. The vaccine was likely to be associated with benign thrombocytopenic purpura, parotitis, joint and limb complaints, febrile convulsions within two weeks of vaccination and aseptic meningitis (mumps) (Urabe strain-containing MMR). Exposure to MMR was unlikely to be associated with Crohn's disease, ulcerative colitis, autism or aseptic meningitis (mumps) (Jeryl-Lynn strain-containing MMR). We could not identify studies assessing the effectiveness of MMR that fulfilled our inclusion criteria even though the impact of mass immunisation on the elimination of the diseases has been largely demonstrated.

AUTHORS' CONCLUSIONS

The design and reporting of safety outcomes in MMR vaccine studies, both pre- and post-marketing, are largely inadequate. The evidence of adverse events following immunisation with MMR cannot be separated from its role in preventing the target diseases.

http://www.ncbi.nlm.nih.gov/pubmed/16235361

"The design and reporting of safety outcomes in MMR vaccine studies, both pre- and post-marketing, are largely inadequate. The evidence of adverse events following immunisation with MMR cannot be separated from its role in preventing the target diseases."

Clinical And Experimental Immunology • November 2005

Anti-phospholipid antibodies following vaccination with recombinant hepatitis B vaccine

Author information

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Abstract

This study was undertaken to evaluate the possible role of hepatitis B recombinant vaccine inducing the synthesis of IgG and IgM anti-cardiolipin antibodies (aCL), antibodies against beta(2)GPI (anti-beta(2)GPI), lupus anti-coagulant (LA), anti-nuclear antibodies and antibodies against extractable nuclear antigens (anti-ENA). The study population consisted of 85 healthy students (63 female, 22 male; mean age 20.8 years), vaccinated with three doses of recombinant DNA hepatitis B vaccine. One month after vaccination with the first dose of hepatitis B vaccine a minority of vaccinated individuals showed changes in IgG or IgM aCL or anti-beta(2)GPI or LA activity ($P < 0.001$). Among subjects in whom changes of IgG anti-beta(2)GPI were observed, a significantly higher number of increased (8/85) than decreased (2/85) values were found ($P < 0.01$). Analyses of paired data showed that differences in aCL or anti-beta(2)GPI levels before vaccination or 1 month later did not reach statistical significance. In two people aCL transitorily reached medium positivity after the first dose of hepatitis B vaccine with a drop 5 months later. Similar evident anti-beta(2)GPI fluctuation was also observed in one person. Another participant was initially low positive for IgG anti-beta2GPI and the levels were increasing after vaccination. Two participants became positive for anti-nuclear antibodies during 6 months' follow-up. There were no sex-dependent differences in tested antibodies observed and no associations between levels of aPL and levels of anti-HBV antibodies. We conclude that HBV can induce aPL, although rarely. In genetically susceptible individuals or together with some other triggers such combination might confer the risk of developing a continuous autoimmune response in an individual.

Full Report

http://www.ncbi.nlm.nih.gov/pmc/articles/PMC1809502/

" In genetically susceptible individuals or together with some other triggers such combination might confer the risk of developing a continuous autoimmune response in an individual."

Editors Note:
aPL or Antiphospholipid Syndrome

Antiphospholipid syndrome or antiphospholipid antibody syndrome (APS or APLS), or often also Hughes syndrome, is an autoimmune, hypercoagulable state caused by antiphospholipid antibodies. APS provokes blood clots (thrombosis) in both arteries and veins as well as pregnancy-related complications such as miscarriage, stillbirth, preterm delivery, and severe preeclampsia.

Antiphospholipid syndrome can be primary or secondary. Primary antiphospholipid syndrome occurs in the absence of any other related disease. Secondary antiphospholipid syndrome occurs with other autoimmune diseases, such as systemic lupus erythematosus (SLE). In rare cases, APS leads to rapid organ failure due to generalised thrombosis; this is termed "catastrophic antiphospholipid syndrome" (CAPS) and is associated with a high risk of death.

Antiphospholipid syndrome often requires treatment with anticoagulant medication such as heparin to reduce the risk of further episodes of thrombosis and improve the prognosis of pregnancy. Warfarin/Coumadin is not used during pregnancy because it can cross the placenta, unlike heparin, and is teratogenic.

Pediatrics And Neurology • November 2005

Macrophagic myofasciitis in childhood: a controversial entity

Author information

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Abstract

Macrophagic myofasciitis is an unusual inflammatory myopathy, which has been almost exclusively reported in French adults with diffuse arthromyalgias and asthenia. It is characterized by an infiltrate of densely packed macrophages, with granular periodic-acid-Schiff positive content, on muscle biopsies at the site of vaccination. The presence of aluminum inclusions in these macrophages points to an inappropriate reaction to aluminum used as an adjuvant in some vaccines. Although in adults this entity is well defined, less than 15 cases have been reported in children. This study describes seven children, younger than 3 years of age, with typical lesions of macrophagic myofasciitis on quadriceps muscle biopsy. In five cases, biopsies were performed to exclude mitochondrial pathology. All the children developed hypotonia and motor or psychomotor delay, associated with others symptoms. Abnormal neuroimaging was evident in six cases. Spectrometry studies detected elevated levels of aluminum in muscle in three of four cases tested. Despite the wide use of vaccines in childhood, macrophagic myofasciitis was rarely observed in children and its characteristic histologic pattern could not be correlated with a distinctive clinical syndrome.

http://www.ncbi.nlm.nih.gov/pubmed/?term=16243223

“Although in adults this entity is well defined, less than 15 cases have been reported in children. This study describes seven children, younger than 3 years of age, with typical lesions of macrophagic myofasciitis on quadriceps muscle biopsy.”

European Journal Of Pediatrics • November 2005

Nineteen cases of persistent pruritic nodules and contact allergy to aluminium after injection of commonly used aluminium-adsorbed vaccines

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Abstract

Rare cases of persistent pruritic nodules, sometimes associated with aluminium (Al) allergy, have been reported after the use of several Al adsorbed vaccines. During vaccine trials in the 1990s a high incidence of pruritic nodules (645 cases/76,000 recipients), in 77% associated with Al allergy, was observed after the administration of diphtheria-tetanus / acellular pertussis (DT/aP) vaccines from a single producer. In the present report 19 children with pruritic nodules after vaccination with Al hydroxide-adsorbed DTaP/polio+Hib (Infanrix, Pentavac) are described. The children had intensely itching nodules at the injection site, often aggravated during upper respiratory tract infections, and local skin alterations. So far, the symptoms have persisted for up to 7 years. The median time between vaccination and onset of symptoms was 1 month. 16 children were epicutaneously tested for Al, all with positive reactions indicating delayed hypersensitivity to Al. The condition is not commonly known but is important to recognise, as the child and the family may suffer considerably. Future vaccinations with Al-adsorbed vaccines may cause aggravation of the symptoms and the Al allergy. Al-containing skin products, such as antiperspirants, may cause contact dermatitis. Nodules may be mistaken for tumours. Even though the incidence of itching nodules and Al allergy after administration of Infanrix, Pentavac and other Al-adsorbed vaccines is probably low, research to replace Al adjuvants seems appropriate. We conclude that intensely itching subcutaneous nodules, lasting for many years, and hypersensitivity to aluminium may occur after DTaP/polio+Hib vaccination of infants.

http://www.ncbi.nlm.nih.gov/pubmed/?term=16044278

“... intensely itching subcutaneous nodules, lasting for many years, and hypersensitivity to aluminium may occur after DTaP/polio + Hib vaccination of infants.”

Medical Hypotheses • 2005

Do cytosine guanine dinucleotide (CpG) fragments induce vasoactive neuropeptide mediated fatigue-related autoimmune disorders?

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Abstract

Autoimmune dysfunction of certain vasoactive neuropeptides (e.g., vasoactive intestinal peptide, pituitary adenylate cyclase activating polypeptide) may be implicated in a range of disorders associated with fatigue-like states (chronic fatigue syndrome, Gulf War syndrome) and even sudden infant death syndrome (SIDS). The important roles of these vasoactive neuropeptides make them a vulnerable target for autoimmune dysfunction. They are known to be associated with heat shock proteins for intracellular functioning with which they may form immunostimulating complexes. Cytosine guanine dinucleotide (CpG) fragments are potently immunogenic DNA fragments which serve as friend or foe recognition systems between bacterial (hypomethylated) and mammalian (methylated) DNA and are being assessed for suitability for use in human vaccines as adjuvants. Interactions between CpG fragments, heat shock proteins and vasoactive neuropeptides may be associated with fatigue-related autoimmune conditions.

http://www.ncbi.nlm.nih.gov/pubmed/15922114

“Interactions between CpG fragments, heat shock proteins and vasoactive neuropeptides may be associated with fatigue-related autoimmune conditions.”

“In this study, 24.5% of asymptomatic children from 6 months to 5 years of age were sensitized to one or more contact allergens, and thimerosal was the second most prevalent allergen ...”

Dermatitis • 2005

Hypersensitivity Reactions to Vaccine Components

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Excerpt

This article will review adverse cutaneous events consistent with hypersensitivity reactions to the following ingredients in vaccines: aluminum, thimerosal, 2-phenoxyethanol, formaldehyde, and neomycin.

Despite the low clinical relevance of thimerosal allergy, the rate of thimerosal sensitivity has increased during the last decade, probably because of the increase in vaccines administered during infancy. With the initiation of a mass vaccination campaign in Austria in 1981, the administration of thimerosal-containing vaccines for tick-borne encephalitis (TBE) increased from 6% in 1980 to 86% in 2001. The growing number of people immunized to TBE has been concomitant with an increase in thimerosal-sensitized individuals in Austria.[14,20]

Bruckner and colleagues investigated the prevalence of positive patch-test results using the TRUE Test system (Mekos Laboratories A/S, Hillerød, Denmark) on children under 5 years of age to determine whether sensitization to contact allergens was common in infancy.[21]

In this study, 24.5% of asymptomatic children from 6 months to 5 years of age were sensitized to one or more contact allergens, and thimerosal was the second most prevalent allergen (after nickel). Vaccines thus appear to sensitize children to thimerosal at a younger age than expected, given the unlikeliness of contact exposure in this age group to other thimerosal-containing products. Osawa and colleagues also demonstrated this phenomenon by associating DTP vaccination with thimerosal sensitivity in a guinea pig model.[22]

To determine whether patients with thimerosal allergy could tolerate vaccination, Audicana and colleagues evaluated tolerance to thimerosal-containing vaccines in 125 patients sensitized to mercury derivatives and/or thimerosal.[23] Patch-test results in this patient population revealed that 45% of patients had positive reactions to thimerosal (0.05% in petrolatum), 74% had positive reactions to metallic mercury (0.5% in petrolatum), and 70% had positive reactions to mercury chloride (0.1% in water). In 10 cases, of all mercury derivatives tested, thimerosal yielded the only positive patch-test result. A questionnaire revealed that the likely source of sensitization in the 57 thimerosal patch-test-positive patients was vaccination.

Full Report

http://www.medscape.com/viewarticle/516045

Virchows Archives • January 2006

Sudden infant death syndrome (SIDS) shortly after hexavalent vaccination: another pathology in suspected SIDS?

Author information

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Abstract

Experts from panels of the European Agency for the Evaluation of Medical Products have investigated whether there might be a link between hexavalent vaccines and some cases of deaths that occurred. Participants included pathologists with experience in the field of vaccines and sudden infant death syndrome who conducted autopsies. However, to the best of our knowledge, little, if any, attention was paid to examination of the brainstem and the cardiac conduction systems on serial sections, nor was the possibility of a triggering role of the vaccine in these deaths considered. Herein we report the case of a 3-month-old female infant dying suddenly and unexpectedly shortly after being given a hexavalent vaccination. Examination of the brainstem on serial sections revealed bilateral hypoplasia of the arcuate nucleus. The cardiac conduction system presented persistent fetal dispersion and resorptive degeneration. This case offers a unique insight into the possible role of hexavalent vaccine in triggering a lethal outcome in a vulnerable baby. Any case of sudden unexpected death occurring perinatally and in infancy, especially soon after a vaccination, should always undergo a full necropsy study according to our guidelines.

http://www.ncbi.nlm.nih.gov/pubmed/16231176

“This case offers a unique insight into the possible role of hexavalent vaccine in triggering a lethal outcome in a vulnerable baby. Any case of sudden unexpected death occurring perinatally and in infancy, especially soon after a vaccination, should always undergo a full necropsy study according to our guidelines.”

Vaccine • April 2006

Low-dose intraperitoneal Freund's adjuvant: toxicity and immunogenicity in mice using an immunogen targeting amyloid-beta peptide

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Abstract

Complete Freund's adjuvant (CFA) is effective for potentiating immune responses in mice when administered subcutaneously, and is often more potent when given intraperitoneally (i.p.). However, the the potential toxicity of i.p. administration in mice has led investigators and Institutional Animal Care and Use committees to increasingly view the use of CFA i.p. with reservation. We evaluated whether an 80% reduction in the dose of CFA administered i.p. to mice, compared to the i.p. doses used in a previous analysis, could abrogate the untoward effects associated with its use, while still maintaining adjuvanticity. Using a novel immunogen targeting the N-terminus of the 42-amino acid amyloid-beta peptide, we compared low dose CFA administered i.p., with three other commonly used adjuvants given i.p.: alum, incomplete Freunds adjuvant (IFA) and monophoshoryl lipid A + trehalose dicorynomycolate (MPL + TDM). The results of the study showed that, though the reduction in intraperitoneal dose of CFA mitigated transient weight loss and leukocytosis observed previously with higher doses of i.p. CFA, all mice administered CFA or IFA i.p. developed abdominal adhesions and granulomatous peritonitis. Mice from all adjuvant groups, however, appeared to tolerate the respective adjuvants well and excellent comparative immunogenicity was observed in mice immunized with the Freunds and MPL + TDM adjuvants. Consequently, we conclude that though a high-titered, humoral response may be generated using low dose CFA administered i.p., the accompanying toxicity remains significant, and thus alternative adjuvants and/or routes should be considered.

http://www.ncbi.nlm.nih.gov/pubmed/?term=16307832

"Consequently, we conclude that though a high-titered, humoral response may be generated using low dose CFA [still used in several vaccines today] administered i.p., the accompanying toxicity remains significant, and thus alternative adjuvants and/or routes should be considered."

“Adverse cardiorespiratory events including apnea, bradycardia, and desaturations have been described following administration of the first diphtheria-tetanus-pertussis-inactivated polio-Haemophilus influenzae type B (DTP-IPV-Hib) immunization to preterm infants.”

BMC Pediatrics • June 2006

Frequency of apnea, bradycardia, and desaturations following first diphtheria-tetanus-pertussis-inactivated polio-Haemophilus influenzae type B immunization in hospitalized preterm infants

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Abstract

Background

Adverse cardiorespiratory events including apnea, bradycardia, and desaturations have been described following administration of the first diphtheria-tetanus-pertussis-inactivated polio-Haemophilus influenzae type B (DTP-IPV-Hib) immunization to preterm infants. The effect of the recent substitution of acellular pertussis vaccine for whole cell pertussis vaccine on the frequency of these events requires further study.

http://www.ncbi.nlm.nih.gov/pubmed/16784533

"... the outbreak lasted for approximately 2 months, suggesting that varicella in vaccinated persons was contagious and that 99% varicella vaccination coverage was not sufficient to prevent the outbreak."

Pediatrics • June 2006

One dose of varicella vaccine does not prevent school outbreaks: is it time for a second dose?

Author information

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OBJECTIVES

The implementation of a routine childhood varicella vaccination program in the United States in 1995 has resulted in a dramatic decline in varicella morbidity and mortality. Although disease incidence has decreased, outbreaks of varicella continue to be reported, increasingly in highly vaccinated populations. In 2000, a varicella vaccination requirement was introduced for kindergarten entry in Arkansas. In October 2003, large numbers of varicella cases were reported in a school with high vaccination coverage. We investigated this outbreak to examine transmission patterns of varicella in this highly vaccinated population, to estimate the effectiveness of 1 dose of varicella vaccine, to identify risk factors for vaccine failure, and to implement outbreak control measures.

METHODS

A retrospective cohort study involving students attending an elementary school was conducted. A questionnaire was distributed to parents of all of the students in the school to collect varicella disease and vaccination history; parents of varicella case patients were interviewed by telephone. A case of varicella was defined as an acute, generalized, maculopapulovesicular rash without other apparent cause in a student or staff member in the school from September 1 to November 20, 2003. Varicella among vaccinated persons was defined as varicella-like rash that developed >42 days after vaccination. In vaccinated persons, the rash may be atypical, maculopapular with few or no vesicles. Cases were laboratory confirmed by polymerase chain reaction, and genotyping was performed to identify the strain associated with the outbreak.

RESULTS

Of the 545 students who attended the school, 88% returned the questionnaire. Overall varicella vaccination coverage was 96%. Forty-nine varicella cases were identified; 43 were vaccinated. Three of 6 specimens tested were positive by polymerase chain reaction. The median age at vaccination of vaccinated students in the school was 18 months, and the median time since vaccination was 59 months. Forty-four cases occurred in the East Wing, where 275 students in grades kindergarten through 2 were located, and vaccination coverage was 99%. In this wing, varicella attack rates among unvaccinated and vaccinated students were 100% and 18%, respectively. Vaccine effectiveness against varicella of any severity was 82% and 97% for moderate/severe varicella. Vaccinated cases were significantly milder compared with unvaccinated cases. Among the case patients in the East Wing, the median age at vaccination was 18.5 and 14 months among non-case patients. Four cases in the West Wing did not result in further transmission in that wing. The Arkansas strains were the same as the common varicella-zoster virus strain circulating in the United States (European varicella-zoster virus strain).

CONCLUSIONS

Although disease was mostly mild, the outbreak lasted for approximately 2 months, suggesting that varicella in vaccinated persons was contagious and that 99% varicella vaccination coverage was not sufficient to prevent the outbreak. This investigation highlights several challenges related to the prevention and control of varicella outbreaks with the 1-dose varicella vaccination program and the need for further prevention of varicella through improved vaccine-induced immunity with a routine 2-dose vaccination program. The challenges include: 1-dose varicella vaccination not providing sufficient herd immunity levels to prevent outbreaks in school settings where exposure can be intense, the effective transmission of varicella among vaccinated children, and the difficulty in the diagnosis of mild cases in vaccinated persons and early recognition of outbreaks for implementing control measures. The efficacy of 2 doses of varicella vaccine compared with 1 dose was assessed in a trial conducted among healthy children who were followed for 10 years. The efficacy for 2 doses was significantly higher than for 1 dose of varicella vaccine. This higher efficacy translated into a 3.3-fold lower risk of developing varicella >42 days after vaccination in 2- vs 1-dose recipients. Of the children receiving 2 doses, 99% achieved a glycoprotein-based enzyme-linked immunosorbent assay level of > or =5 units (considered a correlate of protection) 6 weeks after vaccination compared with 86% of children who received 1 dose. The 6-week glycoprotein-based enzyme-linked immunosorbent assay level of > or =5 units has been shown to be a good surrogate for protection from natural disease. Ten years after the implementation of the varicella vaccination program, disease incidence has declined dramatically, and vaccination coverage has increased greatly. However, varicella outbreaks continue to occur among vaccinated persons. Although varicella disease among vaccinated persons is mild, they are contagious and able to sustain transmission. As a step toward better control of varicella outbreaks and to reduce the impact on schools and public health officials, in June 2005, the Advisory Committee on Immunization Practices recommended the use of a second dose of varicella vaccine in outbreak settings. Early recognition of outbreaks is important to effectively implement a 2-dose vaccination response and to prevent more cases. Although the current recommendation of providing a second dose of varicella vaccine during an outbreak offers a tool for controlling outbreaks, a routine 2-dose recommendation would be more effective at preventing cases. Based on published data on immunogenicity and efficacy of 2 doses of varicella vaccine, routine 2-dose vaccination will provide improved protection against disease and further reduce morbidity and mortality from varicella.

http://www.ncbi.nlm.nih.gov/pubmed/16740809

Health & Place • June 2006

Environmental mercury release, special education rates, and autism disorder: an ecological study of Texas

Author information

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Abstract

The association between environmentally released mercury, special education and autism rates in Texas was investigated using data from the Texas Education Department and the United States Environmental Protection Agency. A Poisson regression analysis adjusted for school district population size, economic and demographic factors was used. There was a significant increase in the rates of special education students and autism rates associated with increases in environmentally released mercury. On average, for each 1,000 lb of environmentally released mercury, there was a 43% increase in the rate of special education services and a 61% increase in the rate of autism. The association between environmentally released mercury and special education rates were fully mediated by increased autism rates. This ecological study suggests the need for further research regarding the association between environmentally released mercury and developmental disorders such as autism. These results have implications for policy planning and cost analysis.

http://www.ncbi.nlm.nih.gov/pubmed/16338635

“On average, for each 1,000 lb of environmentally released mercury, there was a 43% increase in the rate of special education services and a 61% increase in the rate of autism.”

Vaccine • Volume 24, Issues 31–32 • July 2006

Unexplained cases of sudden infant death shortly after hexavalent vaccination

Author Information

Zinka B, Rauch E, Buettner A, Ruëff F, Penning R.

Report available for purchase:

http://www.sciencedirect.com/science/article/pii/S0264410X05004688

CMAJ • August 2006

Two successive outbreaks of mumps in Nova Scotia among vaccinated adolescents and young adults

Author Information

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From Nova Scotia Health Promotion and Protection (Watson-Creed, Saunders, Scott)
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Abstract

Background

Before the widespread use of vaccine, mumps was the most common cause of viral meningitis (up to 10% of mumps infections). Vaccination programs have resulted in a drop of more than 99% in the number of reported mumps cases in the United States and Canada. Although rare in Canada, outbreaks have recently occurred throughout the world, including a large outbreak in the United Kingdom, where more than 56,000 cases were reported in 2004–2005.

Methods

Two recent outbreaks in Nova Scotia were investigated by public health officials. Cases were defined by laboratory confirmation of infection (i.e., isolation of mumps virus by culture) or clinical diagnosis in people epidemiologically linked to a laboratory-confirmed case. The people infected were interviewed to determine possible links and to identify contacts. Mumps virus was cultured from urine and throat specimens, identified via reverse-transcriptase polymerase chain reaction (RT-PCR) and subjected to phylogenetic analysis to identify the origin of the strain.

Results

The first outbreak involved 13 high-school students (median age 14 yr): 9 who had previously received 2 doses of measles–mumps–rubella vaccine (MMR) and 4 who received a single dose. The second outbreak comprised 19 cases of mumps among students and some staff at a local university (median age 23 yr), of whom 18 had received only 1 dose of MMR (the other received a second dose). The viruses identified in the outbreaks were phylogenetically similar and belonged to a genotype commonly reported in the UK. The virus from the second outbreak is identical to the strain currently circulating in the UK and United States.

Interpretation

The predominance in these outbreaks of infected people of university age not only highlights an environment with potential for increased transmission but also raises questions about the efficacy of the MMR vaccine. The people affected may represent a “lost cohort” who do not have immunity from natural mumps infection and were not offered a 2-dose schedule. Given the current level of mumps activity around the world, clinicians should remain vigilant for symptoms of mumps.

Full Report

http://www.ncbi.nlm.nih.gov/pmc/articles/PMC1550754

“... studies especially on neurotoxicity, genotoxicity,

or carcinogenicity, are previously published in numerous articles.”

Biometals • August 2006

Occurrence, use and potential toxic effects of metals and metal compounds

Ana-Maria Florea, Dietrich Büsselberg

Abstract

Metals and metal compounds are constituents of our natural environment. Their distribution depends on the existence of natural sources (e.g. volcanoes or erosion) and their use in human’s activity. They are transformed naturally (e.g. by bacterial activity) with formation of organic species that influence their mobility and accumulation in abiotic as well as biotic systems. Up to date metal species are released into the environment questioning their influence on human health. Due to their widespread use in human activities such as industry, agriculture and even as medicine (e.g. As, Se, Pt), numerous health risks may be associated with exposure to these substances. Different reports on metal intoxication are documented and studies especially on neurotoxicity, genotoxicity, or carcinogenicity, are previously published in numerous articles. This mini-review gives an overview on the use and the actions of selected metal species of actual scientific concern, with a focus on neuronal cells.

http://link.springer.com/article/10.1007%2Fs10534-005-4451-x

Pediatric Neurology • August 2006

Acute metabolic crisis induced by vaccination in seven Chinese patients

Author information

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Abstract

Seven Chinese patients (5 males and 2 females) with vaccination-induced acute metabolic crisis were reported. Only one male with 21-hydroxylase deficiency had been diagnosed before vaccination. In the remaining six patients, the preexisting diagnoses were not confirmed before the vaccination. Acute metabolic crisis occurred in seven patients between 3 and 12 hours after the administration of Japanese encephalitis, diphtheria, and tetanus toxoids and acellular pertussis, hepatitis B, or measles vaccines. Patients 1 and 2 displayed acute adrenal insufficiencies at the ages of 5 years and 3 months, respectively. Patient 3 had presented with mild motor retardation previously. Patients 4 to 7 were previously healthy, but suffered from fever, seizures, coma, acidosis, and hypoglycemia after being vaccinated. Glutaric aciduria type 1 was evident in case 4. Leigh syndromes were present in Patients 5, 6, and 7. They all died from respiratory failure before 2 years of age. Symmetric foci, cystic cavitations with neuronal loss, and vascular proliferation were observed by postmortem examination. Among the seven patients, although the vaccines were not the primary cause of the acute metabolic crisis, the severe acute episodes occurred coincidentally.

http://www.ncbi.nlm.nih.gov/pubmed/16876007

“Seven Chinese patients with vaccination-induced acute metabolic crisis were reported.”

“The first rotavirus vaccine ... left instead the unfortunate legacy that

live oral rotavirus vaccines may be associated with a serious but rare adverse event: intussusception.”

Pediatrics • August 2006

Rotavirus Vaccination and Intussusception: Can We Decrease Temporally Associated Background Cases of Intussusception by Restricting the Vaccination Schedule?

Author Information

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Abstract

OBJECTIVE

The first rotavirus vaccine that was licensed in the United States, RotaShield, could have prevented the enormous burden of rotavirus diarrhea in American children but left instead the unfortunate legacy that live oral rotavirus vaccines may be associated with a serious but rare adverse event: intussusception. Although large trials indicate that the next generation of rotavirus vaccines is not associated with this complication, many children likely will develop intussusception by chance alone in the 2-week window after immunization, raising concerns about whether these cases might be “caused” by the vaccine. Our objective for this study was to model and compare the number of temporally associated intussusception events that are expected by chance alone under 2 rotavirus vaccination strategies.

CONCLUSIONS

Although an age-restricted vaccination schedule substantially reduced the number of intussusception events that were observed in the 2-week postvaccination window when compared with a schedule with fewer restrictions, this decrease was attributable to a lower rate of vaccine coverage rather than a safer schedule of vaccination. The risk for intussusception did not differ significantly between vaccination strategies. Public health policy and education messages for physicians and parents should be developed to anticipate intussusception events that will occur by chance alone but are temporally related to rotavirus vaccination.

http://pediatrics.aappublications.org/content/118/2/e258

Multiple Sclerosis • October 2006

Elevated urinary excretion of aluminium and iron in multiple sclerosis

Author information

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Abstract

Multiple sclerosis (MS) is a chronic, immune-mediated, demyelinating disease of the central nervous system of as yet unknown aetiology. A consensus of opinion has suggested that the disorder is the result of an interplay between environmental factors and susceptibility genes. We have used a battery of analytical techniques to determine if the urinary excretion of i) markers of oxidative damage; ii) iron and iii) the environmental toxin aluminium and its antagonist, silicon, are altered in relapsing-remitting (RRMS) and secondary progressive MS (SPMS). Urinary concentrations of oxidative biomarkers, MDA and TBARS, were not found to be useful indicators of inflammatory disease in MS. However, urinary concentrations of another potential marker for inflammation and oxidative stress, iron, were significantly increased in SPMS ($P<0.01$) and insignificantly increased in RRMS ($P>0.05$). Urinary concentrations of aluminium were also significantly increased in RRMS ($P<0.001$) and SPMS ($P<0.05$) such that the levels of aluminium excretion in the former were similar to those observed in individuals undergoing metal chelation therapy. The excretion of silicon was lower in MS and significantly so in SPMS ($P<0.05$). Increased excretion of iron in urine supported a role for iron dysmetabolism in MS. Levels of urinary aluminium excretion similar to those seen in aluminium intoxication suggested that aluminium may be a hitherto unrecognized environmental factor associated with the aetiology of MS. If aluminium is involved in MS then an increased dietary intake of its natural antagonist, silicon, might be a therapeutic option.

http://www.ncbi.nlm.nih.gov/pubmed/?term=17086897

“Levels of urinary aluminium excretion similar to those seen in aluminium intoxication suggested that aluminium may be a hitherto unrecognized environmental factor associated with the aetiology of Multiple Sclerosis.”

Journal Of Autoimmunity • November 2006

Fibromyalgia, infection and vaccination: two more parts in the etiological puzzle

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Abstract

As the pathogenesis of fibromyalgia continues to raise debate, multiple putative triggers have been implicated. The current review summarizes the available data linking fibromyalgia to either infection or vaccination. Multiple infectious agents have been associated with the development of either full-blown fibromyalgia (e.g. hepatits C), or with symptom complexes extensively overlapping with that syndrome (e.g. chronic Lyme disease). The cases of Lyme disease, mycoplasma, hepatits C and HIV are detailed. Despite the described associations, no evidence is available demonstrating the utility of antibiotic or anti-viral treatment in the management of fibromyalgia. Possible mechanistic links between fibromyalgia and HIV are reviewed. Associations have been described between various vaccinations and symptom complexes including fibromyalgia and chronic fatigue syndrome. The case of Gulf War syndrome, a functional multisystem entity sharing many clinical characteristics with fibromyalgia is discussed, with emphasis on the possibility of association with administration of multiple vaccinations during deployment in the Persian Gulf and the interaction with stress and trauma. Based on this example a model is proposed, wherein vaccinations function as co-triggers for the development of functional disorders including fibromyalgia, in conjunction with additional contributing factors.

http://www.ncbi.nlm.nih.gov/pubmed/17071055

“Based on this example a model is proposed, wherein vaccinations function as co-triggers for the development of functional disorders including fibromyalgia, in conjunction with additional contributing factors.”

Egyptian Journal Of Immunology • 2006

Possible immunological disorders in autism: concomitant autoimmunity and immune tolerance

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Abstract

Autism is a pervasive developmental disorder that affect children early in their life. Immunological disorders is one of several contributing factors that have been suggested to cause autism. Thirty autistic children aged 3-6 years and thirty non-autistic psychologically-free siblings were studied. Circulating IgA and IgG autoantibodies to casein and gluten dietary proteins were detected by enzyme-immunoassays (EIA). Circulating IgG antibodies to measles, mumps and rubella vaccine (M.M.R) and cytomeglovirus were investigated by EIA. Results revealed high seropositivity for autoantibodies to casein and gluten: 83.3% and 50% respectively in autistic children as compared to 10% and 6.7% positivity in the control group. Surprisingly, circulating anti-measles, anti-mumps and anti-rubella IgG were positive in only 50%, 73.3% and 53.3% respectively as compared to 100% positivity in the control group. Anti-CMV IgG was positive in 43.3% of the autistic children as compared to 7% in the control group. It is concluded that, autoimmune response to dietary proteins and deficient immune response to measles, mumps and rubella vaccine antigens might be associated with autism, as a leading cause or a resulting event. Further research is needed to confirm these findings.

http://www.ncbi.nlm.nih.gov/pubmed/17974154

“It is concluded that, autoimmune response to dietary proteins and deficient immune response to measles, mumps and rubella vaccine antigens might be associated with autism, as a leading cause or a resulting event.”

Vaccine • January 2007

DTP with or after measles vaccination is associated with increased in-hospital mortality in Guinea-Bissau

Author information

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Abstract

BACKGROUND
The sequence of routine immunisations may be important for childhood mortality. Three doses of diphtheria-tetanus-pertussis vaccine (DTP) should be given at 6, 10, and 14 weeks and measles vaccine (MV) at 9 months of age. The sequence is not always respected. We examined in-hospital mortality of children having received DTP with or after measles vaccine.

SETTING
The only paediatric ward in Bissau, Guinea-Bissau.

PARTICIPANTS
Children hospitalised during two periods in 1990-1996 and 2001-2002 who had received MV prior to hospitalisation.

MAIN OUTCOME MEASURE
The all-cause case fatality at the hospital for children aged 6-17 months.

RESULT
The case fatality was increased for children who had received DTP with or after measles vaccine compared with children who had received measles vaccine as the most recent vaccine, the ratio being 2.53 (1.37-4.67) and 1.77 (0.92-3.41) in the two periods, respectively. The combined estimate was 2.10 (1.34-3.28). These results were not explained by differences in nutritional status, number of doses of DTP or discharge policy.

CONCLUSION
Administration of DTP with, or after MV, may reduce the beneficial effect of MV.

http://www.ncbi.nlm.nih.gov/pubmed/17092614

“The case fatality was increased for children who had received DTP with or after measles vaccine compared with children who had received measles vaccine as the most recent vaccine, the ratio being 2.53 (1.37-4.67) and 1.77 (0.92-3.41) in the two periods, respectively.”

Brain Research • May 2007

Effects of postnatal formaldehyde exposure on pyramidal cell number, volume of cell layer in hippocampus and hemisphere in the rat: a stereological study

Author information

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Abstract

The purpose of the present study was to determine whether exposure of neonatal rats to formaldehyde (FA) had either early or delayed effects on the numbers of pyramidal cells in the cornu ammonis (CA) of the hippocampus. Neonatal Wistar rats were exposed to 0 ppm (control group), 6 ppm and 12 ppm (high concentration group) of FA concentrations throughout the 30-day period following the birth by placing them for 6 h/day in a glass chamber containing FA vapor. Then, some of the animals from each FA-treated group were anesthetized and decapitated at the day 30, and the remaining ones were killed at the day 90. The brains were removed immediately and fixed in 10% neutral-buffered FA solution. The Cavalieri principle was used to determine the volumes of the CA and the entire cerebral hemisphere. The optical fractionator counting method was used to estimate the total number of pyramidal cells in the CA. The appearance of pyramidal cells was normal under light microscopy at both postnatal day (PND) 30 and PND 90 in all groups. There were concentration-related volume changes of CA at PND 30 and PND 90; low concentration of FA significantly increased, whereas high concentration decreased the volume of CA in comparison of the control at PND 30. Importantly, high concentration of FA at PND 90 increased the volume of CA in comparison of the low concentration but not with the control. Furthermore, low and high concentrations of FA decreased the volume of hemisphere at PND 30, whereas a reverse effect of these concentrations was observed at the hemisphere of PND 90 in comparison of the control. In both CA and cerebral hemisphere, an age-related volume decrease in both control and low/high concentration groups were found. On the other hand, there were significant age-related reductions in the total number of pyramidal cells at 90 days of age irrespective of the groups examined. Rats treated with high concentration FA were seen to have significantly fewer pyramidal cell neurons than either the animals treated with low concentration FA or control groups ($p<0.01$). These observations indicate that pyramidal cells in the hippocampus may be vulnerable to FA exposure during the early period of life.

http://www.ncbi.nlm.nih.gov/pubmed/?term=17346681

“These observations indicate that pyramidal cells in the hippocampus may be vulnerable to Formaldehyde exposure during the early period of life.”

Journal Of Pediatrics • August 2007

Primary immunization of premature infants with gestational age <35 weeks: cardiorespiratory complications and C-reactive protein responses associated with administration of single and multiple separate vaccines simultaneously

Author information

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Abstract

OBJECTIVE

To determine the incidence of cardiorespiratory events and abnormal C-reactive protein (CRP) level associated with administration of a single vaccine or multiple separate vaccines simultaneously.

STUDY DESIGN

Prospective observational study on 239 preterm infants at > or =2 months of age in the neonatal intensive care unit (NICU). Each infant received either a single vaccine or multiple vaccines on one day. CRP levels and cardiorespiratory manifestations were monitored for 3 days following immunization.

RESULTS

Abnormal elevation of CRP level occurred in 85% of infants administered multiple vaccines and up to 70% of those given a single vaccine. Overall, 16% of infants had vaccine-associated cardiorespiratory events within 48 hours postimmunization. In logistic regression analysis, abnormal CRP values were associated with multiple vaccines (OR, 15.77; 95% CI 5.10-48.77) and severe intraventricular hemorrhage (IVH) (OR, 2.28; 95% CI 1.02-5.13). Cardiorespiratory events were associated marginally with receipt of multiple injections (OR, 3.62; 95% CI 0.99-13.25) and significantly with gastroesophageal reflux (GER) (OR, 4.76; 95% CI 1.22-18.52).

CONCLUSION

CRP level is expected to be elevated in the 48 hours following immunization. In a minority of infants immunized, cardiorespiratory events were associated with presumed need for intervention. Underlying medical conditions and possibly multiple injections are associated with cardiorespiratory events. Precautionary monitoring following immunizations is warranted.

http://www.ncbi.nlm.nih.gov/pubmed/?term=17643770

“In a minority of infants immunized [16%], cardiorespiratory events were associated with presumed need for intervention.”

Pediatrics • August 2007

Risk of Serious Neurologic Disease After Immunization of Young Children in Britain and Ireland

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Abstract

OBJECTIVE

We sought to investigate the risk of serious neurologic disease after immunization in early childhood.

METHODS

The results of a 3-year prospective study of children (2–35 months old) in Britain and Ireland with encephalitis and/or severe illness with convulsions and fever were linked to each child's vaccine history. Cases were reported via the British Paediatric Surveillance Unit's network. The self-controlled case-series method was used to investigate associations between immunization and acute potential adverse events. The risk periods investigated were 0 to 3 and 0 to 7 days post–diphtheria, tetanus, whole cell pertussis, Haemophilus influenzae type b or meningococcal C conjugate vaccine and 6 to 11 and 15 to 35 days post–measles, mumps, rubella vaccine.

RESULTS

A total of 157 disease episodes from 155 children met the analytical case definition. There were 11 cases of herpes simplex encephalitis and 23 cases of primary human herpesvirus 6 and/or 7 infection. There was no evidence of a raised relative incidence of serious neurologic disease in any of the specified risk periods with the exception of a raised relative incidence of 5.68 in the 6–11 days after measles, mumps, rubella vaccine. Based on this relative incidence, between 3 and 6 of the 6 cases in this period were estimated to be attributable to the vaccine with a best estimate of 5. The 6 cases all had fever with convulsions lasting >30 minutes; in all but 1, there was complete recovery by discharge from hospital. Of the 5 patients who recovered, 1 had a concurrent primary human herpesvirus 6 infection and one a primary human herpesvirus 7.

CONCLUSIONS

Six to 11 days after measles, mumps, rubella vaccine there is an increased risk of fever and convulsions lasting >30 minutes. All 6 of the episodes temporally related to immunization met the criteria for complex febrile convulsions. The estimated attributable risk of serious neurological disease was similar to that previously found for measles vaccine.

http://pediatrics.aappublications.org/content/120/2/314

"All 6 of the episodes temporally related to immunization met the criteria for complex febrile convulsions."

Journal Of Inorganic Biochemistry • September 2007

Induction of specific micro RNA (miRNA) species by ROS-generating metal sulfates in primary human brain cells

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Abstract

Iron- and aluminum-sulfate together, at nanomolar concentrations, trigger the production of reactive oxygen species (ROS) in cultures of human brain cells. Previous studies have shown that following ROS induction, a family of pathogenic brain genes that promote inflammatory signalling, cellular apoptosis and brain cell death is significantly over-expressed. Notably, iron- and aluminum-sulfate induce genes in cultured human brain cells that exhibit expression patterns similar to those observed to be up-regulated in moderate- to late-stage Alzheimer's disease (AD). In this study we have extended our investigations to analyze the expression of micro RNA (miRNA) populations in iron- and aluminum-sulfate treated human neural cells in primary culture. The main finding was that these ROS-generating neurotoxic metal sulfates also up-regulate a specific set of miRNAs that includes miR-9, miR-125b and miR-128. Notably, these same miRNAs are up-regulated in AD brain. These findings further support the idea that iron- and aluminum-sulfates induce genotoxicity via a ROS-mediated up-regulation of specific regulatory elements and pathogenic genes that redirect brain cell fate towards progressive dysfunction and apoptotic cell death.

http://www.ncbi.nlm.nih.gov/pubmed/?term=17629564

"Iron- and aluminum-sulfate together, at nanomolar concentrations, trigger the production of reactive oxygen species (ROS) in cultures of human brain cells. Previous studies have shown that following reactive oxygen species (ROS) induction, a family of pathogenic brain genes that promote inflammatory signalling, cellular apoptosis and brain cell death is significantly over-expressed."

Archives Of Neurology • November 2007

Optic Neuritis and Vaccination Investigation: Failure to Consider Significant Sex Differences and Multiple Vaccine Combinations

Renata J. M. Engler, MD; Mary Klote, MD;
Michael R. Nelson, MD, PhD

Abstract

In follow-up to recent correspondence related to the study of vaccinations and subsequent optic neuritis by the Centers for Disease Control and Prevention (CDC),1,2 we are deeply concerned regarding the lack of consideration of sex differences in incidence of disease for the ICD-9 code 377.3, a common finding for autoimmune disorders, particularly in young adults aged 18 to 39 years. The Defense Medical Surveillance System (DMSS) demonstrates that in the population of service members of greatest concern, there is a consistent pattern, regardless of year for review, of increased disease incidence by first visit in women compared with men. This sex difference is also independent of race. The Figure was extracted from the remote access program to data contained within the DMSS offered by the Army Medical Surveillance Activity.3 Similar sex differences were identified for ICD-9 codes for optic neuritis, unspecified (377.30); optic papillitis (377.31); retrobulbar neuritis, acute (377.32); and optic neuritis, other (377.39) during the period between January 1, 1998, and December 31, 2003. It is of increasing concern in the context of medical evidence and research that sex differences are not adequately considered in both research design and data analysis. Given the mandatory nature of immunizations in the military health system and the fact that most visits involve complex and sometimes new mixtures, concern for sex-based risk differences is not a minor question and merits far more attention on the agenda of vaccine safety surveillance.

http://archneur.jamanetwork.com/article.aspx?articleid=794738&resultClick=3

“we are deeply concerned
regarding the lack of consideration
of sex differences in incidence of disease ...
there is a consistent pattern, regardless of year
for review, of increased disease incidence
by first visit in women compared with men ...”

Report of the Subcommittee on Science and Technology • November 2007

FDA Science and Mission at Risk

FDA Mission Statement

"The FDA is responsible for protecting the public health by assuring the safety, efficacy, and security of human and veterinary drugs, biological products, medical devices, our nation's food supply, cosmetics, and products that emit radiation. The FDA is also responsible for advancing the public health by helping to speed innovations that make medicines and foods more effective, safer, and more affordable; and helping the public get the accurate, science-based information they need to use medicines and foods to improve their health."

FINDINGS OF THE SUBCOMMITTEE

The FDA cannot fulfill its mission
because its scientific base has eroded and its scientific organizational structure is weak.

The FDA cannot fulfill its mission
because its scientific workforce does not have sufficient capacity and capability.

The FDA cannot fulfill its mission
because its information technology (IT) infrastructure is inadequate.

FDA does not have the capacity to ensure the safety of food for the nation.

The development of medical products based on "new science" cannot be adequately regulated by the FDA.

The FDA cannot provide the information infrastructure support to regulate products based on new science.

The FDA IT infrastructure is obsolete, unstable, and
lacks sufficient controls to ensure continuity of operations or to provide effective disaster recovery services.

There is insufficient capacity in modeling, risk assessment and analysis.

The FDA has experienced decreasing resources in the face of increasing responsibilities.

The FDA science agenda lacks a coherent structure and vision,
as well as effective coordination and prioritization.
The IT workforce is insufficient and suboptimally organized.
The FDA has an inadequate and ineffective program for scientist performance.
Recommendations of excellent FDA reviews are seldom followed.
The FDA has inadequate funding for professional development.

The FDA has not taken sufficient advantage of external and internal collaborations.

The FDA lacks the information science capability and information infrastructure
to fulfill its regulatory mandate.

The nation's food supply is at risk. Crisis management in FDA's two food safety centers, Center for Food Safety and Applied Nutrition (CFSAN) and Center for Veterinary Medicine (CVM), has drawn attention and resources away from FDA's ability to develop the science base and infrastructure needed to efficiently support innovation in the food industry, provide effective routine surveillance, and conduct emergency outbreak investigation activities to protect the food supply.

FDA's inability to keep up with scientific advances means that American lives are at risk. While the world of drug discovery and development has undergone revolutionary change — shifting from cellular to molecular and gene-based approaches — FDA's evaluation methods have remained largely unchanged over the last half century. Likewise, evaluation methods have not kept pace with major advances in medical devices and use of products in combination.

The turnover rate in FDA science staff in key scientific areas is twice that of other government agencies. There are insufficient programs of measurement to determine worker performance. There is insufficient investment in professional development, which means that the workforce does not keep up with scientific advances. Finally, for various reasons, the FDA does not have sufficiently extensive collaboration with external scientists, thus limiting infusion of new knowledge and missing opportunities to leverage resources.

FDA's failure to retain and motivate its workforce puts FDA's mission at risk. Inadequately trained scientists are generally risk-averse, and tend to give no decision, a slow decision or, even worse, the wrong decision on regulatory approval or disapproval. During our encounters with staff and center leadership, we were struck by the near unanimity that the shortage of science staff (due to lack of resources to hire) and the inability to recruit and retain needed expertise are serious, longstanding challenges. Internal expertise and experience to provide the science capability and capacity needed in highly specialized and fast-evolving areas is disturbingly limited. The lack of a trained workforce means that the FDA is ineffective in responding to emerging fields that require individuals and work teams with multidisciplinary skills built on very complex, highly specialized, often esoteric bodies of knowledge.

The Subcommittee was extremely disturbed at the state of the FDA IT infrastructure .. the IT workforce is insufficient. The IT situation at FDA is problematic at best — and at worst it is dangerous. Many of the FDA systems reside on technology that has been in service beyond the usual life cycle. Systems fail frequently, and even email systems are unstable — most recently during an E.coli food contamination investigation. More importantly, reports of product dangers are not rapidly compared and analyzed, inspectors' reports are still hand written and slow to work their way through the compliance system, and the system for managing imported products cannot communicate with Customs and other government systems (and often miss significant product arrivals because the system cannot even distinguish, for example, between road salt and table salt).

There are inadequate emergency backup systems in place: recent system failures have resulted in loss of FDA data. Critical data reside in large warehouses sequestered in piles and piles of paper documents. There is no backup of these records, which include valuable clinical trial data. The FDA has inadequate extramural funding programs and collaborations to accelerate the development of critical health information exchanges in order to support clinical trials and pharmacovigilance activities.

In contrast to previous reviews that warned crises would arise if funding issues were not addressed, recent events and our findings indicate that some of those crises are now realities and American lives are at risk.

Medical Veritas • 2008

Current childhood vaccine programs:

An overview with emphasis on the Measles-Mumps-Rubella (MMR) vaccine and of its compromising of the mucosal immune system

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Abstract

Both common observation and official statistics confirm that there have been dramatic increases in chronic physical and mental illnesses in American children, such as autism, asthma, and allergies since the introduction of the MMR vaccine in 1978. Government health officials have denied a relationship with vaccines, but U.S. Congressional hearings on vaccine safety (1999 to Dec. 2004) revealed a total absence of vaccine safety tests that would meet current scientific standards, so that it can be assumed that many vaccine reactions are taking place unrecognized. Prior to the introduction of vaccines, the Th1 cellular immune system of the gastrointestinal and respiratory systems served as the primary defense systems with the Th2 hu- moral immune system in the bone marrow, serving a secondary role.

There is a school of thought that the "minor childhood diseases" of earlier times, including measles, mumps, chicken pox, and rubella, which involved the epithelial tissues of skin, respiratory, and/or gastrointestinal tracts, served a necessary purpose in challenging, strengthening, and estab- lishing the dominance of Th1 cellular immune system during early childhood. Current vaccines against these diseases, in contrast, being directed at stimulating antibody production in the bone marrow, are bypassing the cellular immune system and thereby tending to reverse the roles of the cellular and humoral systems, with the former suffering from a lack of challenge. In addition, the cellular immune system is being further compromised by the powerfully immunosuppressive effects of the MMR vaccine. The time is overdue to totally rethink and redirect our current childhood vaccine program.

http://www.vacinfo.org/buttram.pdf

"Both common observation and official statistics confirm that there have been dramatic increases in chronic physical and mental illnesses in American children, such as autism, asthma, and allergies since the introduction of the MMR vaccine in 1978. Government health officials have denied a relationship with vaccines, but U.S. Congressional hearings on vaccine safety (1999 to Dec. 2004) revealed a total absence of vaccine safety tests that would meet current scientific standards, so that it can be assumed that many vaccine reactions are taking place unrecognized."

Medical Veritas 2008

Vaccines, depression, and neurodegeneration after age 50 years: another reason to avoid the recommended vaccines

by Russell L. Blaylock, MD, CCN

There is growing evidence that a number of the psychiatric disorders are strongly related to glutamate excess. Likewise, recent studies have shown a connection between chronic inflammation and these same disorders. A compelling body of research links these two observations, glutamate excess (an excitotoxicity marker) and chronic inflammation (immune over-reactivity). It is known that systemic activation of the immune system also activates the brain's special immune system, which is regulated by the microglia. Based on results of studies of the sickness behavior response to natural infections, neuroscientists have deciphered much of the mechanism responsible for the behavioral effects associated with intense systemic immune activation, including social isolation, depression, anxiety, and a loss of appetite. Most of these symptoms are shared by the major depressive disorders. Other studies have linked neurodegeneration and a worsening of neurodegenerative diseases to systemic immune activation. This paper demonstrates the known links between: systemic immune activation, brain microglial activation, and both major depressive disorder and a worsening of neurodegenerative diseases. Because a number of vaccines are being recommended to adults, the risk of precipitating or worsening these disorders is quite real. The mechanism for this process is discussed.

http://www.vacinfo.org/man1742_1747.pdf

"This paper demonstrates the known links between: systemic immune activation, brain microglial activation, and both major depressive disorder and a worsening of neurodegenerative diseases. Because a number of vaccines are being recommended to adults, the risk of precipitating or worsening these disorders is quite real."

“Adjuvants ... are challenging to develop and license because

adjuvant compounds that stimulate strong protective immunity also frequently induce significant toxicity.”

Frontiers In Bioscience • January 2008

Rationally-designed vaccine adjuvants: separating efficacy from toxicity

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Abstract

Adjuvants, substances included in many vaccines in order to improve immune responses, are challenging to develop and license because adjuvant compounds that stimulate strong protective immunity also frequently induce significant toxicity. Adjuvant design and development has until recently been largely empirical; but with the current knowledge that most adjuvants act via receptors of the innate immune system, molecular-based approaches are rapidly advancing the field. Data support the concept that proinflammatory pathways induced by innate immune receptor triggering underlie many of the observed toxic effects. Importantly, the cellular signaling pathways that lead to inflammation are known, for a number of innate immune receptors, to be distinct from those that are involved in the costimulation of protective adaptive immune responses, leading to approaches for attenuating inflammatory signaling that should lead to safer and more effective vaccine adjuvants. This article addresses whether there is a clear rationale for the separation of toxicity from efficacy in the function of adjuvants based upon innate immune receptor ligands.

http://www.ncbi.nlm.nih.gov/pubmed/?term=17981755

“Maternal body weight was lowered at 7.5%. Number of pups born was lowered at 7.5%.

Lowered body weight was observed in male and female offspring ...”

Reproductive Toxicology • January 2008

Evaluation of developmental neurotoxicity of polysorbate 80 in rats

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Abstract

The developmental neurotoxicity of polysorbate 80 (PS80) was evaluated in rats. Crl:CD(SD) rats were given drinking water containing PS80 at 0, 0.018, 0.13, 1.0, or 7.5% (0, 0.035, 0.245, 1.864, or 16.783ml/kgbw/day) on day 0 of pregnancy through day 21 after delivery. Pregnant rats were allowed to deliver spontaneously. Potential adverse effects of pre- and post-natal exposure on the development and function of the nervous system in offspring of rats given PS80 were examined. Maternal body weight was lowered at 7.5%. Number of pups born was lowered at 7.5%. There were no compound-related effects on locomotor activity of offspring on postnatal days (PNDs) 14-15, 17-18, 20-21 and 33-37. No compound-related changes were found in developmental landmarks, sexual maturation, or reflex responses. Although decreased rate of avoidance responses was noted on PNDs 23-27 in male and female offspring at 7.5%, no compound-related changes were found in performance in the conditioned avoidance response on PNDs 60-67. Histopathological examinations of the brain revealed no toxicological changes. Lowered body weight was observed in male and female offspring at 7.5%. The NOAEL in this study was considered to be 1.0% (1.864ml/mg/kgbw/day).

http://www.ncbi.nlm.nih.gov/pubmed/17961976

Vaccine • March 2008

Kinetics of asthma- and allergy-associated immune response gene expression in peripheral blood mononuclear cells from vaccinated infants after in vitro re-stimulation with vaccine antigen

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Abstract

The global expression of immune response genes in infants after vaccination and their role in asthma and allergy is not clearly understood. Pharmacogenomics is ideally suited to study the involved cellular responses, since the expression of thousands of genes can be assessed simultaneously. Here, array technology was used to assess the expression kinetics of immune response genes with association to asthma and allergy in peripheral blood mononuclear cells (PBMC) of five healthy infants after vaccination with Infanrix-Polio+Hib. At 12h after in vitro re-stimulation of the PBMC with pertussis toxin (PT) antigen, 14 immune response pathways, 33 allergy-related and 66 asthma-related genes were found activated.

http://www.ncbi.nlm.nih.gov/pubmed/?term=18336961

“At 12h after in vitro re-stimulation of the peripheral blood mononuclear cells with pertussis toxin antigen, 14 immune response pathways, 33 allergy-related and 66 asthma-related genes were found activated.”

“... Triton X-100-induced apoptosis ...”

Leukemia Research • March 2008

Release of cytochrome c from mitochondria precedes Bax translocation/activation in Triton X-100-induced apoptosis

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Abstract

The precise mechanisms by which sublytic concentrations of detergents induce apoptosis remain unclear. Recent studies reported the ability of nonionic detergents such as Triton X-100 to induce conformational change of Bax to the active form in vitro. Here we investigated whether activation of Bax might play a role in Triton X-100-induced apoptosis in cells. Although Bax translocation/activation was inhibited by caspase inhibitors, cytochrome c release from mitochondria was not affected in Triton X-100-induced apoptosis in U-937 cells. These results demonstrate that translocation/activation of Bax occurs downstream of cytochrome c release and caspase activation in Triton X-100-induced apoptosis.

http://www.ncbi.nlm.nih.gov/pubmed/17689609

Clinical Vaccine Immunology • March 2008

Considerable Differences in Vaccine Immunogenicities and Efficacies Related to the Diluent Used for Aluminum Hydroxide Adjuvant

Author Information

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Abstract

We are developing an anticandidal vaccine using the recombinant N terminus of Als3p (rAls3p-N). We report that although more rAls3p-N was bound by aluminum hydroxide diluted in saline than by aluminum hydroxide diluted in phosphate-buffered saline (PBS), its immunogenicity and efficacy were superior in PBS. Thus, protein binding, by itself, may not predict the efficacy of some vaccines with aluminum adjuvants.

Full Report

http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2268268/

“Thus, protein binding, by itself, may not predict the efficacy of some vaccines with aluminum adjuvants.”

Oxford Journal • Toxicology Science • March 2008

Modeling Neurodevelopment Outcomes and Ethylmercury Exposure from Thimerosal-Containing Vaccines

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Dear Editor,

The neurotoxic effects of ethylmercury (EtHg) accidentally consumed in Iraq were sufficient to withdraw ethylmercury-containing fungicides as seed dressing. Despite that, not only did thimerosal continue to be used in pharmaceutical preparations but also toxicological interest in EtHg-derived substances diminished considerably and was never addressed with regard to the small quantities used as a vaccine preservative. Thimerosal-containing vaccines (TCV) have no record of overt clinical neurological consequences due to EtHg, and the plausibility of subtle neurotoxic effects in children has been recognized only recently by the United States and other industrialized countries. In this context, we welcome the interesting work of Berman et al. (2008); it is clear that this assiduous study (in immunologically susceptible mice) took into consideration doses and schedules of TCV-Hg concentrations that had been used in infants in the United States. Their mice model does not, however, cover the full extent of modifying factors associated with TCV-Hg exposure in the majority of immature and newborns around the world that still have to depend on TCV.

According to Berman et al. (2008), the United States vaccination scheduled exposed a total of 125 μgHg distributed at 2, 2, and 6 months through TCV (hepatitis B and DTP). This type of vaccine is no longer used in industrialized countries but it is still used all over the world. We know that thimerosal concentrations vary among brands of vaccines and also that immunization schedules vary depending on a country's health policy; not only that but new outbreaks of disease introduce additional new vaccines (which may contain thimerosal) during the first year of life. As an example, the public health services of Brazil, like other countries, still uses several brands of hepatitis B vaccine (containing thimerosal as preservative) with concentrations ranging from 12.5 to 50 μgHg per 0.5 ml shot. Another salient difference between countries that use TCV (like Brazil) and the United States is that in the former country hepatitis B inoculation starts within the first 12–24 h after birth (Marques et al., 2007) and is administered to low-birth weight ≥2000 g (Ministério, da Saúde, 2006 and premature babies who are also recommended a fourth shot as an additional booster (DI/DH/CVE, 2006). In such situations, not only toxicokinetics (TK) but especially toxicodynamics (TD) of EtHg are entirely different between a 1-day-old (with different stages of immaturity and birth weight) and a 60-day-old child (as modeled).

The newborn presents several physiological degrees of immaturity in the excretory system (kidneys and bile formation) and target organ (central nervous system, CNS) that are important modifiers of EtHg TK and TD. These features are inversely accentuated by gestational age and birth weight. Under such circumstances, unbound circulating EtHg in a newborn (and immature) may not be eliminated as fast as in a 2-month-old baby and thus will be readier to cross the more vulnerable blood-brain barrier (BBB). The newborn BBB increases in effectiveness with age; therefore, the free EtHg can more easily penetrate the immature CNS (Dorea, 2007). As a consequence, the smaller the body size and blood volume, the more altered the TD and TK of EtHg. Indeed, Stajich et al. (2000) showed that preterm infants do not metabolize Hg efficiently. Collectively, studies show that larger babies have significantly higher mean liver metallothionein than smaller babies (Dorea, 2007).

Factors associated with protein-binding capacity, excretion mechanisms, and enzyme activities are immature in the neonate and modulate differences in adverse effects between newborns and infants exposed to neurotoxic substances. During the period of immaturity, not only plasma albumin but also total protein concentrations decrease (Dorea, 2007). The best example in differences between neurotoxic effects is the type of albumin and competition for binding sites (due to increased circulatory concentrations of bilirubin). Albumin binding (to bilirubin) is less effective during the first postnatal days and, as a consequence, excess free bilirubin can cross the BBB at early stages of the postnatal CNS immaturity and cause brainstem abnormalities; albumin priming can be effective in attenuating effects caused by unbound bilirubin (Dorea, 2007).

We do not dispute the conclusions drawn by Berman et al. regarding Hg and the neurobiology of autism; however, we think it is possible to take their findings one step further in regards to thimerosal neurotoxicity. We contend that these findings are appropriate for U.S.-like scenarios (as intended by the authors) but are not sufficient to address the current TCV schedules in the majority of newborns and infants around the world. TCV are used worldwide in vaccination schedules that include more of these vaccines at an earlier age. Unfortunately, the differences that set newborns (especially low-birth-weights and prematures) apart from 2-month-old infants have not yet been modeled in experimental studies and remain neglected in TK and TD knowledge of TCV-EtHg exposure. We hope that studies like Berman et al. (2008) can inspire conventional toxicology to address uncertainties regarding current serial EtHg exposure in newborns and infants that have to take TCV.

Full Report

http://toxsci.oxfordjournals.org/content/103/2/414.long

Rheumatology International • April 2008

HBV vaccine and dermatomyositis: is there an association?

Author information

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Abstract

The etiology of dermatomyositis is unknown, but immune mechanisms play an important role. Several dermatological manifestations have been reported among carriers of hepatitis B surface antigen, and after vaccination with the HBV vaccine. Almost all the skin reactions described were peculiar skin eruptions suggestive of an immune complex reaction. Some authors described the occurrence of dermatomyositis after BCG and influenza vaccination. We report a case of a 6-year-old child, who was vaccinated for hepatitis B virus and developed a flu-like disease accompanied by a skin rash, which had the typical features of dermatomyositis. The association of vaccination with autoimmunity is discussed.

http://www.ncbi.nlm.nih.gov/pubmed/18034245

“Several dermatological manifestations have been reported among carriers of hepatitis B surface antigen, and after vaccination with the HBV vaccine. Some authors described the occurrence of dermatomyositis after BCG and influenza vaccination. The association of vaccination with autoimmunity is discussed.”

Clinical Rheumatology • May 2008

Polyglandular autoimmunity with macrophagic myofasciitis

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Abstract

We report a man with chronic fatigue, multiple autoimmune disorders, and a muscle biopsy consistent with macrophagic myofasciitis. This rare and recently described muscle disorder is seen in patients exposed to vaccinations with aluminum hydroxide adjuvant. This case highlights the relationship between macrophagic myofasciitis and autoimmunity.

http://www.ncbi.nlm.nih.gov/pubmed/?term=18180978

“This rare and recently described muscle disorder is seen in patients exposed to vaccinations with aluminum hydroxide adjuvant.”

Toxicological & Environmental Chemistry • June 2008

Hepatitis B triple series vaccine and developmental disability in US children aged 1–9 years

Author Information

Carolyn Gallaghera & Melody Goodmana

Abstract

This study investigated the association between vaccination with the Hepatitis B triple series vaccine prior to 2000 and developmental disability in children aged 1–9 years (n = 1824), proxied by parental report that their child receives early intervention or special education services (EIS). National Health and Nutrition Examination Survey 1999–2000 data were analyzed and adjusted for survey design by Taylor Linearization using SAS version 9.1 software, with SAS callable SUDAAN version 9.0.1. The odds of receiving EIS were approximately nine times as great for vaccinated boys (n = 46) as for unvaccinated boys (n = 7), after adjustment for confounders. This study found statistically significant evidence to suggest that boys in United States who were vaccinated with the triple series Hepatitis B vaccine, during the time period in which vaccines were manufactured with thimerosal, were more susceptible to developmental disability than were unvaccinated boys.

http://www.fourteenstudies.com/pdf/hep_b.pdf

This report is also referenced [17] in
2008 United Nations Environmental Program (UNEP)
report under the subheading ‘New Evidence’

“The odds of receiving special education services were approximately nine times as great for vaccinated boys (n = 46) as for unvaccinated boys (n = 7), after adjustment for confounders. This study found statistically significant evidence to suggest that boys in United States who were vaccinated with the triple series Hepatitis B vaccine, during the time period in which vaccines were manufactured with thimerosal, were more susceptible to developmental disability than were unvaccinated boys.”

United Nations Report: http://www.who.int/immunization/sage/meetings/2012/april/Pichichero_Update_on_safety.pdf

BMJ • June 2008

Effect of 50,000 IU vitamin A given with BCG vaccine on mortality in infants in Guinea-Bissau: randomised placebo controlled trial

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Abstract

OBJECTIVE
To investigate the effect of high dose vitamin A supplementation given with BCG vaccine at birth in an African setting with high infant mortality.

DESIGN
Randomised placebo controlled trial. Setting Bandim Health Project's demographic surveillance system in Guinea-Bissau, covering approximately 90,000 inhabitants. Participants 4345 infants due to receive BCG.

INTERVENTION
Infants were randomised to 50,000 IU vitamin A or placebo and followed until age 12 months.

MAIN OUTCOME MEASURE
Mortality rate ratios.

RESULTS
174 children died during follow-up (mortality=47/1000 person-years). Vitamin A supplementation was not significantly associated with mortality; the mortality rate ratio was 1.07 (95% confidence interval 0.79 to 1.44). The effect was 1.00 (0.65 to 1.56) during the first four months and 1.13 (0.75 to 1.68) from 4 to 12 months of age. The mortality rate ratio in boys was 0.84 (0.55 to 1.27) compared with 1.39 (0.90 to 2.14) in girls (P for interaction=0.10). An explorative analysis revealed a strong interaction between vitamin A and season of administration.

CONCLUSIONS
Vitamin A supplementation given with BCG vaccine at birth had no significant benefit in this African setting. Although little doubt exists that vitamin A supplementation reduces mortality in older children, a global recommendation of supplementation for all newborn infants may not contribute to better survival.

TRIAL REGISTRATION
Clinical trials NCT00168597.

Full Report: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2432170/

"Vitamin A supplementation given with BCG vaccine at birth had no significant benefit in this African setting."

European Journal Of Internal Medicine • July 2008

Status epilepticus and lymphocytic pneumonitis following hepatitis B vaccination

Author information

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Abstract

The case reported refers to a patient who developed status epilepticus in the day of her third dose of hepatitis B vaccination and we review the literature on this subject. A 12 year-old girl, without a relevant previous history, taking no drugs, developed a seizure attack followed by unconsciousness, and eventually died after three days of her third dose of hepatitis B (HB) vaccination. Autopsy study revealed cerebral edema with congestion and herniation and diffuse interstitial type pneumonitis. There seem to be a straight forward time relationship between the third HB vaccine, the event of convulsion and the sudden death of the patient. We suggest that, in some cases, vaccination may be the triggering factor for autoimmune and neurological disturbances in genetically predisposed individuals and physicians should be aware of this possible association.

http://www.ncbi.nlm.nih.gov/pubmed/18549949

“A 12 year-old girl, without a relevant previous history, taking no drugs, developed a seizure attack followed by unconsciousness, and eventually died after three days of her third dose of hepatitis B (HB) vaccination. Autopsy study revealed cerebral edema with congestion and herniation and diffuse interstitial type pneumonitis. There seem to be a straight forward time relationship between the third HB vaccine, the event of convulsion and the sudden death of the patient. We suggest that, in some cases, vaccination may be the triggering factor for autoimmune and neurological disturbances in genetically predisposed individuals ...”

Forensic Science International • August 2008

Beta-tryptase and quantitative mast-cell increase in a sudden infant death following hexavalent immunization

Author information

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Abstract

The association between sudden infant death syndrome and immunization is frequently discussed. Serious adverse events following vaccination have generally been defined as those adverse events that result in permanent disability, hospitalization or prolongation of hospitalization, life threatening illness, congenital anomaly or death. They are generally referred to the inherent properties of the vaccine (vaccine reaction) or some error in the immunization process (programme error). The event could also be totally unrelated but only temporally linked to immunization (coincidental event). A fatal case of a 3-month-old female infant, who died within 24 h of vaccination with hexavalent vaccine is presented. Clinical data, post-mortem findings (acute pulmonary oedema, acute pulmonary emphysema), quali-quantitative data collected from immunohistochemical staining (degranulating mast cells) and laboratory analysis with a high level of beta-tryptase in serum, 43.3 microg/l, allows us to conclude that acute respiratory failure likely due to post hexavalent immunization-related shock was the cause of death.

http://www.ncbi.nlm.nih.gov/pubmed/18538957

"A fatal case of a 3-month-old female infant, who died within 24 h of vaccination with hexavalent vaccine is presented. Clinical data, post-mortem findings (acute pulmonary oedema, acute pulmonary emphysema), quali-quantitative data collected from immunohistochemical staining (degranulating mast cells) and laboratory analysis with a high level of beta-tryptase in serum, 43.3 microg/l, allows us to conclude that acute respiratory failure likely due to post hexavalent immunization-related shock was the cause of death."

The Journal of Immunology • April 15, 2008

The Adjuvants Aluminum Hydroxide and MF59 Induce Monocyte and Granulocyte Chemoattractants and Enhance Monocyte Differentiation toward Dendritic Cells

Author Information

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Abstract

Aluminum hydroxide (alum) and the oil-in-water emulsion MF59 are widely used, safe and effective adjuvants, yet their mechanism of action is poorly understood. We assessed the effects of alum and MF59 on human immune cells and found that both induce secretion of chemokines, such as CCL2 (MCP-1), CCL3 (MIP-1□), CCL4 (MIP-1□), and CXCL8 (IL-8), all involved in cell recruitment from blood into peripheral tissue. Alum appears to act mainly on macrophages and monocytes, whereas MF59 additionally targets granulocytes. Accordingly, monocytes and granulocytes migrate toward MF59-conditioned culture supernatants. In monocytes, both adjuvants lead to increased endocytosis, enhanced surface expression of MHC class II and CD86, and down-regulation of the monocyte marker CD14, which are all phenotypic changes consistent with a differentiation toward dendritic cells (DCs). When monocyte differentiation into DCs is induced by addition of cytokines, these adjuvants enhanced the acquisition of a mature DC phenotype and lead to an earlier and higher expression of MHC class II and CD86. In addition, MF59 induces further up-regulation of the maturation marker CD83 and the lymph node-homing receptor CCR7 on differentiating monocytes. Alum induces a similar but not identical pattern that clearly differs from the response to LPS. This model suggests a common adjuvant mechanism that is distinct from that mediated by danger signals. We conclude that during vaccination, adjuvants such as MF59 may increase recruitment of immune cells into the injection site, accelerate and enhance monocyte differentiation into DCs, augment Ag uptake, and facilitate migration of DCs into tissue-draining lymph nodes to prime adaptive immune responses.

Full Report: http://www.jimmunol.org/content/180/8/5402.full

"Aluminum hydroxide (alum)
and the oil-in-water emulsion MF59 [squalene]
are widely used, safe and effective adjuvants, yet
their mechanism of action is poorly understood."

Autoimmunity Review • October 2008

Chronic fatigue syndrome with autoantibodies—the result of an augmented adjuvant effect of hepatitis-B vaccine and silicone implant

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Abstract

Background

Chronic fatigue syndrome (CFS) that defines by prolonged fatigue and other manifestations, was recently integrated into a spectrum of central sensitivity syndromes including several diseases as fibromylagia. CFS etiology is multi-factorial commonly triggered by infectious agents. Vaccines, induce an immune response similarly to infections, and may trigger just like infections autoimmune diseases, CFS and fibromyalgia. Furthermore vaccines contain an adjuvant which enhances their immune stimulation.

Case Presentation

A 56-year-old woman was diagnosed with CFS accompanied by fibromyalgia, demyelination and autoantibodies. Her illness begun following the 2nd dose of hepatitis-B vaccine, and was aggravated by the 3rd vaccination. She underwent silicone breast implantation 6 years before vaccination with no adverse events. However, between the 2nd and 3rd vaccination she suffered a breast injury with local inflammation. Upon explanation of her breast implants silicone leak was observed.

Discussion

Vaccines have been reported to precede CFS mainly following exposure to multiple vaccinations (e.g. the Gulf war syndrome), or as an adverse response to the vaccine adjuvant (e.g. the macrophagic myofasciitis syndrome). Silicone is considered an adjuvant to the immune system, and may induce "the adjuvant disease". Silicone implant, especially silicone leak relationship with autoimmunity and CFS has been the focus of considerable debates.

Conclusion

Our patient illness started following hepatitis-B vaccine, suggesting that it was caused or accelerated by vaccination. In parallel to vaccination our patient suffered from breast injury, which might represent the time of silicone leak. The exposure to the adjuvant, silicone, might have augmented her immune response to the vaccine. To the best of our knowledge this is the first case of combined adverse effect to vaccine and silicone. Vaccine safety in individuals with silicone implants requires further studies.

http://www.ncbi.nlm.nih.gov/pubmed/18725327

"... the changes induced by MF59 and alum share common features ..."

"Vaccines have been reported to precede Chronic Fatigue Syndrome mainly following exposure to multiple vaccinations (e.g. the Gulf war syndrome), or as an adverse response to the vaccine adjuvant (e.g. the macrophagic myofasciitis syndrome)."

Pediatric Infectious Disease Journal • October 2008

Mumps epidemiology and immunity: the anatomy of a modern epidemic

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Abstract

The success of the measles, mumps, and rubella 2-dose vaccination program led public health officials in 1998 to set a goal to eliminate endemic transmission of mumps virus by 2010 in the United States. The large outbreak of mumps in the spring of 2006 has led public health officials to re-evaluate this goal and to recognize that the transmission and epidemiology of mumps in highly vaccinated populations may be different than anticipated. During 2006, a total of 6584 confirmed and probable cases of mumps were reported to the Centers for Disease Control and Prevention and most of these, 5865, occurred between January 1 and July 31. The peak of the outbreak was in April and seemed to be focused on college campuses in 9 midwestern states with Iowa having the highest attack rate. College campuses with mumps outbreaks included ones with 77% to 97% of students having had 2 doses of a mumps vaccine. Diagnosing mumps proved to be problematic in vaccinated persons (ie, laboratory tests seemed to be insensitive and some apparent mumps cases had mild nonclassic illness). The outbreak demonstrated that mumps can sometimes transmit efficiently in highly vaccinated populations and the clinical and laboratory diagnosis of mumps in vaccinated persons is more difficult than in naive persons. The reason for this mumps outbreak is not clear but probably results from multiple factors contributing to an overall increase in susceptibility and/or transmission.

http://www.ncbi.nlm.nih.gov/pubmed/18820583

“The outbreak demonstrated that mumps can sometimes transmit efficiently in highly vaccinated populations and the clinical and laboratory diagnosis of mumps in vaccinated persons is more difficult than in naive persons.”

Vaccine • November 2008

Vaccine immunogenetics: bedside to bench to population

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Abstract

The immunogenetic basis for variations in immune response to vaccines in humans remains largely unknown. Many factors can contribute to the heterogeneity of vaccine-induced immune responses, including polymorphisms of immune response genes. It is important to identify those genes involved directly or indirectly in the generation of the immune response to vaccines. Our previous work with measles reveals the impact of immune response gene polymorphisms on measles vaccine-induced humoral and cellular immune responses. We demonstrate associations between genetic variations (single nucleotide polymorphisms, SNPs) in HLA class I and class II genes, cytokine, cell surface receptor, and toll-like receptor genes and variations in immune responses to measles vaccine. Such information may provide further understanding of genetic restrictions that influence the generation of protective immune responses to vaccines, and eventually the development of new vaccines.

http://www.ncbi.nlm.nih.gov/pubmed/18598732

“The immunogenetic basis for variations in immune response to vaccines in humans remains largely unknown.”

Alternative Therapies In Health And Medicine • November 2008

The history of vaccinations in the light of the autism epidemic

Author information

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Abstract

Autism has been characterized as a behavioral disorder since it was first described by Leo Kanner in 1943. The number of autistic children has increased over the last decade. The incidence of autism was 1 in 10000 before the 1970s and has steadily increased to 1 in 150 in 2008 with a male:female predominance of 4:1. The cause of this epidemic has remained unknown, but several hypotheses have been studied. Many of these suggest an environmental trigger, such as the ethyl mercury contained in the preservative thimerosal, which has been used in vaccines since 1931. Other possible triggers associated with vaccinations are chemical toxins and live viruses. James has published studies suggesting a genetic predisposition in the families of autistic children, exposing them to a deficiency in glutathione and an inability to detoxify heavy metals. Vargas has shown autism to encompass ongoing inflammation in the brains of autistic children. The Hannah Poling vaccine decision was a landmark case. Poling's family was awarded funds for ongoing medical care of an autistic child who was found to have mitochondrial dysfunction exacerbated by vaccines that left her with autistic behavior and seizures. Several studies have emerged supporting the fact that a significant number of autistic children do have mitochondrial dysfunction. The impact that the Poling case will have on the ability of parents of autistic children to gain access to funds to enable them to properly care for their children remains to be seen.

http://www.ncbi.nlm.nih.gov/pubmed/19043939

"Poling's family was awarded funds for ongoing medical care of an autistic child who was found to have mitochondrial dysfunction exacerbated by vaccines that left her with autistic behavior and seizures. Several studies have emerged supporting the fact that a significant number of autistic children do have mitochondrial dysfunction. The impact that the Poling case will have on the ability of parents of autistic children to gain access to funds to enable them to properly care for their children remains to be seen."

European Journal Of Internal Medicine • December 2008

Systemic polyarteritis nodosa following hepatitis B vaccination

Author information

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Abstract

The authors report a patient who developed systemic polyarteritis nodosa two months after hepatitis B vaccination and review the literature concerning this vaccination and the development of autoimmune conditions, mainly vasculitis. A 14-year-old boy who had no relevant previous history and who was not taking any drugs presented with a livedo reticularis, fever, loss of weight, testicular pain, and paresthesias two months after receiving the third dose of a hepatitis B vaccination. Inflammatory parameters (ESR and CRP) were high. The patient met the ACR diagnostic criteria for polyarteritis nodosa. He received corticosteroids and immunosuppressants and showed improvement. After reviewing the 27 cases of vasculitis after hepatitis B vaccination reported in the current literature, the authors suggest that, in some cases, vaccination may be the triggering factor for vasculitis in individuals with a genetic predisposition. Physicians should be aware of this possible association.

http://www.ncbi.nlm.nih.gov/pubmed/19046721

“After reviewing the 27 cases of vasculitis after hepatitis B vaccination reported in the current literature, the authors suggest that, in some cases, vaccination may be the triggering factor for vasculitis in individuals with a genetic predisposition.”

“There are currently over 100 human diseases

that are considered to be autoimmune or chronic inflammatory affecting

5-10% of the world population and spanning through all medical specialties.”

Journal Of Autoimmunity • December 2008

The autoimmunologist: geoepidemiology, a new center of gravity, and prime time for autoimmunity

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Abstract

There are currently over 100 human diseases that are considered to be autoimmune or chronic inflammatory affecting 5-10% of the world population and spanning through all medical specialties. As a result, health care costs are enormous and the clinical management is often challenging, particularly considering the comorbidity rates and the multi-organ involvement of each condition. We herein propose the creation of a new specialist, coined the autoimmunologist, to overcome the current limitations in the diagnostic process and clinical follow-up of patients with autoimmune diseases. More importantly, we also propose the creation of regional centers of excellence in autoimmunity where clinical research and management, as well as basic research may be united and interact in ideal synergy to ultimately create real translational research and provide better health care.

http://www.ncbi.nlm.nih.gov/pubmed/?term=18838248

"In our study Oral Polio Virus at birth

had a sex-differential effect on mortality."

PLoS ONE • 2008

Sex-Differential Effect on Infant Mortality of Oral Polio Vaccine Administered with BCG at Birth in Guinea-Bissau—A Natural Experiment

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Beverley J. Shea, Editor

Abstract

Background

The policy to provide oral polio vaccine (OPV) at birth was introduced in low-income countries to increase coverage. The effect of OPV at birth on overall child mortality was never studied. During a trial of vitamin A supplementation (VAS) at birth in Guinea-Bissau, OPV was not available during several periods. We took advantage of this "natural experiment" to test the effect on mortality of receiving OPV at birth.

Methodology

Between 2002 and 2004, the VAS trial randomised normal-birth-weight infants to 50,000 IU VAS or placebo administered with BCG. Provision of OPV at birth was not part of the trial, but we noted whether the infants received OPV or not. OPV was missing during several periods in 2004. We used Cox proportional hazards models to compute mortality rate ratios (MRR) of children who had received or not received OPV at birth.

Principal Findings

A total of 962 (22.1%) of the 4345 enrolled children did not receive OPV at birth; 179 children died within the first year of life. Missing OPV at birth was associated with a tendency for decreased mortality (adjusted MRR=0.69 (95% CI=0.46–1.03)), the effect being similar among recipients of VAS and placebo. There was a highly significant interaction between OPV at birth and sex (p=0.006). Not receiving OPV at birth was associated with a weak tendency for increased mortality in girls (1.14 (0.70–1.89)) but significantly decreased mortality in boys (0.35 (0.18–0.71)).

Conclusions

In our study OPV at birth had a sex-differential effect on mortality. Poliovirus is almost eradicated and OPV at birth contributes little to herd immunity. A randomised study of the effect of OPV at birth on overall mortality in both sexes is warranted.

http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2605256/

Medical Veritas • 2008

Current childhood vaccine programs: An overview with emphasis on the Measles-Mumps-Rubella (MMR) vaccine and of its compromising of the mucosal immune system

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Abstract

Both common observation and official statistics confirm that there have been dramatic increases in chronic physical and mental illnesses in American children, such as autism, asthma, and allergies since the introduction of the MMR vaccine in 1978. Government health officials have denied a relationship with vaccines, but U.S. Congressional hearings on vaccine safety (1999 to Dec. 2004) revealed a total absence of vaccine safety tests that would meet current scientific standards, so that it can be assumed that many vaccine reactions are taking place unrecognized. Prior to the introduction of vaccines, the Th1 cellular immune system of the gastrointestinal and respiratory systems served as the primary defense systems with the Th2 humoral immune system in the bone marrow, serving a secondary role.

There is a school of thought that the "minor childhood diseases" of earlier times, including measles, mumps, chicken pox, and rubella, which involved the epithelial tissues of skin, respiratory, and/or gastrointestinal tracts, served a necessary purpose in challenging, strengthening, and establishing the dominance of Th1 cellular immune system during early childhood. Current vaccines against these diseases, in contrast, being directed at stimulating antibody production in the bone marrow, are bypassing the cellular immune system and thereby tending to reverse the roles of the cellular and humoral systems, with the former suffering from a lack of challenge. In addition, the cellular immune system is being further compromised by the powerfully immunosuppressive effects of the MMR vaccine. The time is overdue to totally rethink and redirect our current childhood vaccine program.

Concerns about increasing incidence of childhood autism and related disorders

Many years ago in our medical practice we began asking teachers if, during their teaching careers, they had observed a change in children. Without exception, they replied that there had been a dramatic change, most notably since the early 1980s. Steadily increasing numbers of children, they reported, were showing autistic-like behaviors, were restless, impulsive, less focused, less able to concentrate, and therefore less able to learn.

It has been documented that a sharp and persisting rise in the incidence of childhood autism commenced following the 1978 introduction of the MMR vaccine in the U.S.A. [1-2], a time when mercury-laced Hepatitis B and Hemophilus influenza type b vaccines were also introduced. For a number of years previously the live measles, mumps, and rubella vaccines had been administered separately with negligible increases in autism. It was only after they were combined that the incidence of autism began soaring with 1 in 150 children up to eight years age, according to U.S. multisite study in 2000 [3], as compared with 1 in 10,000 several generations ago. According to more recent information, the incidence of autism may be even higher, with 1 in 88 military children in U.S.A. having autism [4], and according to the Vaccine Autoimmune Project (VAP), one in 67 in U.S.A. and 1 in 86 in the United Kingdom having autism [5]. Considering that the incidence of autism in boys is approximately four times greater than in girls, the relative incidence of autism in boys would be even greater. Finally, as estimated by VAP, the average lifetime cost of caring for autistic children will be about $3.2 million dollars per child.

In addition to the autism epidemic, in 2004 almost five million children were classified as learning disabled [6], which represents a three-fold increase since 1976-7 according to the Digest of Education Statistics [7].

Comparable increases have taken place in attention deficit hyperactive disorder (ADHD), with four and one half million children between ages 3 and 17 being diagnosed with this condition in 2004 [8].

In a bulletin sponsored by the American Academy of Pediatrics, January, 2004, entitled "AUTISM A.L.A.R.M.", in addition to an announcement of the increasing prevalence of autism at that time, it was announced that 1 in 6 American children were diagnosed with a developmental disorder and/or behavioral disorder.

In a similar fashion the incidence of asthma has increased from roughly two and a half million children, ages 0-17 years in 1979 [8] to nine million children 0-17 years in 2004 [8], (roughly 12% of that age group), a time period in which this age-group population increased 114% compared to a 360% increase in asthma.

Autoimmune diseases are also increasing, including juvenile diabetes, multiple sclerosis, Guillain-Barre Syndrome, and Crohn's inflammatory bowel disease. Based on the work of Vijendra Singh, who demonstrated marked elevations of brain antibodies in the form of myelin basic protein antibodies in autistic children [9-10], autism itself can be considered an autoimmune disorder.

Current studies implicating vaccines as primary causal agents of autism and related disorders

In what may be the most comprehensive publication to date on the pathophysiology of adverse vaccine reactions, Russell Blaylock has compiled a mass of evidence that repeated stimulation of the systemic immune system results in first priming of microglia of the developing brain, following by intense microglial reaction with each successive series of vaccinations [16]

In explanation, microglia and astrocytes are first-line-immunological responder cells located in the brain which defend against foreign infectious invaders. Normally this response, such as to a viral infection, is of limited duration and harmless to the brain. However, when the microcytes and astrocytes are overstimulated for prolonged periods, which vaccines are designed to bring about, this extended activation can be very destructive to the brain.

Because of the critical dependence of the developing brain on a timed sequence of cytokine and excitatory amino acid fluctuation, according to Blaylock, sequential vaccinations can result in alterations of this critical process that will not only result in synaptic and dendritic loss, but abnormal (nerve) pathway development. When microglia are excessively activated by vaccines, especially chronically, they secrete a number of inflammatory cytokines, free radicals, lipid peroxidation products, and the two excitotoxins, glutamate and quinolenic acid, which may become highly destructive to the brain when these cells are excessively stimulated for prolonged periods. This process was suggested as the central mechanism resulting in the pathological as well as clinical features of autism [16].

Since the U.S. Congressional Hearings on issues of vaccine safety ended in December, 2004, credible and statistically significant studies have begun appearing that: a) meet the established criteria for effective safety tests and b) without exception in my opinion, have implicated vaccines as central causal factors in today's epidemic of autism and related disorders. Several are listed below:

• As published in the Annals of Neurology [17], Diana Vargas and colleagues examined the brains from autopsies of 11 autistic patients, ranging in ages from 5 to 44 years, in which they found the presence of extensively activated microglia and astrocytes along with elevations of cytokines and chemokines, which are immune system proteins involved in inflammatory processes. As the first study of its kind, it tends to support Blaylock's theory

that overstimulation of the brain's microglia and astrocytes for excessively prolonged periods resulting from current vaccine programs plays a central causal role in today's epidemic of childhood autism.

• Surveys from four widely separated geographic areas have shown higher rates of asthma in fully vaccinated children as compared with those with limited or no vaccines [18-21].

• A study on primary immunization of 239 premature infants with gestational ages of less that 35 weeks was conducted by M. Pourcyrous et al. (Journal of Pediatrics [22], to determine the incidence of cardiorespiratory events and abnormal C-reactive protein (CRP) levels associated with administration of a single vaccine or multiple vaccines simultaneously at or about two months age. (CRP is a standard blood test to measure body inflammation.) CRP levels and cardiorespiratory events were monitored for three days following immunizations in a neonatal intensive care unit sponsored by the University of Tennessee. Elevations of CRP levels occurred in 70% of infants administered single vaccines and in 85% of those given multiple vaccines, 43% of which reached abnormal levels. Overall, 16% of infants had vaccine-associated cardiorespiratory events with episodes of apnea (cessation of breathing) and bradycardia. Most important, 17% of those receiving single vaccines had intraventricular brain hemorrhages, with an incidence of 24% of those receiving multiple vaccines. (This is the first study of its kind, showing that brain hemorrhages can commonly take place in vulnerable infants, now being misdiagnosed as Shaken Baby Syndrome in hospital emergency rooms.) It should be noted that each and every one of the preceding adverse manifestations could be attributed to vaccine-induced brain inflammation.

• Though long denied by health officials, the action of mercury in causing brain inflammation in autistic children tends to be confirmed by Sajdel, Sulkowska, et al. [23]. Also the first of its kind, this study compared the cerebellar levels of the oxidative stress marker, 3-nitrotyrosine (3-NT), mercury (Hg), and the antioxidant, selenium (Se) between autistic and normal children. Average cerebellar 3-NT levels were statistically elevated by 68% in autistic children, cerebellar Hg by 68%, and mercury levels relative to protective selenium by 75% in autistic cases in comparison to controls.

• In a study along similar lines to the S. Sulkowska study above, X. Ming et al. [24] reviewed their animal model of autism, showing that oxidative stress from methylmercury or valproic acid exposures in early postnatal life of mice resulted in aberrant social, cognitive, and motor behavior. They also found that Trolox, a water-soluble vitamin E derivative, was capable of attenuating a number of these adverse neurobehavioral side effects.

• A telephone survey commissioned by the nonprofit group, Generation Rescue, compared vaccinated with unvaccinated boys in nine counties of Oregon and California [25]. The survey included nearly 12,000 households with children ranging in age from 4 to 17 years, including more than 17,000 boys among whom 991 were described as being completely unvaccinated. The survey found that, compared to unvaccinated boys, vaccinated boys were 155% more likely to have a neurological disorder, 224% more likely to have ADHD, and 61% more likely to have autism. For older vaccinated boys in the 11-17 age bracket, the results were even more pronounced, with 158% more likely to have neurological disorders, 317% more likely to have ADHD, and 112% more likely to have autism.

• In October, 1998 the French government abandoned its mandatory hepatitis B vaccine program for school children after more than 15,000 law suits were filed for brain damage and autoimmune reactions including arthritis, multiple sclerosis, and lupus.

Vaccine adjuvants—their role in inducing prolonged immune response to vaccines and their potentially adverse consequences

• As reviewed by Blaylock [16], adjuvants are substances added to vaccine formulations during manufacturing that are designed to boost the overall immune system response when the vaccine is injected. These substances include albumin, several forms of aluminum, formaldehyde, various amino acids, DNA residues, egg protein, gelatin, surfactants, monosodium glutamate(MSG), Thimerosal (50% ethyl mercury), and various antibiotics.

• Contrary to public avowals as to the removal of mercury from vaccines, at time of this writing it is still present in the USA as a preservative in the multi-dose vials of tetanus-toxoid booster vaccines, the Menomune vaccine, the JE-Vax, and the inactivated influenza vaccines, including the "bird-flu" vaccine. Also it's used in the manufacturing process of many vaccines to remove contaminants, which currently leaves trace residues of mercury in seven other vaccine formulations. Even these trace amounts are potentially toxic because of the universally recognized principle of toxicology, that combinations of toxins will increase toxicity exponentially; that is, two heavy metals will increase toxicity 10-fold, or three heavy metals increase toxicity 100-fold. In vaccines, the combinations would be mercury and aluminum. The same principle applies in other forms of toxic chemicals [26-28].

• A study that was conducted in Lima, Peru by J. Laurente and colleagues [29] should remove all doubts about the potential dangers of mercury-containing thimerosal as a vaccine additive: To determine if thimerosal administration in amounts equivalent to vaccine content produces neurotoxic effects on the encephalon in postnatal hamsters and on the experimentation animals' development, three serial thimerosal injections were given on birth days 7, 9, and 11, with controls receiving only saline injection. Test animals subsequently showed statistically significant reduction in both weight and stature compared with controls. Neurotoxic effects were also produced at encephalic (brain) level at the hippocampus, cerebral cortex, and cerebellum. On tissue slides there was decrease in neuronal density, neuronal necrosis, and axonal demyelinization in test animals.

• In vaccines, virtually insoluble polymeric aluminum hydroxy compounds serve to dramatically boost and prolong the immune reaction to the vaccination by prolonged activation of the macrophagic immune sub-system in some people [30-35].

Ongoing mass (herd) immunizations – are they necessary?

• Vaccine proponents would have us believe that mass vaccine programs have been largely responsible for controlling virtually all of the former epidemics of killer childhood diseases in industrialized nations, In my opinion, with the exception of small-pox and the possible exception of the polio vaccine, the facts do not bear this out. According to the Metropolitan Life Insurance Company, from 1911 to 1935 the four leading causes of child- hood deaths from infectious diseases in the USA were diphtheria, pertussis (whooping cough), scarlet fever, and measles. Yet, by 1945 the combined death rates from these causes had declined by 95%, before implementation of mass vaccine programs [39]. Other sources provided much the same pattern of information [40-41]. Furthermore, according to a report in Morbidity and Mortality Weekly Report, July 30, 1999, improvements in sanitation, water quality, hygiene, and the introduction of antibiotics have been the most important factors in control of infectious disease in the past century. Although vaccines were mentioned, they were not included among the major factors [42].

The MMR vaccine and childhood autism: a hypothetical model

• As mentioned earlier, it was only after the combination of the measles, mumps, and rubella live viruses into a single vaccine in the USA in 1978 that the incidence of childhood autism showed a sharp and dramatic increase 1-2]. Prior to that time the three viral vaccines had been in use a number of years, but given separately without significant increases in autism.

• In addition to the Blaylock model of microglial overstimulation, also undoubtedly playing a major role [16], there are two plausible explanations for increases in autism following the MMR vaccine: First, protein sequences in the measles virus have been found to have similarities to those in brain tissues [43], so that by process of mimicry, the formation of antibodies against the measles virus would tend to cross react adversely with the brain.

Second, and probably far more important, viruses are inherently immunosuppressive, in contrast to bacterial infections which stimulate the immune system, as reflected in the fact that viral infections generally lower white blood counts in contrast to bacterial infections, which raise white counts. The measles virus is exceptionally potent in this regard, being powerfully suppressive to cellular immunity [44-46], with the suppressive action of measles largely attributed to its suppression of interleukin 12, on which cellular immunity is dependent [45]. Consequently the combining of three viral vaccines into a single combination may substantially increase the immunosuppressive vital effect, bringing about, in varying degrees, an immune paralysis in the infant. Under these circumstances the measles virus may spread into various tissues of the body. As with combinations of toxic chemicals that bring exponential increases in toxicities [26-28], combinations in viral vaccines may bring exponential increases in their toxic, immunosuppressive effects.

• In support of this hypothesis, Wakefield et al. have demonstrated live measles virus in the small intestinal lymph nodes in children with the autistic-colitis syndrome, with the only possible source being from the live virus in the MMR vaccine [47].

• In his various lectures in this country, Wakefield stressed that it was only following the introduction of the MMR vaccine in the United Kingdom in 1987 that the rapid increase in childhood the colitis/autistic syndrome began to be seen. This pattern was further confirmed by checking back into the records of public health departments of the United Kingdom and finding reports of autism occurring among children contracting two such childhood diseases simultaneously, such as chicken pox and measles, or mumps and measles.

• As reviewed by Blaylock [16], a number of studies have shown that live viruses used in vaccines can enter the brain and reside there for a lifetime. One study, in which autopsied tissues from the elderly were examined for the presence of the measles virus, found that 20% of brains had live measles virus and that 45% of other organs were infested as well [48].

• As another study suggesting that active brain invasion by the measles virus in autistic children from the MMR vaccination, Bradstreet et al. [49] examined cerebrospinal fluid from three autistic children, which revealed the presence of measles virus genomic RNA.

• As to other viral vaccines, as reported by Bernard Rimland, the chicken pox vaccine is also playing a role in these cases.

• "The federal government's Vaccine Adverse Event Reporting System (VAERS), which supposedly documents adverse reactions to vaccines, received nearly 10,000 reports involving the chickenpox vaccine between March, 1995 and December, 1999. Some of these reactions included brain inflammation, neurological damage, immune system abnormalities, seizures, and death. It is important to note, by the way, that since reporting adverse events is not mandatory, only an estimated 1 to 10% of adverse events are reported to VAERS."[50]

• In addition, articles by Gary Goldman seriously question the efficacy and advisability of universal varicella vaccination [51,52].

• Immunosuppressive effects have also been reported from the rubella vaccine. In a study of eighteen school girls, ages 11 to 13 years by Pukhalsky et al., profound depression of interferon gamma (a key mediator of cellular immunity) was found 30 days following rubella vaccine [53].

Returning to the MMR vaccine, F. Imani and K. Kehoe found a previously unrecognized side effect by incubating the MMR vaccine with a line of human plasma cells, which resulted in increase in the expression of allergy-related IgE antibodies, and secondarily a decrease in protective IgG antibodies. Based on these findings, the authors concluded that viral vaccines may be playing a role in the increasing incidence of asthma and other allergic diseases [54].

John B. Classen, M.D., and epidemiologic studies concerning a suspected causal relationship between vaccines and the rising incidence of Insulin-Dependent Diabetes mellitus (IDDM)

• In 1998 John Classen, M.D. gave a presentation at a conference held by the American College of Medicine in which he reviewed 32 published articles, five authored by himself, indicating a causal relationship between vaccines and the rising incidence of IDDM. Nations represented in the papers included New Zealand, Canada, the United Kingdom, Denmark, Finland, Sweden, the U.S., and Holland. Single vaccines were used including haemophilus, hepatitis B, pertussis, BCG, and smallpox.

• A prototype was one conducted in Finland by Classen and reported in the British Medical Journal [58]. In this study, from all children born in Finland between October 1, 1985 and August 31, 1987, approximately 116,000 were randomized as test subjects to receive four doses of haemophilus vaccine starting at three months of age, or one dose starting at 24 months. 125,500 unvaccinated children served as controls. Each group was followed until age 10 years for development of IDDM. The incidence at seven years for those receiving four doses, those receiving one dose, and those receiving none was 261, 237, and 207 respectively with relative risks of 1.2, 1.14, and 1 for those receiving no vaccine.

• In virtually all of the reports from other countries the results were very similar, indicating a slight but consistent increase in IDDM following each of the single vaccines listed above. Classen interpreted these results as indicating that it was not the type of vaccination that mattered so much as the immunologic impact of vaccination itself. Typically there was a delay of 3 to 5 years between vaccines and onset of IDDM.

Quotations by Classen during the 1998 conference included:

"Vaccinating every child against every disease is fundamentally unsound."

"There is a 3.78-fold increased risk of insulin-dependent diabetes mellitus in children from today's vaccines."

"All autoimmune diseases are increasing in incidence.
General immune (over) stimulation from vaccines is a cause of autoimmunity."

Summary and conclusions

• Over eons of time nature has evolved two major branches of the immune system, the Th1 cellular system located in the mucous membranes of the gastrointestinal and respiratory systems, and the Th2 humoral system, which involves the production of antigen-specific antibodies by plasma cells in bone marrow. Both systems are incredibly complex both in the timing of their developments and their functions. Since a large majority of infectious microorganisms enter the body through the mucous membranes, the cellular immune system has evolved as the primary immune defense system of the body, with the humoral system serving as a secondary or backup role. For these reasons, evolutionary challenges have required the cellular immune system to become more effective in dealing with infectious micro-organisms, especially intracellular viral infections [57]. This is undoubtedly the reason that vaccine-induced immunities to measles, mumps, chicken pox, and rubella, which bypass the cellular immune system, are of limited duration requiring repeated vaccinations. The natural diseases of former times, in contrast, were dealt with much more effectively by the cellular immune system, almost always conferring permanent immunity.

• The reader may well question that we have innumerable viruses passing around in the population today. Would they not serve the same purposes as measles, chicken pox, mumps, and rubella? Perhaps, except that chicken pox, mumps, rubella, and especially measles affect and challenge the epithelial tissues of the skin, respiratory (rubella),

and gastrointestinal tracts (measles, chicken pox, and mumps) in ways that few if any other viruses do.

• As reviewed above, a newborn infant comes into the world with a rudimentary immune system which requires a series of challenges to bring it to full functional capacity, a process requiring approximately three years. In earlier times these challenges were largely in the forms of the "minor childhood diseases" listed above. With time and experience it is becoming evident that, in addition to those already mentioned, another flaw in today's vaccine programs is that the injectable vaccines, directed at stimulating antibody production in the bone marrow, are bypassing the cellular immune system, leaving it relatively unchallenged and therefore relatively weak and stunted during the critical infant/childhood period. In addition, there are the powerfully immunosuppressive effects of the MMR vaccine and other viral vaccines, to which the cellular immune system is uniquely vulnerable. These processes appear to be progressively undermining and eroding the cellular immune system, and unless discontinued or changed, may lead to an immunological collapses. Perhaps it already has for some children.

• It is or should be manifestly apparent that the humoral antibody-producing system of the bone marrow can never functionally replace the far more efficient cellular immune system.

• For this reason, in my opinion, any children's vaccine program which does not allow the cellular (mucosal) immune system to develop unhampered in a natural way from natural challenges will be self-defeating. This would necessarily require a delay of childhood vaccines until two or three years of age. With this delay, the minor childhood viral diseases might well return, but would this be a bad thing? The dangers of chicken pox and mumps have been greatly exaggerated. Because of concerns for congenital rubella, the rubella vaccine could be delayed to later years, as the infection itself is very mild. Historically, measles did have some serious consequences including encephalitis, blindness or death in about 1 in 150 cases. However, there are other answers. Nutrition has been one of the missing links all along. In third world countries where measles has resulted in high mortality, this has usually been associated with malnutrition. One example of nutritional intervention is vitamin A therapy, authorized by the World Health Organization in developing nations, which has significantly reduced both mortality and morbidity from measles.

• A study in Afghanistan which showed significantly greater morbidity and mortality from measles in children administered aspirin and Tylenol than those not given these medications [62], so that these should be avoided with measles.

• Then too, we now have antibiotics for secondary infections associated with measles, which they did not have in the days when measles carried a small but significant rate of morbidities and mortality, much of which was from secondary infections.

• All of the above lies in the future. For today's parents the Autism Research Institute with headquarters in San Diego, California (www.AutismResearchInstitute.com) has made the following safety recommendations in childhood vaccines:

- Never vaccinate a sick child, even if he or she just has a runny nose.
- Never give more than two vaccines simultaneously.
- Rather than the MMR vaccine, request that these viral vaccines be given separately, preferably six months apart; give measles last; and do not give any other vaccines for at least 1 year after measles. Some compounding pharmacies do provide these individual vaccines.
- Administer vitamins A, D and C before and after vaccines.
- Never allow a vaccine containing any level of the mercurial compound, Thimerosal.

At time of this writing in late 2008, 50 micrograms of Thimerosal is still present in each 0.5- mL dose of vaccine from multi-dose vials of influenza vaccines and multi-dose vials of tetanus booster vaccines, but not in single dose vials of these vaccines. A total of 17 vaccines formulations are still approved and available for use that contain some level of Thimerosal; 10 of these 17 vaccine formulations contain a preservative level of Thimerosal.

• Any overview on vaccines would be incomplete without mention of the work of the highly published immunologist, H. H. Fudenberg, and his work in developing clinical applications of transfer factor, which is a low molecular weight extract of lymphocytes, capable of enhancing or inducing cell-mediated immunity de novo (without immunizations) in an antigen specific fashion [63-64].

• Finally, in view of gross deficiencies of vaccine safety testings, as documented by the U.S. Congressional Hearings on issues of vaccine safety (1999-December, 2004), the time is long overdue for a total rethinking and redirecting of current childhood vaccine programs. Until the safety of such programs can be assured by thorough and dependable safety testing, any further mandating of childhood vaccines will remain morally and ethically untenable.

http://www.know-vaccines.org/PDF/MMRmucosalIS.pdf

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The Safety Profile of Varicella Vaccine: A 10-Year Review

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Abstract Excerpts

Reports of breakthrough varicella

There were 5054 reports of breakthrough varicella, for a reporting rate of 0.9 reports/ 10,000 doses of vaccine distributed. Fifty-one reports (1%) met the regulatory definition of "serious."

Secondary transmission

The VZVIP confirmed 3 cases of secondary transmission of Oka VZV. The Oka VZV was present in a 30-year-old pregnant woman who developed 100 vesicular lesions 16 days after her 1-year-old son developed □30 vesicular lesions 24 days after varicella vaccination. She elected to have a therapeutic abortion, and the products of conception were negative for VZV by PCR analysis [5]. In the second report, the Oka VZV strain was also present in a 4-month-old boy who developed 25 lesions 19 days after his 1-year-old sibling developed 2 vesicular lesions 14 days after vaccination. The third case in which Oka VZV was identified occurred in a 35-year-old father who developed >100 lesions 17 days after his 1-year-old son developed 12 vesicular lesions 17 days after vaccination. In each of the 3 confirmed secondary-transmission cases, the vaccine recipient had a postvaccination rash and had close, household contact with the susceptible individual.

Additionally, there were 2 reported cases of possible secondary transmission, in which it was reported that the presence of Oka VZV was identified by an outside laboratory [6, 7]. The specimens for these cases were not analyzed through or confirmed by the VZVIP.

Neurologic AEs

Neurologic syndromes, such as encephalitis, aseptic meningitis, and cerebellar ataxia, have been reported in the postmarketing environment after administration of Varivax. There were 30 (CSF) specimens analyzed by PCR (table 1) from patients with reports of such syndromes. The reported AEs associated with these reports included encephalitis (12 patients), meningitis (5 patients), ataxia (5 patients), transverse myelitis (3 patients), seizures (3 patients), demyelinating disorder (1 patient), and hemiparesis (1 patient). The 5 meningitis reports associated with HZ listed in the "HZ" subsection above are different from the cases of meningitis listed in this subsection and are not included here. None of the CSF specimens from these neurologic reports had Oka VZV identified by PCR analysis. Several of these reports have been described elsewhere [1, 4].

Herpes Zoster

There were 697 reports of HZ occurring 1-3509 days (median, 362 days) after vaccination in patients 13 months to 68 years of age (median age, 3.4 years). Four hundred patients (65%) for whom age was reported were <5 years of age. Table 2 compares the HZ reports in which PCR analysis identified Oka VZV and wild-type VZV strains.

The site of HZ was more likely to correlate with the site of vaccine injection in reports in which Oka VZV was identified. PCR was more likely to identify wild-type VZV than Oka VZV if the time to onset was within 42 days of vaccination. However, 2 reports in which HZ was diagnosed within 42 days of vaccination had specimens in which Oka VZV was identified. One of these reports was of a child with acute lymphocytic leukemia diagnosed 10 days after vaccination with Varivax. The child eventually developed HZ on 3 occasions: 23, 47, and 116 days after vaccination. PCR analysis of a specimen from the last episode of HZ identified Oka VZV. In the second report, Oka VZV was present in a girl 5 years of age who developed an HZ-like rash in the distribution of the second division of the trigeminal nerve (right side of face and right eye) 25 days after receiving Varivax.

Five patients developed meningitis in association with HZ. Cerebrospinal fluid (CSF) specimens from these patients were negative for VZV. The HZ rash specimens from 2 of the patients had Oka VZV identified; however, in 1 of these reports, enterovirus was identified in the CSF analyzed at the Centers for Disease Control and Prevention (CDC). A third patient had wild-type VZV identified from an HZ rash specimen. Additionally, 1 child who received Varivax at 2-3 years of age had acute lymphocytic leukemia diagnosed at 4 years of age. After treatment with 6-mercaptopurine weekly and methotrexate monthly, he was hospitalized for HZ and mild meningeal signs. A CSF specimen had Oka VZV identified. The child recovered.

Potential conflicts of interest

S.A.G., A.S., P.B., and R.G.S. are salaried employees of Merck and possess stock and stock options in the company.
A.A.G. lectures and consults on varicella-zoster virus vaccines for Merck and GlaxoSmithKline when invited and receives research support from Merck. Additionally, P.S.L., S.P.S., and A.A.G. are in a contractual relationship with Merck through the Varicella Zoster Virus Identification Program.

Full Report:
http://jid.oxfordjournals.org/content/197/Supplement_2/S165.full

Simpsonwood Retreat Center • June 7-8, 2000

Simpsonwood • Scientific Review of Vaccine Safety Datalink Information

Norcross, Georgia

Quotes from and link to transcript with a
Discussion on the following page

"…the number of dose related relationships [between mercury and autism] are linear and statistically significant. You can play with this all you want. They are linear. They are statistically significant."

—Dr. William Weil, American Academy of Pediatrics. Simpsonwood, GA, June 7, 2000

"Forgive this personal comment, but I got called out at eight o'clock for an emergency call and my daughter-in-law delivered a son by c-section. Our first male in the line of the next generation and I do not want that grandson to get a Thimerosal containing vaccine until we know better what is going on. It will probably take a long time. In the meantime, and I know there are probably implications for this internationally, but in the meanwhile I think I want that grandson to only be given Thimerosal-free vaccines."

—Dr. Robert Johnson, Immunologist, University of Colorado, Simpsonwood, GA, June 7, 2000

"But there is now the point at which the research results have to be handled, and even if this committee decides that there is no association and that information gets out, the work has been done and through the freedom of information that will be taken by others and will be used in other ways beyond the control of this group. And I am very concerned about that as I suspect that it is already too late to do anything regardless of any professional body and what they say ... My mandate as I sit here in this group is to make sure at the end of the day that 100,000,000 are immunized with DTP, Hepatitis B and if possible Hib, this year, next year and for many years to come, and that will have to be with thimerosal containing vaccines unless a miracle occurs and an alternative is found quickly and is tried and found to be safe."

—Dr. John Clements, World Health Organization, Simpsonwood, GA, June 7, 2000

"We are in a bad position from the standpoint of defending any lawsuits, this will be a resource to our very busy plaintiff attorneys in this country."

—Dr. Robert Brent, a pediatrician at the Alfred I. duPont Hospital for Children in Delaware. "

"given the sensitivity of the information, we have been able to keep it out of the hands of, let's say, less responsible hands."

—Dr. Bob Chen, head of vaccine safety for the CDC

the study "should not have been done at all" the results "will be taken by others and will be used in ways beyond the control of this group. The research results have to be handled."

— Dr. John Clements, vaccines advisor at the World Health Organization

Link to Simpsonwood Document: http://thinktwice.com/simpsonwood.pdf

The truth behind the vaccine cover-up

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Abstract

On June 7-8, 2000 a secret conference was held at the Simpsonwood Conference Center in Norcross, Georgia to discuss a study examining the link between increasing doses of Thimerosal and neurodevelopmental disorders. The study was done using the Vaccine Safety Datalink (VSD) data-base, an official governmental data bank collecting patient vaccination information on the children from the health maintenance organizations (HMOs) being paid to participate. Attending were 51 scientists, representatives of pharmaceutical vaccine manufacturing companies and a representative of the World Health Organization; the public and the media were unlawfully excluded. The conclusions of this meeting were quite startling, since it confirmed a dose-response link between Thimerosal and neurodevelopmental disorders that held up to rigorous statistical analyses.

In their discussion, they make plain why the meeting was held in secret: the conclusions would have destroyed the public's confidence in the vaccine program, and more importantly, their faith in vaccine authorities. When the results of this study were published three years later in the journal Pediatrics, the "problem" had been fixed, in that by adding another set of data from a third HMO, reorganizing the criteria for inclusion and restructuring the patient groupings, a less than statistically significant link was demonstrated. In my analysis I discuss the more outrageous statements made during the meeting and how accepted experts in the field of mercury neurotoxicity were excluded from the meeting.

I was asked to write a paper on some of the newer mechanisms of vaccine damage to the nervous system, but in the interim I came across an incredible document that should blow the lid off the cover-up being engineered by the pharmaceutical companies in conjunction with powerful governmental agencies.

It all started when a friend of mine sent me a copy of a letter from Congressman David Weldon, M.D. to the director of the CDC, Dr Julie L. Gerberding, in which Congressman Weldon alludes to a study by a Doctor Thomas Verstraeten, then representing the CDC, on the connection between infant exposure to Thimerosal-containing vaccines and neurodevelopmental injury. In this shocking letter, Congressman Weldon refers to Dr. Verstraeten's study, which looked at the data from the Vaccine Safety Datalink and found a statistically significant correlation between Thimerosal exposure via vaccines and several neurodevelopmental disorders including tics, speech and language delays, and possibly ADD.

Congressman Weldon questions the CDC director as to why, following this meeting, Dr. Verstraeten published his results almost four years later in the journal Pediatrics to show just the opposite, that is, that except for tics, there was no statistically significant correlation to any neurodevelopmental problems related to Thimerosal exposure in infants. In this letter, Congressman Weldon refers to a report of the minutes of this meeting held in 2000, which exposes some incredible statements by the "experts" making up this study group. The group's purpose was to evaluate and discuss Dr. Verstraeten's interim results and data and make recommendations that would eventually lead to possible alterations in existing vaccine policy.

I contacted Congressman Weldon's legislative assistant and he kindly sent me a complete copy of this report. Now, as usual in these cases, the government did not give up this report willingly; it required a Freedom of Information Act lawsuit to pry it loose. Having read the report twice and having carefully analyzed it, I can see why they did not want any outsiders to see it. It is a bombshell, as you shall see.

To help the reader understand the importance of this report, in this analysis I will not only describe and discuss this report, but also will frequently quote their words directly and supply the exact page number so others can see for themselves.

The official title of the meeting was the "Scientific Review of Vaccine Safety Datalink Information." This conference, held on June 7-8, 2000, at Simpsonwood Retreat Center in Norcross, Georgia, assembled 51 scientists and physicians, five of whom represented vaccine manufacturers. These included Smith Kline Beecham, Merck, Wyeth, North American Vaccine and Aventis Pasteur.

During this conference, these scientists focused on the study of the Datalink material, whose main author was Dr. Thomas Verstraesten and who identified himself as working at the National Immunization Program of the CDC. It was discovered by Congressman Weldon that Dr. Verstraeten left the CDC shortly after this conference to work for the Belgian operations of the pharmaceutical maker GlaxoSmithKline—a recurring regulated agency/regulated-industry pattern that has been given the name "a revolving door". It is also interesting to note that GlaxoSmithKline was involved in several lawsuits over complications secondary to their vaccines.

To start off the meeting, Dr. Roger Bernier, Associate Director for Science in the National Immunization Program (CDC), related some pertinent history. He stated that Congressional action in 1997 required that the FDA review mercury being used in drugs and biologics (vaccines). To meet this mandate, the FDA called for all the registered manufacturers of drugs, including vaccines, to submit the mercury information about their drug products. He notes that a group of European regulators and manufacturers met on April 1999 and acknowledged the situation but made no recommendations or changes. In other words, it was all for show.

At this point Dr. Bernier makes an incredible statement (page 12). He says, "*In the United States there was a growing recognition that cumulative exposure may exceed some of the guidelines*." By guidelines, he is referring to guidelines for mercury exposure safety levels set by several regulatory agencies. The three guidelines were set by the ATSDR (The Agency for Toxic Substances and Disease Registry), the FDA (Food and Drug Administration), and the EPA (Environmental Protection Agency). The most consistently violated safety guideline was the mercury-in-food limit set by the EPA. He further explains that he is referring to children being exposed to Thimerosal in vaccines.

Based on this realization that they were violating safety guidelines, he says that this then "*resulted in a joint statement of the Public Health Service (PHS) and the American Academy of Pediatrics (AAP) in July of last year (1999), which stated that as a long term goal, it was desirable to remove mercury from vaccines because it was a potentially preventable source of exposure*." (Page 12)

As an aside, one has to wonder, where was the Public Health Service and American Academy of Pediatrics during all the years of mercury use in vaccines and why didn't they know that, number one, they were exceeding regulatory safety levels and secondly, why weren't they aware of the extensive literature showing deleterious effects on the developing nervous system of babies? As we shall see, even these "experts" seem to be cloudy on the mercury literature.

Dr. Bernier notes that in August 1999 a public workshop was held in the Lister Auditorium in Bethesda by the National Vaccine Advisory Group and the Interagency Working Group on Vaccines to consider Thimerosal risk in vaccine use. And based on what was discussed in that conference, Merck, one manufacturer of a U.S.-licensed hepatitis B vaccine (HepB) moved to license a "no Thimerosal" formulation for young children but kept making and distributing its Thimerosal-preserved HepB formulation into the mid 2000s while GlaxoS- mithKline,

the other U.S.-licensed HepB maker apparently moved to license a reduced-Thimerosal formulation; apparently, neither firm moved to recall the existing Thimerosal-preserved doses. It is interesting to note that the media took very little interest in what was learned at that meeting and it may have been a secret meeting—probably because it was also a meeting that was not, as required by law, announced publicly. As we shall see, there is a reason why they struggle to keep the contents of all these meetings secret from the public.

Dr. Bernier then notes on page 13 that on October 1999 the Advisory Committee on Immunization Practices (ACIP) "*looked this situation over again and did not express a preference for any of the vaccines that were Thimerosal free*." In this discussion he further notes that the ACIP concluded that the Thimerosal-containing vaccines could be used but the "long-term goal" is to try to remove Thimerosal as soon as possible.

Now, we need to stop and think about what has transpired. We have an important group here, the ACIP that essentially plays a role in vaccine policy affecting tens of millions of children every year. And, we have evidence from the Thimerosal meeting in 1999 that the potential for serious injury to the infant's brain is so serious that a recommendation for removal becomes policy. In addition, they are all fully aware that tiny babies are receiving mercury doses that exceed even EPA safety limits for adults, yet all they can say is that we must "*try to remove Thimerosal as soon as possible.*" Do they not worry about the tens of millions of babies who will continue receiving Thimerosal-containing vaccines until they can get around to stopping the use of Thimerosal?

It should also be noted that it is a misnomer to say "removal of Thimerosal" since they are not removing anything. They just plan to stop adding it to future vaccines once they use up existing stocks, which entails millions of doses. And incredibly, the government allows them to do it. Even more incredibly, the American Academy of Pediatrics and the American Academy of Family Practice similarly endorse this insane policy. In fact, they specifically state that children should continue to receive the Thimerosal-containing vaccines until new Thimerosal-free vaccines can be manufactured at the will of the manufacturers. It was disclosed that Thimerosal was in all influenza, HepB and DPT vaccines, as well as most DtaP vaccines .

Had vaccine safety been their primary concern, as it should be, the most obvious solution was to recommend only single-dose vials, which require no preservative, coupled with a ban on the use of any mercury compound in the manufacture of all drugs. So, why didn't they make this or at least a "no Thimerosal" recommendation? "*Oh*," they exclaim, "*it would add to the cost of the vaccine*." Of course, we are only talking about a few dollars per vaccine at most, certainly worth the health of your child's brain and future. They could use some of the hundreds of millions of dollars they waste on vaccine promotion every year to cover the cost for the poor. Yet, that would cut into some fat-cat's profit and we can't have that.

As they begin to concentrate on the problem at hand we first begin to learn that the greatest problem with the meeting is that they know virtually nothing about what they are doing. On page 15, for example, they admit that there is very little pharmacokinetic data on ethylmercury, the form of mercury in Thimerosal. In fact, they say there is no data on excretion and the data on toxicity is sparse; yet it is recognized to cause hypersensitivity, neurological problems, and even death, and it is known to easily pass the blood-brain barrier and the placental barrier.

Therefore, what they are admitting is that we have a form of mercury that has been used in vaccines since the 1930s and no one has bothered to study the effects on biological systems, especially the brains of infants. Their defense throughout this conference is "*we just don't know the effects of ethylmercury.*" As a solution, they resort to studies on methylmercury because there are thousands of studies on this form of mercury. The major source of this form is seafood consumption.

It takes them awhile to get the two forms of mercury straight, since for several pages of the report they say methylmercury is in Thimerosal rather than ethylmercury. They can be forgiven for this. On page 16, Dr. Johnson, an immunologist and pediatrician at the University of Colorado School of Medicine and the National Jewish Center for Immunology and Respiratory Medicine, notes that he would like to see the incorporation of wide margins of safety, that is 3 to 10-fold margins of safety to "*account for data uncertainties*." What he means is that there are so many things we do not know about this toxin that we had better use very wide margins of safety. For most substances the FDA uses a 100-fold margin of safety.

The reason for this, which they do not mention, is that in a society of hundreds of millions of people, there are groups of people who are much more sensitive to the toxin than others. For instance, the elderly, the chronically ill, the nutritionally deficient, small babies, premature babies, those on certain medications and those with inborn defects in detoxification, just to name a few. In fact, premature babies and low birth weight babies were excluded from the main study since (1) some had the highest mercury levels, (2) these would be hard to study, and (3) they had the most developmental problems possibly related to the mercury. In other words, including these babies might endanger their claims of safety.

It should also be noted that all participants at this conference ignored the differences in total mercury exposure among infants and small children living in different geographical areas. For example, a child's mother who had dental amalgams, who regularly eats high-methymercury-containing seafood and lives in an area with high atmospheric mercury levels will have much higher total mercury exposure than one exposed to little dietary, dental, and environmental mercury.

Also on page 16, Dr. Johnson makes an incredible statement, one that defines the problem we have in this country with the promoters of these vaccines. He states, "*As an aside, we found a cultural difference between vaccinologist and environmental health people in that many of us in the vaccine arena have never thought about uncertainty factors before. We tend to be relatively concrete in our thinking.*" Then he says, "*One of the big cultural events in that meeting ... was when Dr. Clarkson repetitively pointed out to us that we just didn't get it about uncertainty, and he was actually quite right.*"

This is an incredible admission. First, what is a "vaccinologist"? Do you go to school to learn to be one? How many years of residency training are required to be a "vaccinologist"? Are there board exams? It's an ill-defined term used to describe people who are obsessed with vaccines, not that they actually study the effects of the vaccines, as we shall see throughout this meeting. Most important is the admission by Dr. Johnson that he and his fellow "vaccinologists" are so blinded by their obsession with forcing vaccines on society that they never even considered that there might be factors involved that could greatly affect human health, the so-called "uncertainties". Further, he admits that he and his fellow "vaccinologists" like to think in concrete terms; that is, they are very narrow in their thinking and wear blinders that prevent them from seeing the numerous problems occurring with large numbers of vaccinations in infants and children. Their goal in life is to vaccinate as many people as possible with an ever-growing number of vaccines.

On page 17 his "concrete thinking" once again takes over. He refers to the Bethesda meeting on Thimerosal safety issues and says, "*there was no evidence of a problem, only a theoretical concern that young infants' developing brains were being exposed to an organomercurial*." Of course, as I shall point out later, it is a lot more than a "theoretical concern". He then continues by saying, "*We agree that while there was no evidence of a problem, the increasing number of vaccine injections given to infants, was increasing the theoretical mercury exposure risk.*"

It's hard to conceive of a true scientist not seeing the incredible irony of these statements. The medical literature abounds with studies on the deleterious effects of mercury on numerous enzymes, mitochondrial energy production, synaptic function, dendritic function, neurotubule dissolution and excitotoxicity—yet he sees only a "theoretical risk" associated with an ever increasing addition of Thimerosal-containing vaccines. It is also important to note that these geniuses never even saw a problem in the first place, it was pressure from outside scientists, parents of affected children, and groups representing them that pointed out the problem. They were, in essence, reacting to pressure from outside the "vaccinologist club" and, therefore, had not discovered internally that a problem even "might" exist.

In fact, if these outside groups had not become involved, these "vaccinologists" would have continued to add more and more mercury-containing vaccines to the list of required vaccines. Only when the problem became so obvious, that is of epidemic proportion and the legal profession became involved, would they have even noticed there was a problem. This is a recurring theme in the government's regulatory agencies, as witnessed with fluoride, aspartame, MSG, dioxin and pesticides issues.

It is also interesting that Dr. Johnson did admit that the greatest risk was among low birth weight infants and premature infants. Now why would that be if there existed such a large margin of safety with mercury used in vaccines? Could just a few pounds of body weight make such a dramatic difference? In fact, it does, but it also means that normal birth weight children, especially those near the low range of normal birth weight, are also in greater danger. It also would mean that children receiving doses of mercury higher than the 75 ug in this study would be at high risk as well because their dose, based on body weight, would be comparable to that of the low birth weight child receiving the lower dose. This is never even considered by these "vaccinologist" experts who decide policy for your children.

Now this next statement should shock everyone, but especially the poor who might believe that these "vaccinologist" experts have their best interest in mind. Dr. Johnson says on page 17, "*We agree that it would be desirable to remove mercury from U.S. licensed vaccines, but we did not agree that this was a universal recommendation that we would make because of the issue concerning preservatives for delivering vaccines to other countries, particularly developing countries, in the absence of hard data that implied that there was in fact a problem*."

So, here you have it. The data is convincing enough that the American Academy of Pediatrics and the American Academy of Family Practice, as well as the regulatory agencies and the CDC, all recommend its removal as quickly as possible because of concerns of adverse effects of mercury on brain development, but not for the children in the developing countries. I thought the whole idea of child health programs in the United States directed toward the developing world was to give poor children a better chance in an increasingly competitive world. This policy being advocated would increase the neurodevelopmental problems seen in poor children of developing countries and of this country, impairing their ability to learn and develop competitive minds. Remember, there was a representative of the World Health Organization (WHO), Dr. John Clements, serving on this panel of "experts" who apparently never challenged this statement made by Dr. Johnson.

It also needs to be appreciated that children in developing countries are at a much greater risk of complications from vaccinations and from mercury toxicity than children in developed countries. This is because of poor nutrition, concomitant parasitic and bacterial infections, and a high incidence of low birth weight in these children. We are now witnessing a disaster in African countries caused by the use of older live virus polio vaccines that has now produced an epidemic of vaccine related polio, that is, polio caused by the vaccine itself. In, fact, in some African countries, polio was not seen until the vaccine was introduced.

The WHO and the "vaccinologist experts" from this country now justify a continued polio vaccination program with this dangerous vaccine on the basis that now that they have created the epidemic of polio, they cannot stop the program. In a recent article it was pointed out that this is the most deranged reasoning, since more vaccines will mean more vaccine-related cases of polio. But then, "vaccinologists" have difficulty with these "uncertainties". (Jacob JT. A developing country perspective on vaccine-associated paralytic poliomyelitis. Bulletin WHO 2004; 82:53-58. See commentary by D.M. Salisbury at the end of the article.)

Then Dr. Johnson again emphasizes the philosophy that the health of children is secondary to "the program" when he says, "*We saw some compelling data that delaying the birth dose of HepB vaccine would lead to significant disease burden as a consequence of missed opportunity to immunize.*" This implies that our children would be endangered from the risk of hepatitis B should the vaccine program stop vaccinating newborns with the HepB vaccine.

In fact, this statement is not based on any risk to U.S. children at all and he makes that plain when he states, "that the potential impact on countries that have 10% to 15% newborn hepatitis B exposure risk was very distressing to consider." (page 18) In other words the risk is not to normal U.S. children but to children in developing countries. In fact, hepatitis B is not a risk until the teenage years and after in this country. The only at-risk children are those born to drug abusing parents, to mothers infected with hepatitis B, or to HIV infected parents.

Infectious disease authorities know that 90% of people infected with this virus either have a mild infection and recover or have no symptoms at all. Even pregnant women infected with the virus have only a 20% chance of transmitting the virus to their babies. According to statistics, the United States has one of the lowest rates of hepatitis B infection in the world, with only 53 cases of the infection being reported in children among 3.9 million births. In fact, there were three times as many serious complications from the vaccine as there were children who contracted the disease. The real reason for vaccinating the newborns is to capture them before they can escape the vaccinologists' vaccine program.

This is a tactic often used to scare mothers into having their children vaccinated. For example, vaccinologists say that if children are not vaccinated against measles, millions of children could die during a measles epidemic. They know this is nonsense. What they are using are examples taken from developing countries with poor nutrition and poor immune function in which such epidemic death can occur. In the United States we would not see this because of better nutrition, better health facilities and better sanitation. In fact, most deaths seen during measles outbreaks in the United States occur in children in whom vaccination was contraindicated, when the vaccine did not work or in children with chronic, immune-suppressing diseases.

In fact, most studies show that children catching the measles or other childhood diseases have been either fully immunized or partially immunized. The big secret among "vaccinologists" is that anywhere from 20 to 50% of children are not resistant to the diseases for which they have been vaccinated.

Also on page 18, Dr. Johnson tells the committee that it was Dr. Walter Orenstein who "*asked the most provocative question which introduced a great deal of discussion. That was, should we try to seek neurodevelopmental outcomes from children exposed to varying doses of mercury by utilizing the Vaccine Safety Datalink data from one or more sites.*" (page 18)

I take from this no one had ever even thought of looking at the data that had just been sitting there all these years unreviewed. Children could have been dropping like flies or suffering from terrible neurodevelopmental defects caused by the vaccine program and no one in the government would have known. In fact, that is exactly what the data suggested was happening, at least as regards neurodevelopmental delays.

We should also appreciate that the government sponsored two conferences on the possible role of metals, aluminum and mercury, being use in vaccines, without any change in vaccine policy occurring after the meetings. These meetings were held a year before this year's 2000 meeting and before any examination of the data which was being held tightly by the CDC (which was denied to other independent, highly qualified researchers). I will talk more about what was discussed in the aluminum conference later. It is very important and is only briefly referred to in this conference for a very good reason. If the public knew what was discussed at the aluminum meeting no one would ever get a vaccination using the presently manufactured types of vaccines again.

Despite what was discussed in the aluminum meeting and the scientific literature on the neurotoxicity of aluminum, Dr. Johnson makes the following remark; "*Aluminum salts have a very wide margin of safety. Aluminum and mercury are often simultaneously administered to infants, both at the same site and at different sites*." Also on page 20, he states, "*However, we also learned that there is absolutely no data, including animal data, about the potential for synergy, additively or antagonism, all of which can occur in binary metal mixtures...*"

It is important here to appreciate a frequently used deception by those who are trying to defend an indefensible practice. They use the very same language just quoted, that is, that there is no data to show, etc., etc. They intend it to convey the idea that the issue has been looked at and studied thoroughly and no toxicity was found. In truth, it means that no one has looked at this possibility and there have been no studies that would give us an answer one way or the other.

In fact, we know that aluminum is a significant neurotoxin and that it shares many common mechanisms with mercury as a neurotoxin. For example, they are both toxic to neuronal neurotubules, interfere with antioxidant enzymes, poison DNA repair enzymes, interfere with mitochondrial energy production, block the glutamate reuptake proteins (GLT-1 and GLAST), bind to DNA and interfere with neuronal membrane function. Toxins that share toxic mechanisms are almost always additive and frequently synergistic in their toxicity. So, Dr. Johnson's statement is sheer nonsense.

A significant number of studies have shown that both of these metals play a significant role in all of the neurodegenerative disorders. It is also important to remember, both of these metals accumulate in the brain and spinal cord. This makes them accumulative toxins and therefore much more dangerous than rapidly excreted toxins.

To jump ahead, on page 23 Dr. Tom Sinks, Associate Director for Science at the National Center for Environmental Health at the CDC and the Acting Division Director for Division of Birth Defects, Developmental Disabilities and Health, asks, "*I wonder is there a particular health outcome that is related to aluminum salts that may have anything that we are looking at today?*" Dr. Martin Meyers, Acting Director of the National Vaccine Program Office, answers, "*No, I don't believe there are any particular health concerns that were raised*." This is after an aluminum conference held the previous year that did, indeed, find significant health concerns and extensive scientific literature showing aluminum to be of great concern.

On page 24 Dr. William Weil, a pediatrician representing the Committee on Environmental Health of the American Academy of Pediatrics, brings some sense to the discussion by reminding them that, "*there are just a host of neurodevelopmental data that would suggest that we've got a serious problem. The earlier we go, the more serious the problem.*" Here he means that the further back you go during the child's brain development, the more likely the damage to the infant. I must give him credit; at least he briefly recognized that a significant amount of brain development does take place later—that is after birth. He also reminds his colleagues that aluminum produced severe dementia and death in dialysis cases. He concludes by saying, "*To think there isn't some possible problem here is unreal.*" (page 25)

Not to let it end there, Dr. Meyers adds, "*We held the aluminum meeting in conjunction with the metal ions in biology and medicine meeting, we were quick to point out that in the absence of data we didn't know about additive or inhibitory activities.*" Once again we see the "no data" ploy. There is abundant data on the deleterious effects of aluminum on the brain, a significant portion of which came out in that very meeting.

Dr. Johnson also quotes Dr. Thomas Clarkson, who identifies himself as associated with the mercury program at the University of Rochester, as saying that delaying the HepB vaccine for 6 months or so would not affect the mercury burden (page 20). He makes the correct conclusion when he says, "*I would have thought that the difference was in the timing. That is you are protecting the first six months of the developing central nervous system.*" Hallelujah, for a brief moment I thought that they had stumbled on one of the most basic concepts in neurotoxicology. Then Dr. Meyers dashed my hopes by saying that single, separated doses would not affect blood levels at all. At this juncture, we need a little enlightenment. It is important to appreciate that mercury is a fat soluble metal. That is, it is stored in the body's fat. The brain contains 60% fat and therefore is a common site for mercury storage. Now, they establish in this discussion that about half of methylmercury is excreted over several months when ingested. A recent study found that ethylmercury has a half-life of 7 days.

A significant proportion of the mercury will enter the brain (it has been shown to easily pass through the blood-brain barrier) where it is stored in the phospholipids (fats). It should also be appreciated that when cleared from the blood, the ethylmercury enters the bowel, where it is re-circulated many times over—each time depositing more mercury in the child's brain.

With each new vaccine dose, and remember, at the time of this conference, these children were receiving as many as 36 doses of these vaccines by age 2 years, many of which contained mercury—another increment of mercury is added to the brain storage depot. This is why we call mercury an accumulative poison. They never once, not once, mention this vital fact throughout the entire conference. Not once. Moreover, they do so for a good reason; it gives the unwary, those not trained in neuroscience, assurance that all that matters here is blood levels.

In fact, on page 163, Dr. Robert Brent, a developmental biologist and pediatrician at Thomas Jefferson University and Dupont Hospital for Children, says that we don't have data showing accumulation and "*that with the multiple exposures you get an increasing level, and we don't know whether that is true or not.*" He redeems himself somewhat by pointing out that some of the damage is irreversible and with each dose more irreversible damage occurs and in that way it is accumulative.

On page 21 Dr. Thomas Clarkson makes the incredible statement implying that he knows of no studies that show exposure to mercury after birth or at six months would have deleterious effects. Dr. Isabelle Rapin, a neurologist for children at Albert Einstein College of Medicine, follows up by saying that "*I am not an expert on mercury in infancy*" but she knows it can affect the nerves (peripheral nervous system). So, here is one of our experts admitting that she knows little about the effects of mercury on the infant. My question is: Why is she here? Dr. Rapin is a neurologist for children at Albert Einstein College of Medicine who stated that she has a keen interest in developmental disorders, in particular those involving language and autism, yet she knows little about the effects of mercury on the infant brain.

This conference is concerned with the effects of mercury in the form of Thimerosal on infant brain development, yet throughout this conference our experts, especially the "vaccinologists", seem to know little about mercury except limited literature that shows no toxic effects except at very high levels. None of the well known experts were invited, such as Dr. Michael Aschner from Bowman Grey School of Medicine or Dr. Boyd Haley, who has done extensive work on the toxic effects of low concentrations of mercury on the CNS (Central Nervous System). They were not invited because they would be harmful to the true objective of this meeting, and that was to exonerate mercury in vaccines.

Several times throughout this conference, Dr. Brent reminds everyone that the most sensitive period for the developing brain is during the early stages of pregnancy. In fact, he pinpoints the 8th to 18th week as the period of neuromaturation. In fact, the most rapid period of brain maturation, synaptic development and brain pathway development, is during the last three months of pregnancy continuing until two years after birth. This is often referred to as the "brain growth spurt". This is also not mentioned once in this conference, again because if mothers knew that their child's brain was busy developing for up to two years after birth, they would be less likely to accept this safety of mercury nonsense these "vaccinologists" proclaim.

The brain develops over 100 trillion synaptic connections and tens of trillions of dendritic connections during this highly sensitive period. Both dendrites and synapses are very sensitive, even to very low doses of mercury and other toxins. It has also been shown that subtoxic doses of mercury can block the glutamate transport proteins that play such a vital role in protecting the brain against excitotoxicity. Compelling studies indicate that damage to this protective system plays a major role in most of the neurodegenerative diseases and abnormal brain development as well.

Recent studies have shown that glutamate accumulates in the brains of autistic children, yet these experts seem to be unconcerned about a substance (mercury) that is very powerful in triggering brain excitotoxicity.

It is also interesting to see how many times Dr. Brent emphasizes that we do not know the threshold for mercury toxicity for the developing brain. Again, that is not true. We do know and the Journal of Neurotoxicology states that anything above 10µg (micrograms) is neurotoxic. The WHO in fact states that there is no safe level of mercury.

On page 164 Dr. Robert Davis, Associate Professor of Pediatrics and Epidemiology at the University of Washington, makes a very important observation. He points out that in a population like the United States you have individuals with varying levels of mercury from other causes (diet, living near coal-burning facilities, etc.) and by vaccinating everyone you raise those with the highest levels even higher and bring those with median levels into a category of higher levels. The "vaccinologists" with their problem of "concrete thinking" cannot seem to appreciate the fact that not everyone is the same. That is, they fail to see these "uncertainties".

To further emphasize this point, let's consider a farming family that lives within three miles of a coal-burning electrical plant. Since they also live near the ocean they eat seafood daily. The fertilizers, pesticides and herbicides used on the crops contain appreciable levels of mercury. The coal-burning electrical plant emits high levels of mercury in the air they breathe daily and the seafood they consume has levels of mercury higher than EPA safety standards. This means that any babies born to these people will have very high mercury levels.

Once born, they are given numerous vaccines containing even more mercury, thereby adding significantly to their already high mercury burden. Are these "vaccinologists" trying to convince us that these children don't matter and that they are to be sacrificed at the alter of "vaccine policy"?

Recent studies by neurotoxicologists have observed that as our ability to detect subtle toxic effects improves, especially on behavior and other neurological functions, we lower the level of acceptable exposure. In fact, Dr. Sinks brings up that exact point, using lead as an example. He notes that as our neurobehavioral testing improved, we lowered the acceptable dose considerably and continue to do so. Dr. Johnson had the audacity to add, "*The smarter we get, the lower the threshold.*" Yet, neither he, nor the other participants seem to be getting any smarter concerning this issue.

Dr. Robert Chen, Chief of Vaccine Safety and Development at the National Immunization Program at the CDC, then reveals why they refuse to act on this issue. He says, "*the issue is that it is impossible, unethical to leave kids unimmunized, so you will never, ever resolve that issue. So then we have to refer back from that.*" (page 169) In essence, immunization of the kids takes precedence over safety concerns with the vaccines. If the problem of vaccine toxicity cannot be solved, he seems to be saying, then we must accept that some kids will be harmed by the vaccines. In fact, we are now seeing that the harm from the vaccines exceeds the benefit of disease prevention.

Dr. Brent makes the statement that he knows of no known genetic susceptibility data on mercury and therefore assumes there is a fixed threshold of toxicity. That is, that everyone is susceptible to the same dose of mercury and there are no genetically hypersensitive groups of people. In fact, a recent study found just such a genetic susceptibility in mice. In this study researchers found that mice susceptible to autoimmunity developed neurotoxic effects to their hippocampus, including excitotoxicity, not seen in other strains of mice. They even hypothesize that the same may be true in humans, since familial autoimmunity increases the likelihood of autism in offspring. (Hornig M, Chian D, Lipkin WI. Neurotoxic effects of postnatal Thimerosal are mouse strain dependent. Mol Psychiatry 2004 Sep.;9(9):833–45).

For the next quotation you need a little discussion to be able to appreciate the meaning. They are discussing the fact that in Dr. Verstraeten's study frightening correlations were found between the higher doses of Thimerosal and problems with neurodevelopment, including ADD and autism. The problem with the study was that there were so few children that had been administered Thimerosal-free vaccines, that a true control group could not be used. Instead they had to use children getting 12.5µg of mercury as the control and some even wanted to use the control dose as 37.5µg. So the controls had mercury levels that could indeed cause neurodevelopmental problems. Even with this basic flaw, a strong positive correlation was found between the dose of mercury given and these neurodevelopmental problems.

It was proposed that a group of children receiving non-Thimerosal vaccines be compared to those who had Thimerosal. In fact, we later learn that a large group of children could have been used as a Thimerosal-free control. It seems that for two years before this conference, the Bethesda Naval Hospital had been using unlicensed reduced-Thimerosal vaccines in place of the U.S.-licensed Thimerosal-preserved vaccines to immunize their outpatient children. Unfortunately, in general, these children were too young for the symptoms of neurodevelopmental-regressive autism to be manifest when Verstraten began his studies in the late 1990s.

So, now to the quote: Dr. Braun responds to the idea of starting a new study using such Thimerosal-free controls by saying, "*Sure we will have the answer in five years. The question is what can we do now with the data we have?*" (page 170) Well, we have the answer to that, they simply covered this study up, declared that Thimerosal is of no concern and continued the unaltered policy. That is, they can suggest that the pharmaceutical manufacturers of vaccines remove the Thimerosal but not make it mandatory or examine the vaccines to make sure they have removed it.

Let us take a small peek at just how much we can trust the pharmaceutical manufacturers to do the right thing. Several reports of major violations of vaccine manufacturing policy have been cited by the regulatory agencies. This includes obtaining plasma donations without taking adequate histories on donors as to disease exposures and previous health problems, poor record keeping on these donors, improper procedures, and improper handing of specimens.

That these are not minor violations is emphasized by the discovery that a woman with variant Mad Cow Disease was allowed to give plasma to be used in vaccines in England. In fact, it was learned only after the contaminated plasma was pooled and used to make millions of doses of vaccines that her disease was discovered. British health officials told the millions of vaccinated not to worry, since the "experts" have no idea if it will really spread the disease.

Contamination of vaccines is a major concern in this country as well, as these regulatory violations make plain. It is also important to note that no fines were given, just warnings.

Conclusions by the study group

At the end of the conference, a poll was taken asking two questions. One was, Do you think that there is sufficient data to make a causal connection between the use of Thimerosal-containing vaccines and neurodevelopmental delays? Second, do you think further study is called for based on this study?

First, let us see some of the comments on the question of doing further studies. Dr. Paul Stehr-Green, Associate Professor of Epidemiology at the University of Washington School of Public Health and Community Medicine, who voted yes, gave as his reason, "*The implications are so profound these should be examined further.*" (page 180) Meanwhile, Dr. Brent interjects his concern that the lawyers will get hold of this information and begin filing lawsuits. He says, "*They want business and this could potentially be a lot of business.*" (page 191)

Dr. Loren Koller, Pathologist and Immunotoxicologist at the College of Veterinary Medicine, Oregon State University, is to be congratulated for recognizing more is involved in the vaccine effects than just ethylmercury (page

192). He mentions aluminum and even the viral agents beings used as other possibilities. This is especially important in the face of Dr. R. K. Gherardi's identification of macrophagic myofascitis, a condition causing profound weakness and multiple neurological syndromes, one of which closely resembled multiple sclerosis.

Both human studies and animal studies have shown a strong causal relationship to the aluminum hydroxide or aluminum phosphate used as vaccine adjuvants. More than 200 cases have been identified [1000s across the globe since this report was written] in European countries and the United States and have been described as an "emerging condition".

Here are some of the neurological problems seen with the use of aluminum hydroxide and aluminum phosphate in vaccines. In two children aged 3 and 5 years, doctors at the All Children's Hospital in St. Petersburg, Florida described chronic intestinal pseudo-obstruction, urinary retention, and other findings indicative of a generalized loss of autonomic nervous system function (diffuse dysautonomia). The 3-year old had developmental delay and hypotonia (loss of muscle tone). A biopsy of the children's vaccine injection site disclosed elevated aluminum levels.

In a study of some 92 patients suffering from this emerging syndrome, eight developed a full-blown demyelinating Central Nervous System disorder (i.e., multiple sclerosis) [Authier FJ, Cherin P, et al. Central nervous system disease in patients with macrophagic myofasciitis. Brain 2001;124:974–83]. This included sensory and motor symptoms, visual loss, bladder dysfunction, cerebellar signs (loss of balance and coordination) and cognitive (thinking) and behavioral disorders.

Dr. Gherardi, the French physician who first described the condition in 1998, has collected over 200 proven cases. One third of these developed an autoimmune disease such as multiple sclerosis. Of critical importance is his finding that even in the absence of obvious autoimmune disease there is evidence of chronic immune stimulation caused by the injected aluminum, known to be a very powerful immune adjuvant.

The reason this is so important is that there is overwhelming evidence that chronic immune activation in the brain (activation of microglial cells in the brain) is a major cause of damage in numerous degenerative brain disorders, from multiple sclerosis to the classic neurodegenerative diseases (Alzheimer's disease, Parkinson's and ALS). In fact, I have presented evidence that chronic immune activation of CNS microglia is a major cause of autism, attention deficit disorder and Gulf War Syndrome.

Dr. Gherardi emphasizes that once the aluminum is injected into the muscle, the immune activation persists for years. In addition, we must consider the effect of the aluminum that travels to the brain itself. Numerous studies have shown harmful effects when aluminum accumulates in the brain. A growing amount of evidence points to high brain aluminum levels as a major contributor to Alzheimer's disease and possibly Parkinson's disease and ALS (Lou Geherig's disease). This may also explain the 10X increase in Alzheimer's disease in those receiving the flu vaccine 5 years in a row. (Dr. Hugh Fudenberg, in press, Journal of Clinical Investigation). It is also interesting to note that a recent study found that aluminum phosphate produced a 3X elevation in blood levels of aluminum, as did aluminum hydroxide (Flarend RE, Hem SL, et al. In vivo absorption of aluminum-containing vaccine adjuvants using 26Al. Vaccine 1997 Aug.-Sept.;15:1314–8).

Of course, in this conference, our illustrious experts tell us that there is "*no data showing an additive or synergistic effect between mercury and aluminum*."

Dr. Rapin expressed her concern over public opinion when this information eventually gets out. She says (page 197), they are going to be captured by the public and we had better make sure that "*(a) we counsel them carefully and (b) that we pursue this because of the very important public health and public implications of the data.*" Dr. Johnson adds, "*the stakes are very high...*" From this, how can one conclude anything other than the fact that at least these scientists were extremely concerned by what was discovered by this study examining the Vaccine Safety Datalink material? They were obviously terrified that the information would leak out to the public. Stamped in bold letters at the top of each page of the study were the words: "DO NOT COPY OR RELEASE" and "CONFIDENTIAL".

This is not the wording one would expect on a clinical study of vaccine safety; rather you would expect it on top-secret NSA or CIA files. Why was this information being kept secret? The answer is obvious—it might endanger the vaccine program and indict the federal regulatory agencies for ignoring this danger for so many years. Our society is littered with millions of children who have been harmed in one degree or another by this vaccine policy. In addition, let us not forget the millions of parents who have had to watch helplessly as their children have been destroyed by this devastating vaccine program.

Dr. Bernier on page 198 says, "*the negative findings need to be pinned down and published.*" Why was he so insistent that the "negative findings" be published? Because he said, "*other less responsible parties will treat this as a signal.*" By that he means, a signal of a problem with Thimerosal-containing vaccines. From this, I assume he wants a paper that says only that nothing was found by the study. As we shall see, he gets his wish.

In addition, on page 198, Dr. Rapin notes that a study in California found a 300X increase in autism following the introduction of certain vaccines. She quickly attributes this to better physician recognition. Two things are critical to note at this point. She makes this assertion on better physician recognition without any data at all, just her wishful thinking. If someone pointing out the dangers of vaccines were to do that, she would scream "junk science". Second, Dr. Weil on page 207, attacks this reasoning when he says, "t*he number of dose related relationships are linear and statistically significant. You can play with this all you want. They are linear. They are statistically significant.*" In other words, how can you argue with results that show a strong dose/response relationship between the dose of mercury and neurodevelopmental outcomes? The higher the mercury levels in the children the greater the number of neurological problems. He continues by saying that the increase in neurobehavioral problems is probably real. He tells them that he works in a school system with special education programs and "*I have to say the number of kids getting help in special education is growing nationally and state by state at a rate not seen before. So there is some kind of increase. We can argue about what it is due to.*" (page 207)

Dr. Johnson seems to be impressed by the findings as well. He says on page 199, "*This association leads me to favor a recommendation that infants up to two years old not be immunized with Thimerosal-containing vaccines if suitable alternative preparations are available.*" Incredibly, he quickly adds, "*I do not believe the diagnosis justifies compensation in the Vaccine Compensation Program at this point.*" It is interesting to note that one of our experts in attendance is Dr. Vito Caserta, the Chief Officer for the Vaccine Injury Compensation Program.

At this point Dr. Johnson tells the group of his concerns for his own grandchild. He says, (page 200) "*Forgive this personal comment, but I got called out at eight o'clock for an emergency call and my daughter-in-law delivered a son by C-section. Our first male in the line of the next generation and I do not want that grandson to get a Thimerosal-containing vaccine until we know better what is going on. It will probably take a long time. In the meantime, and I know there are probably implications for this internationally, but in the meanwhile I think I want that grandson to only be given Thimerosal-free vaccines.*"

So, we have a scientist sitting on this panel which will eventually make policy concerning all of the children in this country, as well as other countries, who is terrified about his new grandson getting a Thimerosal-containing vaccine but he is not concerned enough about your child to speak out and try to stop this insanity. He allows a cover-up to take place after this meeting adjourns and remains silent.

It is also interesting to note that he feels the answers will be a long time coming, but in the mean time, his grandson will be protected. The American Academy of Pediatrics, The American Academy of Family Practice, the AMA,

CDC and every other organization will endorse these vaccines and proclaim them to be safe as spring water, but Dr. Johnson and some of the others will keep their silence.

It is only during the last day of the conference that we learn that most of the objections concerning the positive relationship between Thimerosal-containing vaccines and ADD and ADHD were bogus. For example, Dr. Rapin on page 200 notes that all children in the study were below age 6 and that ADD and ADHD are very difficult to diagnose in pre-schoolers. She also notes that some children were followed for only a short period.

Dr. Stein adds that in fact the average age for diagnosis of ADHD was 4 years and 1 month, a very difficult diagnosis to make with the guidelines, as published by the American Academy of Pediatrics, limiting diagnosis to 6 to 12 year olds. Of course, he was implying that too many were diagnosed as ADHD. Yet, a recent study found that the famous Denmark study that led to the announcement by the Institute of Medicine that there was no relationship between autism and the MMR vaccine, used the same tactic. They cut off the age of follow-up at age six.

It is known that many cases appear after this age group, especially with ADD and ADHD. In fact, most learning problems appear as the child is called on to handle more involved intellectual material. Therefore, the chances are that they failed to diagnose a number of cases by stopping the study too early.

Several of the participants tried to imply that autism was a genetic disorder and therefore could have nothing to do with vaccines. Dr. Weil put that to rest with this comment, "*We don't see that kind of genetic change in 30 years*." In other words, how can we suddenly see a 300% increase in a genetically related disorder over such a short period? It is also known that there are two forms of autism, one that is apparent at birth and one that develops later in childhood. The former has not changed in incidence since statistics have been kept; the other is epidemic.

One interesting exchange, which involves two studies in children born to mothers consuming high intakes of mercury-contaminated fish, ends up providing their justification for the view that mercury is of no danger to children vaccinated with vaccines containing Thimerosal. One study in the journal Neurotoxicology, examined children living in the Republic of Seychelles. This study examined the effect of prenatal exposure to mercury through the mother's consumption of fish high in methylmercury.

A battery of developmental milestone tests were done and no adverse effects were reported in the study done by Dr. Clarkson and co-workers, the very same person in this conference. He never mentions that a follow-up study of these same children did find a positive correlation between methylmercury exposure and poor performance on a memory test. In a subsequent study of children living on the Faroe Islands exposed to methylmercury, researchers also found impairments of neurodevelopment. This experiment was done by scientists from Japan.

Throughout the remainder of this discussion, Dr. Clarkson and others refer to these two studies. When they are reminded that the Faroe study did find neurological injury to the children, they counter by saying that this was prenatal exposure to mercury and not exposure following birth as would be seen with vaccination. The idea being that prenatally the brain is undergoing neural formation and development making it more vulnerable. As I have mentioned, this rapid brain growth and development continues for two years after birth and even at age 6 years the brain is only 80% formed.

Dr. Clarkson keeps referring to the Seychelles study which demonstrated that the children reached normal neurodevelopmental milestones as shown by a number of tests. Dr Weil points out on page 216 that this tells us little about these children's future brain function. He says, "*I have taken a lot of histories of kids who are in trouble in school. The history is that developmental milestones were normal or advanced and they can't read at second grade, they can't write at third grade, they can't do math in the fourth grade and it has no relationship as far as I can tell to the history we get of the developmental milestones. So I think this is a very crude measure of neurodevelopment.*"

In other words, both of these studies tell us nothing about the actual development of these children's brain function except that they reached the most basic of milestones. To put this another way, your child may be able to stack blocks, recognize shapes and have basic language skills, but later in life she/he could be significantly impaired when it came to higher math, more advanced language skills (comprehension) and ability to compete in a very competitive intellectual environment, like college or advanced schooling. The future of such children would be limited to the more mundane and intellectually limited jobs.

Postnatal brain development, that is from birth to age six or seven, involves the fine tuning of synaptic connections, dendritic development and pathway refinement, all of which prepare the brain for more complex thinking. These brain elements are very sensitive to toxins and excessive immune stimulation during this period. This fact is never mentioned at the conference.

In addition, it must be remembered that the children in these two studies were exposed only to methylmercury and not the combined neurotoxic effect of mercury, aluminum and excessive and chronic activation of the brain's immune system (microgia). This is what makes it so incredible, that several of these "vaccinologists" and so-called experts would express doubt about the "biological plausibility" of Thimerosal or any vaccine component causing neurodevelopmental problems. The medical literature is exploding with such studies. The biological plausibility is very powerful.

Mercury, for example, even in low concentrations, is known to impair energy production by mitochondrial enzymes. The brain has one of the highest metabolic rates of any organ and impairment of its energy supply, especially during development, can have devastating consequences. In addition, mercury, even in lower concentrations, is known to damage DNA and impair DNA repair enzymes, which again plays a vital role in brain development. Mercury is known to impair neurotubule stability, even in very low concentrations. Neurotubules are absolutely essential to normal brain cell function. Mercury activates microglial cells, which increases excitotoxicity and brain free radical production as well as lipid peroxidation, central mechanisms in brain injury. In addition, even in doses below that which can cause obvious cell injury, mercury impairs the glutamate transport system, which in turn triggers excitotoxicity, a central mechanism in autism and other neurological disorders. Ironically, aluminum also paralyzes this system.

On page 228, we see another admission that the government has had no interest in demonstrating the safety of Thimerosal-containing vaccines despite over 2000 articles showing harmful effects of mercury. Here we see a reference to the fact that the FDA "*has a wonderful facility in Arkansas with hundreds of thousands of animals*" available for any study needed to supply these answers on safety. The big question to be asked is – So, why has the government ignored the need for research to answer these questions concerning Thimerosal safety? You will recall in the beginning the participants of this conference complained that there were just so few studies or no studies concerning this "problem".

Again, on page 229 Dr, Brent rails about the lawsuit problem. He tells the others that he has been involved in three lawsuits related to vaccine injuries leading to birth defects and concluded, "*If you want to see junk science, look at those cases...*" He then complains about the type of scientists testifying in these cases. He adds, "*But the fact is those scientist are out there in the United States.*" In essence, he labels anyone who opposes the "official policy" on vaccines as a junk scientists. We have seen in the discussion who the "junk scientists" really are.

Knowing that what they have found can cause them a great deal of problems he adds, "*The medical/legal findings in this study, causal or not, are horrendous.... If an allegation was made that a child's neurobehavioral findings were caused by Thimerosal-containing vaccines, you could readily find a junk scientist who will support the claim with a reasonable degree of certainty.*" On page 229 he then admits that they are in a bad position because they have no data for their defense. Now, who are the junk scientists?

Is a "real scientist" one who has no data, just wishful thinking and a "feeling" that everything will be all right? Are real scientists the ones who omit recognized experts on the problem in question during a conference because it might endanger the "program"? Are they the ones who make statements that they don't want their grandson to get Thimerosal-containing vaccines until the problem is worked out, but then tell millions of parents that the vaccines are perfectly safe for their children and grandchildren?

Dr. Meyers on page 231 put it this way, "My own concern, and a couple of you said it, there is an association between vaccines and outcomes that worries both parents and pediatricians." He sites other possible connections to vaccine-related neurobehavioral and neurodevelopmental problems including the number of vaccines being given, the types of antigens being used, and other vaccine additives.

Dr. Caserta tells the group that he attended the aluminum conference the previous year and learned that metals could often act differently in biological systems when existing as an ion. This is interesting in the face of the finding that fluoride when combined to aluminum forms a compound that can destroy numerous hippocampal neurons at a concentration of 0.5 ppm in drinking water. It seems that aluminum readily combines with fluoride to form this toxic compound. With over 60% of communities having fluoridated drinking water this becomes a major concern.

It has also been learned that fluoroaluminum compounds mimic the phosphate and can activate G-proteins. G-proteins play a major role in numerous biological systems, including endocrine, neurotransmitters, and as cellular second messengers. Some of the glutamate receptors are operated by a G- protein mechanism.

Over the next ten to fifteen pages, they discuss how to control this information so that it will not get out and if it does how to control the damage. On page 248 Dr. Clements has this to say: "*But there is now the point at which the research results have to be handled, and even if this committee decides that there is no association and that information gets out, the work has been done and through the freedom of information that will be taken by others and will be used in other ways beyond the control of this group. And I am very concerned about that as I suspect that it is already too late to do anything regardless of any professional body and what they say*."

In other words, he wants this information kept not only from the public but also from other scientists and pediatricians until they can be properly counseled. In the next statement he spills the beans as to why he is determined that no outsider get hold of this damaging information. He says, "*My mandate as I sit here in this group is to make sure at the end of the day that 100,000,000 are immunized with DTP, Hepatitis B and if possible Hib, this year, next year, and for many years to come, and that will have to be with Thimerosal-containing vaccines unless a miracle occurs and an alternative is found quickly and is tried and found to be safe*."

This is one of the most shocking statements I have ever heard. In essence, he is saying, I don't care if the vaccines are found to be harmful and destroying the development of children's brains, these vaccines will be given now and forever. His only concern, by his own admission, is to protect the vaccine program even if it is not safe. Dr. Brent refers to this as an "*eloquent statement.*"

On page 253, we again see that these scientists have a double standard when it comes to their children and grandchildren. Dr. Rapin raises the point about a loss of an IQ point caused by Thimerosal exposure. She says, "*Can we measure the IQ that accurately, that this one little point is relevant?*" Then she answers her own question by saying, "*Even in my grandchildren, one IQ point I am going to fight about.*" Yet, they are saying in unison, in essence—"To hell with your children"—to the rest of America.

It is also interesting that they bring up the history of lead as a neurobehavioral toxin. Dr. Weil noted that the neurotoxicologists and regulatory agencies have lowered the acceptable level from 10 to 5µg. In fact, some feel that even lower levels are neurotoxic to the developing brain. Before the toxicologists began to look at lead as a brain toxin in children most "experts" assumed it was not toxic even at very high levels. Again, it shows that "experts" can be wrong and it is the public who pays the price.

Dr. Chen on page 256 expresses his concern about this information reaching the public. He remarks, "*We have been privileged so far that given the sensitivity of information, we have been able to manage to keep it out of, let's say, less responsible hands...*" Dr. Bernier agrees and notes, "*This information has been held fairly tightly*." Later he calls it "*embargoed information*" and "*very highly protected information*."

That they knew the implications of what they had discovered was illustrated by Dr. Chen's statement on page 258. He says, "*I think overall there was this aura that we were engaged in something as important as anything else we have ever done. So I think that this was another element to this that made this a special meeting.*" You may remember, Dr. Weil emphasized that the data analysis left no doubt that there was a strong correlation between neurodevelopmental problems and exposure to Thimerosal-containing vaccines. So if they understood the importance of this finding and this was the most important thing they have ever dealt with, why was this being kept from the public? In fact, it gets even worse.

Just so you will not doubt my statement that this audience of experts was not objective, I give you the words of Dr. Walter Orenstein, Director of the National Immunization Program at the CDC, on page 259. He tells the group, "*I have seen him (Verstraeten) in audience after audience deal with exceedingly skeptical individuals...*" "Exceedingly skeptical individuals" does that sound like objective scientists who wanted to look at the data with a clear mind, or were they scientists who were convinced before the meeting was held that there was no danger to children from Thimerosal or any other vaccine component?

In one of the closing remarks (page 257) Dr. Bernier says, "*the other thing I was struck by was the science*," meaning the science expressed by the attendees of the meeting. Then Dr, Orenstein adds, "*I would also like to thank Roger Bernier who pulled off this meeting in rather short notice...*" Here is a meeting that has been called one of the most important they have ever dealt with and we learn that it was "pulled off" on short notice. In addition, we were told that the results of this meeting would lead to eventual vaccine policy. He then has the nerve to add: "*In a sense this meeting addresses some of the concerns we had last summer when we were trying to make policy in the absence of a careful scientific review. I think this time we have gotten it straight.*"

Well, I hate to be the one to break the news, but he didn't get it straight. There was little or no science in this meeting; rather it was composed of a lot of haggling and nit picking over epidemiological methodology and statistical minutia in an effort to discredit the data, all without success. In fact, the so-called mercury experts admitted they had to do some quick homework to refresh their memories and learn something about the subject.

Conclusions

This top secret meeting was held to discuss a study done by Dr. Thomas Verstraeten and his co-workers using Vaccine Safety Datalink data as a project collaboration between the CDC's National Immunization Program (NIP) and four HMOs. The study examined the records of 110,000 children. Within the limits of the data, they did a very thorough study and found the following:

1. Exposure to Thimerosal-containing vaccines at one month was associated significantly with the misery and unhappiness disorder that was dose related. That is, the higher the child's exposure to Thimerosal the higher the incidence of the disorder. This disorder is characterized by a baby that cries uncontrollably and is fretful more so than that seen in normal babies.

2. A nearly significant increased risk of ADD with 12.5µg exposure at one month.

3. With exposure at 3 months, they found an increasing risk of neurodevelopmental disorders, including speech disorders, with increasing exposure to Thimerosal. This was statistically significant.

It is important to remember that the control group was not children without Thimerosal exposure but, rather, those at 12.5µg exposure. This means that there is a significant likelihood that even more neurodevelopmental problems would have been seen had they used a real control population. No one disagreed that these findings were significant and troubling. Yet, when the final study was published in the journal Pediatrics, Dr. Verstraeten and co-workers reported that no consistent associations were found between Thimerosal-containing vaccine exposure and neurodevelopmental problems. In addition, he lists himself as an employee of the CDC, not disclosing the fact that at the time the article was accepted, he worked for GlaxoSmithKline, a vaccine manufacturing company.

So how did they do this bit of prestidigitation? They simply added another HMO to the data: the Harvard Pilgrimage. (Additionally there were other manipulations, e.g., altering inclusion criteria, discarding children receiving the highest total dose, splitting children into separate groups, using only one HMO's data in some cases, expressing effects ratios in terms of per dose of mercury.) Congressman Dave Weldon noted in his letter to the CDC Director that this HMO had been in receivership by the state of Massachusetts because its records were in shambles. Yet, this study was able to make the embarrassing data from Dr. Verstraeten's previous study disappear. Attempts by Congressman Weldon to force the CDC to release the data to an independent researcher, Dr. Mark Geier, a researcher with impeccable credentials and widely published in peer-reviewed journals, have failed and the CDC now claims that the original data-sets Verstraeten et al. used have been "lost".

It is obvious that a massive cover-up is in progress, as we have seen with so many other scandals, such as fluoride, food-based excitotoxins, pesticides, aluminum, and now vaccines. I would caution those critical of the present vaccine policy not to put all their eggs in one basket, that is, with Thimerosal as being the main culprit. There is no question that it plays a significant role, but there are other factors that are also critical, including aluminum, fluoroaluminum complexes, and chronic immune activation of brain microglia. I believe that repeated, closely spaced, sequential vaccinations given during the most active period of brain development is the major cause of autism.

In fact, excessive, chronic microglial activation can explain many of the effects of excessive vaccine exposure as I point out in two recently published articles. One property of both aluminum and mercury is microglial activation. With chronic microglial activation, large concentrations of excitotoxins are released as well as neurotoxic cytokines. These have been shown to destroy synaptic connections, dendrites and cause abnormal pathway development in the developing brain as well as in the adult brain.

In essence, too many vaccines are being given to children during the brain's most rapid growth period. Known toxic metals are being used in vaccines, interfering with brain metabolism and antioxidant enzymes, damaging DNA and DNA repair enzymes and triggering excitotoxicity. Removing the mercury will help but will not solve the problem because overactivation of the brain's immune system will cause varying degrees of neurological damage to the highly-vulnerable developing brain.

Full Report With References:

www.vacinfo.org/man1714_1726.pdf

DNA Repair Amsterdam • January 2009

DNA Repair Modulates The Vulnerability Of The Developing Brain To Alkylating Agents

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Abstract

Neurons of the developing brain are especially vulnerable to environmental agents that damage DNA (i.e., genotoxicants), but the mechanism is poorly understood. The focus of the present study is to demonstrate that DNA damage plays a key role in disrupting neurodevelopment. To examine this hypothesis, we compared the cytotoxic and DNA damaging properties of the methylating agents methylazoxymethanol (MAM) and dimethyl sulfate (DMS) and the mono- and bifunctional alkylating agents chloroethylamine (CEA) and nitrogen mustard (HN2), in granule cell neurons derived from the cerebellum of neonatal wild type mice and three transgenic DNA repair strains. Wild type cerebellar neurons were significantly more sensitive to the alkylating agents DMS and HN2 than neuronal cultures treated with MAM or the half-mustard CEA. Parallel studies with neuronal cultures from mice deficient in alkylguanine DNA glycosylase (Aag-/-) or O6-methylguanine methyltransferase (Mgmt-/-), revealed significant differences in the sensitivity of neurons to all four genotoxicants. Mgmt-/- neurons were more sensitive to MAM and HN2 than the other genotoxicants and wild type neurons treated with either alkylating agent. In contrast, Aag-/- neurons were for the most part significantly less sensitive than wild type or Mgmt-/- neurons to MAM and HN2. Aag-/- neurons were also significantly less sensitive than wild type neurons treated with either DMS or CEA. Granule cell development and motor function were also more severely disturbed by MAM and HN2 in Mgmt-/- mice than in comparably treated wild type mice. In contrast, cerebellar development and motor function were well preserved in MAM treated Aag-/- or MGMT overexpressing (MgmtTg+) mice, even as compared with wild type mice suggesting that AAG protein increases MAM toxicity, whereas MGMT protein decreases toxicity. Surprisingly, neuronal development and motor function were severely disturbed in MgmtTg+ mice treated with HN2. Collectively, these in vitro and in vivo studies demonstrate that the type of DNA lesion and the efficiency of DNA repair are two important factors that determine the vulnerability of the developing brain to long-term injury by a genotoxicant.

http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2692311/

“Neurons of the developing brain are especially vulnerable to environmental agents that damage DNA (i.e., genotoxicants), but the mechanism is poorly understood. Collectively, these in vitro and in vivo studies demonstrate that the type of DNA lesion and the efficiency of DNA repair are two important factors that determine the vulnerability of the developing brain to long-term injury by a genotoxicant.”

“Of these 1162 cases, 1105 were considered to be related to the vaccination ...”

European Journal of Pediatrics • January 2009

Discolored leg syndrome after vaccination—descriptive epidemiology

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Abstract

Discoloration of the leg following vaccination is a relatively unknown entity. We carried out a study of discolored leg syndrome (DLS) during a 10-year consecutive period with the objective of characterizing DLS in infants following vaccination received in the Dutch National Vaccination Program as well as its occurrence and association with different vaccines. Discolored leg syndrome was defined as an even or patchy red, blue or purple discoloration of the leg(s) and/or leg petechiae with or without swelling. All reports of adverse events following immunization that were made to the passive surveillance system between 1994 and 2003 were included—a total of 1162 identified cases. Red, blue, purple discoloration and isolated petechiae were reported in 39, 19, 27 and 14% of these cases, respectively. Of these 1162 cases, 1105 were considered to be related to the vaccination, based on a predefined risk window with symptom onset after vaccination (48 h for discolorations and 2 weeks for petechiae). Of the 1105 cases, about 50% occurred after DTP-IPV+Hib1 vaccinations, and 30% occurred after DTP-IPV+Hib2 vaccinations. Discolored leg syndrome was frequently accompanied by fierce crying (78%). The median time interval between vaccination and the occurrence of DLS was 3.8 ± 46.7 h, and the median duration was short (2 ± 61.7 h). Advancing the vaccination schedule from 3 to 2 months of age caused a small increase in DLS. Discolored leg syndrome manifested mainly after the first and/or second vaccination. In addition to dose, the occurrence of DLS may be slightly age-dependent and self-limiting. The pathophysiology is unknown but may be the result of a vasomotor reaction. Future studies should elucidate the recurrence rate, identify risk factors and assess late outcomes.

http://link.springer.com/article/10.1007%2Fs00431-008-0707-0

“... Triton X-100 (TX)-induced apoptosis.”

Biochemical And Biophysical Research Communications • January 2009

Differential roles for Bak in Triton X-100- and deoxycholate-induced apoptosis

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Abstract

We recently reported that Bax activation occurs downstream of caspase activation in Triton X-100 (TX)-induced apoptosis. Here, Bak was found to be activated in TX-induced apoptosis. Although z-VAD-fmk completely suppressed Bax activation, it only partially attenuated TX-induced Bak activation. Moreover, activation of both Bak and Bax was detected in apoptosis induced by deoxycholate, a physiological detergent in bile. z-VAD-fmk completely suppressed deoxycholate-induced Bak as well as Bax activation. Furthermore, Bak siRNA attenuated TX- but not deoxycholate-induced caspase activation. These results suggest that Bak activation may occur upstream of caspase activation in TX- but not deoxycholate-induced apoptosis and that the mechanism of TX-induced apoptosis may differ from that of deoxycholate-induced apoptosis at least with regard to the role for Bak.

http://www.ncbi.nlm.nih.gov/pubmed/19041633

Journal Of Neuroimmunology • February 2009

Elevated immune response in the brain of autistic patients

Author information

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Abstract

This study determined immune activities in the brain of ASD patients and matched normal subjects by examining cytokines in the brain tissue. Our results showed that proinflammatory cytokines (TNF-alpha, IL-6 and GM-CSF), Th1 cytokine (IFN-gamma) and chemokine (IL-8) were significantly increased in the brains of ASD patients compared with the controls. However the Th2 cytokines (IL-4, IL-5 and IL-10) showed no significant difference. The Th1/Th2 ratio was also significantly increased in ASD patients.

Conclusion

ASD patients displayed an increased innate and adaptive immune response through the Th1 pathway, suggesting that localized brain inflammation and autoimmune disorder may be involved in the pathogenesis of ASD.

http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2770268/

“ASD patients displayed an increased innate and adaptive immune response through the Th1 pathway, suggesting that localized brain inflammation and autoimmune disorder may be involved in the pathogenesis of ASD.”

"... these occurrences support an association between

receipt of aluminium adjuvant and sterile abscesses in susceptible patients."

BMJ Case Reports • March 2009
Findings that shed new light on the possible pathogenesis of a disease or an adverse effect

Recurrent sterile abscesses following aluminium adjuvant-containing vaccines

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Summary

Abscess formation following immunisation is a previously reported complication, generally associated with microbial contamination of the vaccine. Less commonly, such abscesses have been sterile. Here we describe two children evaluated in the Center for Disease Control and Prevention (CDC)-funded Clinical Immunization Safety Assessment (CISA) network who developed recurrent sterile abscesses after administration of vaccines containing aluminium adjuvant, either individually or in combination. Although the abscesses healed without sequelae, these occurrences support an association between receipt of aluminium adjuvant and sterile abscesses in susceptible patients. For patients with similar symptoms, clinicians may wish to choose a vaccine formulation containing the least amount of aluminium adjuvant.

http://casereports.bmj.com/content/2009/bcr.09.2008.0951.long

Mutation Research • March 2009

Formaldehyde exposure and leukemia: a new meta-analysis and potential mechanisms

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Abstract

Formaldehyde is an economically important chemical, to which more than 2 million U.S. workers are occupationally exposed. Substantially more people are exposed to formaldehyde environmentally, as it is generated by automobile engines, is a component of tobacco smoke and is released from household products, including furniture, particleboard, plywood, and carpeting. The International Agency for Research on Cancer (IARC) recently classified formaldehyde as a human carcinogen that causes nasopharyngeal cancer and also concluded that there is "strong but not sufficient evidence for a causal association between leukemia and occupational exposure to formaldehyde". Here, we review the epidemiological studies published to date on formaldehyde-exposed workers and professionals in relation to lymphohematopoietic malignances. In a new meta-analysis of these studies, focusing on occupations known to have high formaldehyde exposure, we show that summary relative risks (RRs) were elevated in 15 studies of leukemia (RR=1.54; confidence interval (CI), 1.18-2.00) with the highest relative risks seen in the six studies of myeloid leukemia (RR=1.90; 95% CI, 1.31-2.76). The biological plausibility of this observed association is discussed and potential mechanisms proposed. We hypothesize that formaldehyde may act on bone marrow directly or, alternatively, may cause leukemia by damaging the hematopoietic stem or early progenitor cells that are located in the circulating blood or nasal passages, which then travel to the bone marrow and become leukemic stem cells. To test these hypotheses, we recommend that future studies apply biomarkers validated for other chemical leukemogens to the study of formaldehyde.

http://www.ncbi.nlm.nih.gov/pubmed/?term=18674636

"formaldehyde may act on bone marrow directly or, alternatively, may cause leukemia by damaging the hematopoietic stem or early progenitor cells that are located in the circulating blood or nasal passages, which then travel to the bone marrow and become leukemic stem cells."

Journal Of Neurochemistry • March 2009

Vaccination alone or in combination with pyridostigmine promotes and prolongs activation of stress-activated kinases induced by s tress in the mouse brain

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Abstract

Gulf war illnesses (GWI) are currently affecting thousands of veterans. To date, the molecular mechanisms underlying the pathogenesis of these illnesses remain unknown. During Gulf war I, military personnel were exposed to multiple stressors, one or more vaccines, pyridostigmine (PY), and other chemicals. In our previous studies, we found that stress induces activation of mitogen activated protein-kinase kinase 4 (MKK4) and c-Jun-N-terminal kinase (JNK) in the mouse brain (Liu et al. 2004). Our working hypothesis is that stress, vaccination, and PY may synergistically induce activation of MKK4 and JNK in the brain, leading to over-activation of these kinases and neurological injuries. To test our hypothesis, we examined the effect of key-hole limpet hemocyanin (KLH) immunization alone or in combination with PY on activation of MKK4 and JNK induced by stress. We found that KLH immunization alone had a small effect on MKK4 or JNK activity but it significantly enhanced and prolonged activation of these kinases induced by stress, from a few hours to several days. Additionally, KLH immunization caused activation of p38MAPK. PY treatment further enhanced and prolonged activation of these kinases induced by stress in combination with KLH immunization and triggered activation of caspase-3. Our current studies suggest that stress, vaccination, and PY may synergistically act on multiple stress-activated kinases in the brain to cause neurological impairments in GWI.

http://www.ncbi.nlm.nih.gov/pubmed/?term=15857404

Full Report: http://onlinelibrary.wiley.com/doi/10.1111/j.1471-4159.2005.03093.x/full

“Gulf war illnesses (GWI) are currently affecting thousands of veterans. Our current studies suggest that stress, vaccination, and pyridostigmine may synergistically act on multiple stress-activated kinases in the brain to cause neurological impairments in Gulf war illnesses.”

Deutsches Arzteblatt International • April 2009

Correspondence (letter to the editor): Long Term Side Effects Due to Vaccination And Pharmacovigilance

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We thank the authors for their clear overview of vaccine sceptics' common objections, which are helpful for everyday clinical practice.

Most vaccinations and vaccination advice in Germany are given by general practitioners and pediatricians. Appropriate and responsible advice includes providing information to those about to receive the vaccine and their parents, about rare but possible side effects. These include the possible occurrence of Guillain-Barré syndromes after flu vaccinations (1), for example; the possible association between recombinant hepatitis B vaccine and multiple sclerosis (2), which is still under discussion in current publications; and the unexplained possible association of multiple vaccinations with neurodegenerative disorders in connection with aluminum hydroxide, which to date is the most common vaccine adjuvant in use (3).

Long term side effects due to vaccination can be detected to a sufficiently high quality standard only by means of long term, active pharmacovigilance conducted through independent and sufficiently equipped monitoring systems. To assess the long term safety of vaccines, passive post-vaccination observation by notification of vaccination complications by primary care physicians is not enough: possible causal associations with developing disorders—for example, neurodegenerative disorders—are difficult to state in individual cases years after the vaccine was given.

Full Report

http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2689587/

"... the possible occurrence of Guillain-Barré syndromes after flu vaccinations, for example; the possible association between recombinant hepatitis B vaccine and multiple sclerosis, which is still under discussion in current publications; and the unexplained possible association of multiple vaccinations with neurodegenerative disorders in connection with aluminum hydroxide, which to date is the most common vaccine adjuvant in use ..."

Journal Of Environmental Monitoring • May 2009

JEM spotlight: metal speciation related to neurotoxicity in humans

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Abstract

Improved living conditions have led to a steady increase in the life expectancy of humans in most countries. However, this is accompanied by an increased probability of suffering from neurodegenerative diseases like Alzheimer's disease or Parkinson's disease. Unfortunately, the therapeutic possibilities for curing these diseases are very limited up to now. Many studies indicate that a variety of environmental factors contribute to the initiation and promotion of neurodegenerative diseases. For example, the role of metal exposure and disturbance of metal homeostasis in the brain is discussed in this respect. However, most studies focus on the neurological and toxicological aspects but not on a detailed characterisation of the species of the involved metals. Therefore, this review summarizes the neurotoxic effects of selected metals on humans and focuses on contributions from trace element speciation analysis with relevance to neuroscientific research. In spite of the advance in instrumentation and methodology of speciation analysis there are few applications for matrices like cerebrospinal fluid which is due to limited access to these samples and analytical challenges caused by matrix interferences, low concentrations and limited stability of many trace element species of interest. The most relevant neurotoxic metals aluminium, lead, manganese and mercury are reviewed in detail while further metals like cadmium, arsenic, bismuth and tin are briefly discussed. Current results indicate that knowledge on trace element speciation can contribute to a better understanding of the transport of metals across the neural barriers and potentially of their role in diseased human brains.

http://www.ncbi.nlm.nih.gov/pubmed/19436852

"The most relevant neurotoxic metals aluminium, lead, manganese and mercury are reviewed in detail while further metals like cadmium, arsenic, bismuth and tin are briefly discussed. Current results indicate that knowledge on trace element speciation can contribute to a better understanding of the transport of metals across the neural barriers and potentially of their role in diseased human brains."

American Journal of Epidemiology • May 2009

Re: Determinants Of The Incidence Of Childhood Asthma: A Two-Stage Case-Control Study

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Abstract

In a recent article, Martel et al. (1) took into consideration 47 variables that could influence children's asthma incidence but missed one that has been significantly researched—vaccines. The Quebec, Canada, children enrolled in the study were born between 1990 and 2002. During this time, Canada underwent major changes in types of vaccines and the calendar of immunization for infants and children: Thimerosal was withdrawn from infants' vaccines, some of the vaccines were combined, some new vaccines were introduced, and still others underwent changes in their starting date and subsequent calendar; this without counting parental preference for administration of multiple shots at a single clinical visit.

Some vaccines can contain thimerosal, which is a recognized sensitizer in children (2); additionally, a polymorphism in the glutathione S-transferase gene can alter its metabolism in children. Indeed, glutathione S-transferase M1 deficiency was found to be significantly more frequent among patients who had been sensitized to thimerosal (3). Thyssen et al. (4) speculated that the decrease in allergy in the general population of Denmark could be due to thimerosal's no longer being used as a vaccine preservative in that country. Although contact allergy due to thimerosal is not a contraindication for receipt of vaccines, these reactions are expected to be fewer in the future because of changes in current vaccine formulations (5).

Fombonne et al. (6) have described changes in vaccine formulations and schedules taking place in Canada from 1985 to 2006. The measles-mumps-rubella vaccines were officially incorporated in 1976 and were recommended for use at age 1 year in Quebec; as of 1996, 2 doses of measles-mumps-rubella vaccine were being given at ages 12 and 18 months. A combined diphtheria-tetanus-pertussis vaccine was recommended at ages 2, 4, 6, and 18 months and ages 4–6 years; this vaccine contained 50 μg of thimerosal and was used from 1985 to 1987. In 1988, a Haemophilus influenzae type b vaccine (which also contained thimerosal) was added to the schedule at 18 months of age. As of 1992, the H. influenzae type b vaccines were also administered at ages 2, 4, 6, and 18 months. The poliomyelitis vaccine was administered separately at ages 2, 4, and 18 months and ages 4–6 years from 1987 to 1995. With the exception of the measles-mumps-rubella and poliomyelitis vaccines, all of the vaccines contained 50 μg of thimerosal. Estimated cumulative exposure to thimerosal was 200 μg by age 2 years until 1988; it then increased to 250 μg by 1990. Therefore, as of 1992, cumulative exposure to thimerosal by age 2 years reached 400 μg (6).

Because of mass immunization against meningococcal disease (occurring in 1993), there was additional exposure to thimerosal. Following Fombonne et al.'s (6) reasoning, there could have been different cumulative thimerosal exposures of 300 μg in children born between March 1990 and December 1991 and 450 μg in children born between January 1992 and September 1992. However, both the poliomyelitis and H. influenzae type b vaccines were combined with the diphtheria-pertussis (cellular)-tetanus vaccine in a thimerosal-free formulation in 1996; this pentavaccine was administered at ages 2, 4, 6, and 18 months, with a poliomyelitis-pertussis (cellular)-tetanus booster (thimerosal-free) being given at ages 4–6 years. In 1998, the cellular pertussis vaccine was replaced by the acellular vaccine in the pentavaccine. From 1996 onward, all immunizations were thimerosal-free. Nevertheless, there is 1 additional challenge that has been overlooked (or is difficult to track) by almost all epidemiologic studies that have addressed the issue of vaccines and asthma: multiple applications of different vaccines at a single immunization visit (7).

A study carried out in Canada indicated a negative association between delay in administration of the first dose of diphtheria-pertussis-tetanus vaccine and the development of asthma; a greater association was shown with delays in the first 3 doses (8). De Serres et al. (9) also reported oculorespiratory syndrome as an adverse event that occurred with influenza vaccines used in Canada (2000–2003).

"Thyssen et al. speculated that the decrease in allergy in the general population of Denmark could be due to thimerosal's no longer being used as a vaccine preservative in that country."

Archives Of Diseases In Childhood • Fetal & Neonatal Edition • July 2009

Toxic additives in medication for preterm infants

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Abstract

BACKGROUND
Little is known about exposure of preterm infants to excipients during routine clinical care.

OBJECTIVE
To document excipient exposure in vulnerable preterm babies in a single centre, taking into account chronic lung disease (CLD) as a marker of illness severity.

DESIGN
Excipient exposure after treatment with eight oral liquid medications was determined by retrospectively analysing the drug charts of infants admitted to a neonatal unit.

SETTING
The Leicester Neonatal Service.

PARTICIPANTS
38 infants born between June 2005 and July 2006 who were less than 30 weeks' gestation and 1500 g in weight at birth and managed in Leicester to discharge.

RESULTS
The 38 infants represented 53% of the eligible target group; 7/38 infants had CLD. During their in-patient stay, infants were exposed to over 20 excipients including ethanol and propylene glycol, chemicals associated with neurotoxicity. Infants with CLD were exposed to higher concentrations of these toxins. Infants were also exposed to high concentrations of sorbitol, with some infants being exposed to concentrations in excess of recommended guidelines for maximum exposure in adults.

CONCLUSIONS
Preterm infants are commonly exposed to excipients, some of which are potentially toxic. Strategies aimed at reducing excipient load in preterm infants are urgently required.

http://www.ncbi.nlm.nih.gov/pubmed/?term=19158148

"Preterm infants are commonly exposed to excipients, some of which are potentially toxic."

North American Journal Of Medical Science • July 2009

What is regressive autism and why does it occur? Is it the consequence of multi-systemic dysfunction affecting the elimination of heavy metals and the ability to regulate neural temperature?

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Abstract

There is a compelling argument that the occurrence of regressive autism is attributable to genetic and chromosomal abnormalities, arising from the overuse of vaccines, which subsequently affects the stability and function of the autonomic nervous system and physiological systems. That sense perception is linked to the autonomic nervous system and the function of the physiological systems enables us to examine the significance of autistic symptoms from a systemic perspective. Failure of the excretory system influences elimination of heavy metals and facilitates their accumulation and subsequent manifestation as neurotoxins: the long-term consequences of which would lead to neurodegeneration, cognitive and developmental problems. It may also influence regulation of neural hyperthermia. This article explores the issues and concludes that sensory dysfunction and systemic failure, manifested as autism, is the inevitable consequence arising from subtle DNA alteration and consequently from the overuse of vaccines.

http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3364648/

“This article explores the issues and concludes that sensory dysfunction and systemic failure, manifested as autism, is the inevitable consequence arising from subtle DNA alteration and consequently from the overuse of vaccines.”

Neuropediatrics • August 2009

Macrophagic myofasciitis plus (distinct types of muscular dystrophy)

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Abstract

Macrophagic myofasciitis (MMF) is a well-known lesion following vaccination with aluminium-containing vaccines. It has abundantly been reported in adults and several times in children, often in single patients or in rather small cohorts. Only few of these published reports on children have shown distinct myopathology of another neuromuscular disease except for MMF. Indications for biopsy often were nondescript clinical features in children, such as hypotonia or delay in motor development but, apparently, never that of suspected MMF. Thus, in previous reports as well as in our two patients, encountering MMF in the biopsied tissue specimens was coincidental. Our two unrelated patients with MMF also had two separate types of muscular dystrophy, a merosinopathy and dystrophinopathy, showing a combination of myopathologically well-defined neuromuscular diseases, muscular dystrophies and MMF. Detecting such a combination of two separate conditions may, in the future, be rare when non-invasive techniques, e. g., genetic, will have replaced muscle biopsy in ascertaining hereditary neuromuscular conditions, especially in children.

http://www.ncbi.nlm.nih.gov/pubmed/20135575

“Macrophagic myofasciitis (MMF) is a well-known lesion following vaccination with aluminium-containing vaccines. It has **abundantly** been reported in adults and several times in children, often in single patients or in rather small cohorts. Our two unrelated patients with MMF also had two separate types of muscular dystrophy, a merosinopathy and dystrophinopathy, showing a combination of myopathologically well-defined neuromuscular diseases, muscular dystrophies and MMF.”

Emerging Infectious Diseases • August 2009

Bordetella pertussis strains with increased toxin production associated with pertussis resurgence

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Abstract

Before childhood vaccination was introduced in the 1940s, pertussis was a major cause of infant death worldwide. Widespread vaccination of children succeeded in reducing illness and death. In the 1990s, a resurgence of pertussis was observed in a number of countries with highly vaccinated populations, and pertussis has become the most prevalent vaccine-preventable disease in industrialized countries. We present evidence that in the Netherlands the dramatic increase in pertussis is temporally associated with the emergence of Bordetella pertussis strains carrying a novel allele for the pertussis toxin promoter, which confers increased pertussis toxin (Ptx) production. Epidemiologic data suggest that these strains are more virulent in humans. We discuss changes in the ecology of B. pertussis that may have driven this adaptation. Our results underline the importance of Ptx in transmission, suggest that vaccination may select for increased virulence, and indicate ways to control pertussis more effectively.

http://www.ncbi.nlm.nih.gov/pubmed/?term=19751581

“We present evidence that in the Netherlands the dramatic increase in pertussis is temporally associated with the emergence of Bordetella pertussis strains carrying a novel allele for the pertussis toxin promoter, which confers increased pertussis toxin (Ptx) production. Epidemiologic data suggest that these strains are more virulent in humans.”

Acta Paediatrica • August 2009

Breastfeeding is an essential complement to vaccination

Author information

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Abstract

AIM:
This article explores the role of breastfeeding in different aspects of vaccination in the first 6 months when infants are still developing: (1) pain management; (2) immunomodulation of infants' vaccine responses; (3) metabolism of thimerosal.

METHODS:
Major databases were searched for studies that addressed outcomes of related issues.

RESULTS:
Studies reveal that breastfeeding can: (1) help mothers and infants to cope with the stressful situations that accompany parenteral vaccines; (2) improve response to vaccines in the still maturing immunologic and enterohepatic systems of infants; (3) influence physiologic parameters that can change metabolism of ethylmercury derived from some vaccines.

CONCLUSION:
Health promotion that supports vaccinations should also emphasize early initiation and maintenance of exclusive breastfeeding up until 6 months for maximum protection of the infants with a possible beneficial effect on the vaccine response. Paediatric professionals should inform mothers of the proven benefits of breastfeeding and its importance in complementing vaccination and lowering stress and the risk of untoward reactions on susceptible infants.

http://www.ncbi.nlm.nih.gov/pubmed/19594471

"Health promotion that supports vaccinations should also emphasize early initiation and maintenance of exclusive breastfeeding up until 6 months for maximum protection of the infants with a possible beneficial effect on the vaccine response."

“This study demonstrates

a significant positive association between

the severity of autism and the

relative body burden of toxic metals.”

Journal Of Toxicology • August 2009

The Severity of Autism Is Associated with Toxic Metal Body Burden and Red Blood Cell Glutathione Levels

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Abstract

This study investigated the relationship of children’s autism symptoms with their toxic metal body burden and red blood cell (RBC) glutathione levels. In children ages 3–8 years, the severity of autism was assessed using four tools: ADOS, PDD-BI, ATEC, and SAS. Toxic metal body burden was assessed by measuring urinary excretion of toxic metals, both before and after oral dimercaptosuccinic acid (DMSA). Multiple positive correlations were found between the severity of autism and the urinary excretion of toxic metals. Variations in the severity of autism measurements could be explained, in part, by regression analyses of urinary excretion of toxic metals before and after DMSA and the level of RBC glutathione (adjusted R2 of 0.22–0.45, $P < .005$ in all cases). This study demonstrates a significant positive association between the severity of autism and the relative body burden of toxic metals.

http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2809421/

"... vaccination is depicted as playing an important role in Chronic Fatigue Syndrome onset."

Annals Of The New York Academy Of Science • September 2009

Infection, vaccination, and autoantibodies in chronic fatigue syndrome, cause or coincidence?

Author information

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Abstract

Chronic fatigue syndrome (CFS) is a heterogeneous syndrome of unknown etiology and physiopathology. CFS patients complain about disabling fatigue, depression, difficulty with memory, and concomitant skeletal and muscular pain. Interestingly enough, there is certain overlap between CFS symptoms, autoimmune rheumatic disease, and infectious diseases. Certain neuroendocrine-immune abnormalities have also been described, and autoantibodies commonly described in some autoimmune diseases have been found in CFS patients as well. An increasing number of autoantibodies, mainly directed against other nuclear cell components, have been illustrated. Likewise, an association between some infectious agents, antibody production, and later CFS onset has been reported. Similarly, vaccination is depicted as playing an important role in CFS onset. Recently, a case report pointed toward a causal association between silicone breast linkage, hepatitis B virus vaccination, and CFS onset in a previous healthy woman. Such findings suggest that there is a likely deregulation of the immune system influenced by specific agents (infections, vaccination, and products, such as silicone). Evidence suggests that CFS is a complex disease in which several risk factors might interact to cause its full expression. Thus, although different alterations have been found in CFS patients, undoubtedly the main feature is central nervous system involvement with immunological alterations. Therefore, a new term neuro-psycho-immunology must be quoted. New studies based on this concept are needed in order to investigate syndromes, such as CFS, in which immunological alterations are thought to be associated with concomitant psychological and health disturbances.

http://www.ncbi.nlm.nih.gov/pubmed/19758205

Lupus • November 2009

Transverse myelitis and vaccines: a multi-analysis

Author information

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Abstract

Transverse myelitis is a rare clinical syndrome in which an immune-mediated process causes neural injury to the spinal cord. The pathogenesis of transverse myelitis is mostly of an autoimmune nature, triggered by various environmental factors, including vaccination. Our aim here was to search for and analyze reported cases of transverse myelitis following vaccination. A systematic review of PubMed, EMBASE and DynaMed for all English-language journals published between 1970 and 2009 was preformed, utilizing the key words transverse myelitis, myelitis, vaccines, post-vaccination, vaccination and autoimmunity. We have disclosed 37 reported cases of transverse myelitis associated with different vaccines including those against hepatitis B virus, measles-mumps-rubella, diphtheria-tetanus-pertussis and others, given to infants, children and adults. In most of these reported cases the temporal association was between several days and 3 months, although a longer time frame of up to several years was also suggested. Although vaccines harbor a major contribution to public health in the modern era, in rare cases they may be associated with autoimmune phenomena such as transverse myelitis. The associations of different vaccines with a single autoimmune phenomenon allude to the idea that a common denominator of these vaccines, such as an adjuvant, might trigger this syndrome.

http://www.ncbi.nlm.nih.gov/pubmed/19880568

“We have disclosed 37 reported cases of transverse myelitis associated with different vaccines including those against hepatitis B virus, measles-mumps-rubella, diphtheria-tetanus-pertussis and others, given to infants, children and adults. Although vaccines harbor a major contribution to public health in the modern era, in rare cases they may be associated with autoimmune phenomena such as transverse myelitis. The associations of different vaccines with a single autoimmune phenomenon allude to the idea that a common denominator of these vaccines, such as an adjuvant, might trigger this syndrome.”

Lupus • November 2009

Ten cases of systemic lupus erythematosus related to hepatitis B vaccine

Author information

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Abstract

The objective of this article is to identify common and atypical features of systemic lupus erythematosus diagnosed following hepatitis B vaccination. We analyzed retrospectively the medical records of 10 systemic lupus erythematosus patients from different centers, who developed the disease following hepatitis B vaccination and determined the prevalence of different manifestations and the time association to vaccination. In this case series, 80% of the patients were female, mean age 35 +/- 9 years, of which 20% received one inoculation, 20% received two doses and 60% received all three inoculations. The mean latency period from the first hepatitis B virus immunization and onset of autoimmune symptoms was 56.3 days. All patients were diagnosed with systemic lupus erythematosus, according to the American College of Rheumatology revised criteria within 1 year. The prevalence of some systemic lupus erythematosus manifestations was typical and included involvement of the joints (100%), skin (80%), muscles (60%) and photosensitivity (30%). Other symptoms differed in this unique group of systemic lupus erythematosus patients such as low rate of kidney and hematologic involvement, and a relatively high rate of hepatitis (20%). Neurological (80%) and pulmonary (70%) symptoms were also common in this group. Data from this case-series, and previously documented cases in the literature could only show a temporal relation between hepatitis B vaccination and the appearance of systemic lupus erythematosus. Systemic lupus erythematosus related to vaccine may differ from idiopathic systemic lupus erythematosus in its clinical presentation and may resemble drug-induced systemic lupus erythematosus. Thus, physicians should be alerted to this potential association, its possible long latency period and unique presentations, and be encouraged to report and analyze these cases.

http://www.ncbi.nlm.nih.gov/pubmed/19880567

“Other symptoms differed in this unique group of systemic lupus erythematosus patients such as low rate of kidney and hematologic involvement, and a relatively high rate of hepatitis (20%). Neurological (80%) and pulmonary (70%) symptoms were also common in this group. Systemic lupus erythematosus related to vaccine may differ from idiopathic systemic lupus erythematosus in its clinical presentation and may resemble drug-induced systemic lupus erythematosus.”

“Owing to the adverse effects exerted by adjuvants, there is no doubt that safer adjuvants need to be developed and incorporated into future vaccines.”

Lupus • November 2009

Adjuvants and autoimmunity

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Abstract

Some adjuvants may exert adverse effects upon injection or, on the other hand, may not trigger a full immunological reaction. The mechanisms underlying adjuvant adverse effects are under renewed scrutiny because of the enormous implications for vaccine development. In the search for new and safer adjuvants, several new adjuvants were developed by pharmaceutical companies utilizing new immunological and chemical innovations. The ability of the immune system to recognize molecules that are broadly shared by pathogens is, in part, due to the presence of special immune receptors called toll-like receptors (TLRs) that are expressed on leukocyte membranes. The very fact that TLR activation leads to adaptive immune responses to foreign entities explains why so many adjuvants used today in vaccinations are developed to mimic TLR ligands. Alongside their supportive role, adjuvants were found to inflict by themselves an illness of autoimmune nature, defined as ‘the adjuvant diseases’. The debatable question of silicone as an adjuvant and connective tissue diseases, as well as the Gulf War syndrome and macrophagic myofaciitis which followed multiple injections of aluminium-based vaccines, are presented here. Owing to the adverse effects exerted by adjuvants, there is no doubt that safer adjuvants need to be developed and incorporated into future vaccines. Other needs in light of new vaccine technologies are adjuvants suitable for use with mucosally delivered vaccines, DNA vaccines, cancer and autoimmunity vaccines. In particular, there is demand for safe and non-toxic adjuvants able to stimulate cellular (Th1) immunity. More adjuvants were approved to date besides alum for human vaccines, including MF59 in some viral vaccines, MPL, AS04, AS01B and AS02A against viral and parasitic infections, virosomes for HBV, HPV and HAV, and cholera toxin for cholera. Perhaps future adjuvants occupying other putative receptors will be employed to bypass the TLR signaling pathway completely in order to circumvent common side effects of adjuvant-activated TLRs such as local inflammation and the general malaise felt because of the costly whole-body immune response to antigen.

http://www.ncbi.nlm.nih.gov/pubmed/19880572

National Reviews In Rheumatology • November 2009

Vaccines and autoimmunity

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Abstract

Vaccines have been used for over 200 years and are the most effective way of preventing the morbidity and mortality associated with infections. Like other drugs, vaccines can cause adverse events, but unlike conventional medicines, which are prescribed to people who are ill, vaccines are administered to healthy individuals, thus increasing the concern over adverse reactions. Most side effects attributed to vaccines are mild, acute and transient; however, rare reactions such as hypersensitivity, induction of infection, and autoimmunity do occur and can be severe and even fatal. The rarity and subacute presentation of post-vaccination autoimmune phenomena means that ascertaining causality between these events can be difficult. Moreover, the latency period between vaccination and autoimmunity ranges from days to years. In this article, on the basis of published evidence and our own experience, we discuss the various aspects of the causal and temporal interactions between vaccines and autoimmune phenomena, as well as the possible mechanisms by which different components of vaccines might induce autoimmunity.

http://www.ncbi.nlm.nih.gov/pubmed/19865091

“Most side effects attributed to vaccines are mild, acute and transient; however, rare reactions such as hypersensitivity, induction of infection, and autoimmunity do occur and can be severe and even fatal. Moreover, the latency period between vaccination and autoimmunity ranges from days to years.”

Lupus • November 2009

Vaccination of healthy subjects and autoantibodies: from mice through dogs to humans

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Abstract

Vaccination against pathogenic microorganisms is one of the major achievements of modern medicine, but due to an increasing number of reports of adverse reactions the vaccination procedure has induced also considerable debate. It is well known that certain infections are involved in triggering the production of autoantibodies, which could lead to autoimmune adverse reactions in genetically predisposed subjects. Based on these findings it was assumed that vaccinations might induce similar autoimmune reactions. At present there is no clear-cut evidence that vaccinations are associated with overt autoimmune diseases but it has been demonstrated that in genetically predisposed persons vaccination can trigger the production of autoantibodies and autoimmune adverse reactions. The first studies investigating the production of autoantibodies following vaccination were done in dogs and mice. Several studies investigated the production of autoantibodies following vaccination in patients with autoimmune diseases, but there are only limited data on the autoimmune responses after vaccinations in apparently healthy humans. This review summarizes current evidence on the vaccination-induced autoantibodies in apparently healthy subjects including studies in animals and humans.

http://www.ncbi.nlm.nih.gov/pubmed/?term=19880566

"due to an increasing number of reports of adverse reactions the vaccination procedure has induced also considerable debate ... it has been demonstrated that in genetically predisposed persons vaccination can trigger the production of autoantibodies and autoimmune adverse reactions."

Lupus • November 2009

Vaccines as a trigger for myopathies

Author information

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Abstract

Vaccines are considered to be among the greatest medical discoveries, credited with the virtual eradication of some diseases and the consequent improved survival and quality of life of the at-risk population. With that, vaccines are among the environmental factors implicated as triggers for the development of inflammatory myopathies. The sporadic reports on vaccine-induced inflammatory myopathies include cases of hepatitis B virus, bacillus Calmette-Guérin, tetanus, influenza, smallpox, polio, diphtheria, diphtheria-pertussis-tetanus, combination of diphtheria with scarlet fever and diphtheria-pertussis-tetanus with polio vaccines. However, a significant increase in the incidence of dermatomyositis or polymyositis after any massive vaccination campaign has not been reported in the literature. In study patients with inflammatory myopathies, no recent immunization was recorded in any of the patients. Moreover, after the 1976 mass flu vaccination, no increase in the incidence of inflammatory myopathies was observed. Although rare, macrophagic myofasciitis has been reported following vaccination and is attributed to the aluminium hydroxide used as an adjuvant in some vaccines. Prospective multicenter studies are needed to identify potential environmental factors, including vaccines, as potential triggers for inflammatory myopathies.

http://www.ncbi.nlm.nih.gov/pubmed/19880571

“... macrophagic myofasciitis
has been reported following vaccination
and is attributed to the aluminium hydroxide
used as an adjuvant in some vaccines.”

PLoS One • December 2009

Self-organized criticality theory of autoimmunity

Author information

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Abstract

BACKGROUND
The cause of autoimmunity, which is unknown, is investigated from a different angle, i.e., the defect in immune 'system', to explain the cause of autoimmunity.

METHODOLOGY/PRINCIPAL FINDINGS
Repeated immunization with antigen causes systemic autoimmunity in mice otherwise not prone to spontaneous autoimmune diseases. Overstimulation of CD4(+) T cells led to the development of autoantibody-inducing CD4(+) T (aiCD4(+) T) cell which had undergone T cell receptor (TCR) revision and was capable of inducing autoantibodies. The aiCD4(+) T cell was induced by de novo TCR revision but not by cross-reaction, and subsequently overstimulated CD8(+) T cells, driving them to become antigen-specific cytotoxic T lymphocytes (CTL). These CTLs could be further matured by antigen cross-presentation, after which they caused autoimmune tissue injury akin to systemic lupus erythematosus (SLE).

CONCLUSIONS/SIGNIFICANCE
Systemic autoimmunity appears to be the inevitable consequence of overstimulating the host's immune 'system' by repeated immunization with antigen, to the levels that surpass system's self-organized criticality.

http://www.ncbi.nlm.nih.gov/pubmed/20046868

"Systemic autoimmunity appears to be the inevitable consequence of over-stimulating the host's immune 'system' by repeated immunization with antigen, to the levels that surpass system's self-organized criticality."

Infection, Genetics And Evolution • January 2010

Bordetella pertussis and vaccination: the persistence of a genetically monomorphic pathogen

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Abstract

Before childhood vaccination was introduced in the 1950s, pertussis or whooping cough was a major cause of infant death worldwide. Widespread vaccination of children was successful in significantly reducing morbidity and mortality. However, despite vaccination, pertussis has persisted and, in the 1990s, resurged in a number of countries with highly vaccinated populations. Indeed, pertussis has become the most prevalent vaccine-preventable disease in developed countries with estimated infection frequencies of 1-6%. Recently vaccinated children are well protected against pertussis disease and its increase is mainly seen in adolescents and adults in which disease symptoms are often mild. The etiologic agent of pertussis, Bordetella pertussis, is extremely monomorphic and its ability to persist in the face of intensive vaccination is intriguing. Numerous studies have shown that B. pertussis populations changed after the introduction of vaccination suggesting adaptation. These adaptations did not involve the acquisition of novel genes but small genetic changes, mainly SNPs, and occurred in successive steps in a period of 40 years. The earliest adaptations resulted in antigenic divergence with vaccine strains. More recently, strains emerged with increased pertussis toxin (Ptx) production. Here I argue that the resurgence of pertussis is the compound effect of pathogen adaptation and waning immunity. I propose that the removal by vaccination of naïve infants as the major source for transmission was the crucial event which has driven the changes in B. pertussis populations. This has selected for strains which are more efficiently transmitted by primed hosts in which immunity has waned. The adaptation of B. pertussis to primed hosts involved delaying an effective immune response by antigenic divergence with vaccine strains and by increasing immune suppression through higher levels of Ptx production. Higher levels of Ptx may also benefit transmission by enhancing clinical symptoms. The study of B. pertussis populations has not only increased our understanding of pathogen evolution, but also suggests way to improve pertussis vaccines, underlining the public health significance of population-based studies of pathogens.

http://www.ncbi.nlm.nih.gov/pubmed/19879977

“despite vaccination, pertussis has persisted and, in the 1990s, resurged in a number of countries with highly vaccinated populations. Here I argue that the resurgence of pertussis is the compound effect of pathogen adaptation and waning immunity.”

[resurgence is not a result of the unvaccinated]

Medical Hypotheses • January 2010

Revisiting the possibility of serious adverse events from the whole cell pertussis vaccine: were metabolically vulnerable children at risk?

Author information

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Abstract

In the early 1980's concerns about the safety of the whole cell pertussis vaccine in the United States resulted in declining vaccination rates and the withdrawal of multiple vaccine providers from the market. While the possibility of inflammation and febrile reactions to the vaccine were acknowledged by public health authorities, parents also claimed the vaccine was associated with sudden infant death syndrome and encephalopathy. Epidemiological studies examining this question, however, consistently failed to identify an association. We argue that these reactions may have occurred in metabolically vulnerable children, specifically those with defects in fatty acid oxidation. In these children the combination of anorexia and fever that could be caused by the vaccine may have resulted in hypoglycemic episodes and possibly death. We believe that this association was not detected because these conditions were not recognized at the time and because these conditions are uncommon. Nevertheless, at a population level, enough events could have occurred to cause concern amongst parents.

http://www.ncbi.nlm.nih.gov/pubmed/19660877

"We argue that these reactions may have occurred in metabolically vulnerable children, specifically those with defects in fatty acid oxidation. In these children the combination of anorexia and fever that could be caused by the vaccine may have resulted in hypoglycemic episodes and possibly death. We believe that this association was not detected because these conditions were not recognized at the time and because these conditions are uncommon. Nevertheless, at a population level, enough events could have occurred to cause concern amongst parents."

Pediatrics, Volume 125 / Issue 2 • February 2010

Sibling Transmission of Vaccine-Derived Rotavirus (RotaTeq) Associated With Rotavirus Gastroenteritis

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Abstract

Although rotavirus vaccines are known to be shed in stools, transmission of vaccine-derived virus to unvaccinated contacts resulting in symptomatic rotavirus gastroenteritis has not been reported to our knowledge. We document here the occurrence of vaccine-derived rotavirus (RotaTeq [Merck and Co, Whitehouse Station, NJ]) transmission from a vaccinated infant to an older, unvaccinated sibling, resulting in symptomatic rotavirus gastroenteritis that required emergency department care. Results of our investigation suggest that reassortment between vaccine component strains of genotypes P7[5]G1 and P1A[8]G6 occurred during replication either in the vaccinated infant or in the older sibling, raising the possibility that this reassortment may have increased the virulence of the vaccine-derived virus. Both children remain healthy 11 months after this event and are without underlying medical conditions.

http://pediatrics.aappublications.org/content/125/2/e438

“Although rotavirus vaccines are known to be shed in stools, transmission of vaccine-derived virus to unvaccinated contacts resulting in symptomatic rotavirus gastroenteritis has not been reported to our knowledge.

We document here the occurrence of vaccine-derived rotavirus (RotaTeq, Merck and Co, Whitehouse Station, NJ) transmission from a vaccinated infant to an older, unvaccinated sibling, resulting in symptomatic rotavirus gastroenteritis that required emergency department care.”

Discovery Medicine • February 2010

Vaccines and autoimmune diseases of the adult

Author information

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Abstract

Infectious agents contribute to the environmental factors involved in the development of autoimmune diseases possibly through molecular mimicry mechanisms. Hence, it is feasible that vaccinations may also contribute to the mosaic of autoimmunity. Evidence for the association of vaccinations and the development of these diseases is presented in this review. Infrequently reported post-vaccination autoimmune diseases include systemic lupus erythematosus, rheumatoid arthritis, inflammatory myopathies, multiple sclerosis, Guillain-Barré syndrome, and vasculitis. In addition, we will discuss macrophagic myofasciitis, aluminum containing vaccines, and the recent evidence for autoimmunity following the use of human papillomavirus vaccine.

http://www.ncbi.nlm.nih.gov/pubmed/20193633

“Hence, it is feasible that vaccinations may also contribute to the mosaic of autoimmunity. Evidence for the association of vaccinations and the development of these diseases is presented in this review. In addition, we will discuss macrophagic myofasciitis, aluminum containing vaccines, and the recent evidence for autoimmunity following the use of human papillomavirus vaccine.”

Full Report

http://www.discoverymedicine.com/Hedi-Orbach/2010/02/04/vaccines-and-autoimmune-diseases-of-the-adult/

Discovery Medicine • February 2010

Vaccines and Autoimmune Diseases of the Adult

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Abstract

Infectious agents contribute to the environmental factors involved in the development of autoimmune diseases possibly through molecular mimicry mechanisms. Hence, it is feasible that vaccinations may also contribute to the mosaic of autoimmunity. Evidence for the association of vaccinations and the development of these diseases is presented in this review. Infrequently reported post-vaccination autoimmune diseases include systemic lupus erythematosus, rheumatoid arthritis, inflammatory myopathies, multiple sclerosis, Guillain-Barré syndrome, and vasculitis. In addition, we will discuss macrophagic myofasciitis, aluminum containing vaccines, and the recent evidence for autoimmunity following human papilloma virus vaccine.

Introduction

Systemic and organ-specific autoimmune diseases are known to develop following infectious triggers. Recently we have suggested that certain autoimmune diseases like systemic lupus erythematosus (SLE) may result due to specific viral agents. Furthermore, the spectrum of disease may be influenced by a certain microbial agent in the genetically predisposed individual (Zandman-Goddard et al., 2009).

Vaccines are a prototypic source for natural immune stimulation, but may be involved in pathogenic disease in the setting of aberrant immune system function. Possibly, the burden on the immune system resulting from simultaneous multiple vaccines and even the different types of vaccines may also be an overwhelming challenge in the autoimmune prone individual (Shoenfeld et al., 2008). In this review, we discuss the evidence for the development of autoimmune diseases following infections and vaccinations.

While vaccinations are generally safe, warranted and have virtually eradicated endemic diseases and probably lessened morbidity and mortality, a question arises regarding the evaluation of possible autoimmune phenomena in vaccinated individuals.

Reported post-vaccination autoimmune diseases in the adult include SLE, rheumatoid arthritis (RA), inflammatory myopathies, multiple sclerosis (MS), Guillain-Barré syndrome (GBS), and vasculitis. Evidence for the association of vaccinations and the development of these diseases is presented in this review. In addition, we will discuss macrophagic myofasciitis, post aluminum containing vaccines and the recent support for autoimmunity following human papilloma virus vaccine.

http://www.discoverymedicine.com/Hedi-Orbach/2010/02/04/vaccines-and-autoimmune-diseases-of-the-adult/

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BMJ • March 2010

Effect of revaccination with BCG in early childhood on mortality: randomised trial in Guinea-Bissau

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Abstract

Objective
To determine whether BCG revaccination at 19 months of age reduces overall child mortality.

Design
Randomised trial, with follow-up to age 5.

Setting
A health project in Bissau, Guinea-Bissau, which maintains a health and demographic surveillance system in an urban area with 90,000 inhabitants.

Participants
2871 children aged 19 months to 5 years with low or no reactivity to tuberculin and who were not severely sick on the day of enrolment.

Intervention
BCG vaccination or no vaccination (control).

Main outcome measure
Hazard ratios for mortality.

Results
77 children died during follow-up. Compared with controls, the BCG revaccinated children had a hazard ratio of 1.20 (95% confidence interval 0.77 to 1.89). Two hundred and fifty children were admitted to hospital for the first time between enrolment and the end of the study, with an incidence rate ratio for BCG revaccinated children versus controls of 1.04 (0.81 to 1.33). The trial was stopped prematurely because of a cluster of deaths in the BCG arm of the study. This increase in mortality occurred at a time when many children had received missing vaccinations or vitamin A or iron supplementation; the hazard ratio for BCG revaccinated children compared with controls was 2.69 (1.05 to 6.88) in the period after these campaigns. Throughout the trial, the effect of BCG revaccination on mortality was significantly different (P=0.006) in children who had received diphtheria-tetanus-pertussis (DTP) booster vaccination before enrolment (hazard ratio 0.36, 0.13 to 0.99) and children who had not received the booster before enrolment (1.78, 1.04 to 3.04).

Conclusions
There was no overall beneficial effect of being revaccinated with BCG. The effect of BCG revaccination on mortality might depend on other health interventions.

“77 of 2871 children died during follow-up”

http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2839082/

“77 children died during follow-up. Two hundred and fifty children were admitted to hospital for the first time. There was no overall beneficial effect of being revaccinated with BCG. ”

Cutaneous And Ocular Toxicology • March 2010

Hepatitis B vaccine and uveitis: an emerging hypothesis suggested by review of 32 case reports

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Abstract

OBJECTIVE
To report a possible association between hepatitis B vaccine and uveitis.

METHODS
Spontaneous reports from the National Registry of Drug-Induced Ocular Side Effects, the World Health Organization, and the Food and Drug Administration were collected on hepatitis B vaccine associated with uveitis between 1982 and 2009. In addition, we performed a Medline literature search using the keywords of uveitis, iritis, or vitritis, in combination with vaccines and hepatitis B vaccine. Data garnered from the spontaneous reports included age, gender, adverse drug reaction, temporal association of uveitis with vaccine doses, concomitant drugs, other systemic disease, recovery, and recurrence after repeat dosage.

RESULTS
Thirty-two case reports of uveitis occurring after hepatitis B vaccine were reported to the spontaneous reporting databases. The mean age of the patients was 29 years (1-57 years), with 8 male and 24 female patients. The mean number of days until uveitis was reported after vaccination was 3 days (1-15 days). The uveitis was reported to occur after the first vaccination in 15 patients, after the second vaccination in 3 patients, and after the third vaccination in 3 patients; the duration of time to occurrence of uveitis was not reported for 9 patients. One patient had recurrent uveitis after both the second and third doses of vaccine. One patient had recurrent uveitis after the first and second doses of vaccine.

CONCLUSION
Hepatitis B vaccine may have a possible association with the development of uveitis in some patients. Immune complex deposition and adjuvant effects are potential pathogenic mechanisms.

http://www.ncbi.nlm.nih.gov/pubmed/?term=19947819

“Hepatitis B vaccine may have a possible association with the development of uveitis in some patients. Immune complex deposition and adjuvant effects are potential pathogenic mechanisms.”

Cell Biology And Toxicology • April 2010

Induction of metallothionein in mouse cerebellum and cerebrum with low-dose thimerosal injection

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Abstract

Thimerosal, an ethyl mercury compound, is used worldwide as a vaccine preservative. We previously observed that the mercury concentration in mouse brains did not increase with the clinical dose of thimerosal injection, but the concentration increased in the brain after the injection of thimerosal with lipopolysaccharide, even if a low dose of thimerosal was administered. Thimerosal may penetrate the brain, but is undetectable when a clinical dose of thimerosal is injected; therefore, the induction of metallothionein (MT) messenger RNA (mRNA) and protein was observed in the cerebellum and cerebrum of mice after thimerosal injection, as MT is an inducible protein. MT-1 mRNA was expressed at 6 and 9 h in both the cerebrum and cerebellum, but MT-1 mRNA expression in the cerebellum was three times higher than that in the cerebrum after the injection of 12 microg/kg thimerosal. MT-2 mRNA was not expressed until 24 h in both organs. MT-3 mRNA was expressed in the cerebellum from 6 to 15 h after the injection, but not in the cerebrum until 24 h. MT-1 and MT-3 mRNAs were expressed in the cerebellum in a dose-dependent manner. Furthermore, MT-1 protein was detected from 6 to 72 h in the cerebellum after 12 microg/kg of thimerosal was injected and peaked at 10 h. MT-2 was detected in the cerebellum only at 10 h. In the cerebrum, little MT-1 protein was detected at 10 and 24 h, and there were no peaks of MT-2 protein in the cerebrum. In conclusion, MT-1 and MT-3 mRNAs but not MT-2 mRNA are easily expressed in the cerebellum rather than in the cerebrum by the injection of low-dose thimerosal. It is thought that the cerebellum is a sensitive organ against thimerosal. As a result of the present findings, in combination with the brain pathology observed in patients diagnosed with autism, the present study helps to support the possible biological plausibility for how low-dose exposure to mercury from thimerosal-containing vaccines may be associated with autism.

http://www.ncbi.nlm.nih.gov/pubmed/19357975

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biological plausibility for how low-dose
exposure to mercury from thimerosal
containing vaccines may be associated with autism.”

Disability & Health Journal • April 2010

Sex differences in the evaluation and diagnosis of autism spectrum disorders among children

Author information

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Abstract

BACKGROUND

One of the most consistent features of the autism spectrum disorders (ASDs) is the predominance among males, with approximately four males to every female. We sought to examine sex differences among children who met case definition for ASD in a large, population-based cohort with respect to age at first developmental evaluation, age of diagnosis, influence of cognitive impairment on these outcomes, and sex-specific behavioral characteristics.

METHODS

We conducted a secondary analysis of data collected for a population-based study of the prevalence of ASD. The sample comprised 2,568 children born in 1994 who met the case definition of ASD as established by the Autism and Developmental Disabilities Monitoring (ADDM) Network for ASD surveillance. Children who had a history of developmental disability and behavioral features consistent with the DSM-IV-TR criteria for autistic disorder, Asperger's disorder, and Pervasive Developmental Disorder-Not Otherwise Specified in existing evaluation records were classified as ASD cases via two paths: streamlined and non-streamlined. Streamlined reviews were conducted if there was an ASD diagnosis documented in the records. Data were collected in 13 sites across the United States through the ADDM Network, funded by the Centers for Disease Control and Prevention.

RESULTS

Males constituted 81% of the sample. There were no differences by sex in average age at first evaluation or average age of diagnosis among those with an existing documented chart diagnosis of an ASD. Girls were less likely than boys to have a documented diagnosis (odds ratio [OR] = 0.76, p = .004). This analysis was adjusted for cognitive impairment status. In the logistic model, with the interaction term for sex and cognitive impairment, girls with IQ of 70 or less were less likely than boys with IQ of 70 or less to have a documented diagnosis (OR = 0.70, 95% confidence interval [CI] = 0.50-0.97, p = .035). Boys with IQ greater than 70 were less likely than boys with IQ of 70 or less to have a documented diagnosis (OR = 0.60, 95% CI = 0.49-0.74, p < .001). This finding (less likely to have a documented diagnosis) was also true for girls with IQ greater than 70 (OR = 0.45, 95% CI = 0.32-0.66, p < .001). Girls were more likely to have notations of seizure-like behavior (p < .001). Boys were more likely to have notations of hyperactivity or a short attention span and aggressive behavior (p < .01).

CONCLUSIONS

Girls, especially those without cognitive impairment, may be formally identified at a later age than boys. This may delay referral for early intervention. Community education efforts should alert clinicians and parents to the potential of ASDs in boys and girls.

http://www.ncbi.nlm.nih.gov/pubmed/?term=21122776

"One of the most consistent features of the autism spectrum disorders (ASDs) is the predominance among males, with approximately four males to every female. We sought to examine sex differences among children who met case definition for ASD ..."

PLoS One • May 2010

Oral polio vaccine influences the immune response to BCG vaccination A natural experiment

Author information

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Abstract

BACKGROUND

Oral polio vaccine (OPV) is recommended to be given at birth together with BCG vaccine. While we were conducting two trials including low-birth-weight (LBW) and normal-birth-weight (NBW) infants in Guinea-Bissau, OPV was not available during some periods and therefore some infants did not receive OPV at birth, but only BCG. We investigated the effect of OPV given simultaneously with BCG at birth on the immune response to BCG vaccine.

METHODS AND FINDINGS

We compared the in vitro and the in vivo response to PPD in the infants who received OPV and BCG with that of infants who received BCG only. At age 6 weeks, the in vitro cytokine response to purified protein derivate (PPD) of M. Tuberculosis was reduced in LBW and NBW infants who had received OPV with BCG. In a pooled analysis receiving OPV with BCG at birth was associated with significantly lower IL-13 ($p = 0.041$) and IFN-gamma ($p = 0.004$) and a tendency for lower IL-10 ($p = 0.054$) in response to PPD. Furthermore, OPV was associated with reduced in vivo response to PPD at age 2 months, the prevalence ratio (PR) of having a PPD reaction being 0.75 (0.58-0.98), $p = 0.033$, and with a tendency for reduced likelihood of having a BCG scar (0.95 (0.91-1.00), $p = 0.057$)). Among children with a scar, OPV was associated with reduced scar size, the regression coefficient being -0.24 (-0.43-0.05), $p = 0.012$.

CONCLUSIONS

This study is the first to address the consequences for the immune response to BCG of simultaneous administration with OPV. Worryingly, the results indicate that the common practice in low-income countries of administering OPV together with BCG at birth may down-regulate the response to BCG vaccine.

Full Report

http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2873948/

“Worryingly, the results indicate that the common practice in low-income countries of administering Oral polio vaccine together with Bacille Calmette-Guerin [BCG - tuberculosis] vaccine at birth may down-regulate the response to Bacille Calmette-Guerin [BCG - tuberculosis] vaccine.”

Medical Science Monitor • May 2010

The relative toxicity of compounds used as preservatives in vaccines and biologics

Author information

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Abstract

BACKGROUND
In vaccines/biologics, preservatives are used to prevent microbial growth.

MATERIAL/METHODS
The present study examined: (1) the comparative toxicities of commonly used preservatives in US licensed vaccines to human neurons; and (2) the relative toxicity index of these compounds to human neurons in comparison to bacterial cells.

RESULTS
Using human neuroblastoma cells, the relative cytotoxicity of the levels of the compounds commonly used as preservative in US licensed vaccines was found to be phenol <2-phenoxyethanol < benzethonium chloride < Thimerosal. The observed relative toxicity indices (human neuroblastoma cells/bacterial cells) were 2-phenoxyethanol (4.6-fold) < phenol (12.2-fold) < Thimerosal (>330-fold). In addition, for the compounds tested, except for 2-phenoxyethanol, the concentrations necessary to induce significant killing of bacterial cells were significantly higher than those routinely present in US licensed vaccine/biological preparations.

CONCLUSIONS
None of the compounds commonly used as preservatives in US licensed vaccine/biological preparations can be considered an ideal preservative, and their ability to fully comply with the requirements of the US Code of Federal Regulations (CFR) for preservatives is in doubt. Future formulations of US licensed vaccines/biologics should be produced in aseptic manufacturing plants as single dose preparations, eliminating the need for preservatives and an unnecessary risk to patients.

http://www.ncbi.nlm.nih.gov/pubmed/?term=20424565

“None of the compounds commonly used as preservatives in US licensed vaccine/biological preparations can be considered an ideal preservative, and their ability to fully comply with the requirements of the US Code of Federal Regulations (CFR) for preservatives is in doubt.”

BMJ • June 2010

Ramifications of adverse events in children in Australia

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Many serious adverse reactions to this year's seasonal influenza vaccine have occurred across Australia, and its use remains suspended in children aged 5 years and under.1 2 3 Data released on 1 June 2010 show that 1 in every 110 young children vaccinated with the CSL vaccine had a febrile seizure.3

A previous H1N1 vaccine study published earlier this year showed that a large proportion of children developed fevers after vaccination: between three and six in every 10 children under 3 years, depending on dose.4 The study was, however, underpowered to detect febrile convulsions at the current rates in Australia because it included only 162 children under 3 years.

Fever is the most important risk factor for febrile convulsions. The vaccine manufacturer CSL, which sponsored the trial, and Australia's regulatory body, the Therapeutic Goods Administration, which used these data in approving the vaccine for children, were presumably aware of these important findings.4 But the authors did not discuss the high incidence of fever associated with vaccination,4 and most data were reported without comment in the online only supplementary tables.4

The many children with adverse effects and the subsequent suspension of the vaccine challenge the assumption that regulators are ensuring the safety and efficacy of all marketed therapeutics. Influenza vaccine is said to have "an established record of safety in all age groups."2 However, published data on the effects of vaccinating young children against influenza are comparatively few.5 Some manufacturers have even withheld data from public scrutiny amid general indifference.2 5

Last winter the likelihood that a child without risk factors would die from swine flu was less than one in a million.2 When such a high proportion of children develop moderate to severe febrile reactions to the influenza vaccine, more harm than good seems likely from vaccinating them.

Report available for purchase. I accessed this report using a 14-day free trial:

http://www.bmj.com/content/340/bmj.c2994.long

"... the likelihood that a child without risk factors would die from swine flu was less than one in a million. When such a high proportion of children develop moderate to severe febrile reactions to the influenza vaccine, more harm than good seems likely from vaccinating them."

BMJ • June 2010

Australian government says healthy under 5s should not be given seasonal flu jab

Moynihan R.

http://www.ncbi.nlm.nih.gov/pubmed/20530085

Discovery Medicine • July 2010

Prophylactic HPV vaccines: current knowledge of impact on gynecologic premalignancies

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Abstract

Approaches for cervical cancer prevention are changing. Screening still remains the most effective method for cervical cancer prevention. Guidelines are moving to an older group of women to be screened less frequently with combinations of technologies that include biomarkers and cytology. HPV vaccination is an appropriate option for this older group of women as well, should the woman not wish to make her decision about vaccination until 21 years of age, the age of screening. Parents making decisions about HPV vaccination for their young adolescent daughters need to be fully informed that only continued screening prevents cervical cancer. HPV vaccination reduces the possibility of their daughter having an abnormal Pap test by 10% if the vaccines have not waned by the time the young adolescent becomes sexually active. HPV vaccine efficacy must last at least 15 years to contribute to the prevention of cervical cancers. At this time, protection against cervical intraepithelial neoplasia grade 2/3 (CIN 2/3) is 5 years for Gardasil and 8.4 years for Cervarix. The value of the current protection HPV vaccines offer will be viewed differently by different women. Physicians' ethical duties are to provide full explanation of the risks and benefits of adding HPV vaccination to the ongoing screening programs, and to support women in their personal choice for cervical cancer prevention.

http://www.ncbi.nlm.nih.gov/pubmed/20670593

"Screening still remains the most effective method for cervical cancer prevention. HPV vaccination reduces the possibility of their daughter having an abnormal Pap test by 10% if the vaccines have not waned by the time the young adolescent becomes sexually active."

Reviews Of Environmental Contamination And Toxicology • July 2010

The toxic effects of formaldehyde on the nervous system

Author information

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Abstract

Formaldehyde (FA) is found in the polluted atmosphere of cities, domestic air (e.g., paint, insulating materials, chipboard and plywood, fabrics, furniture, paper), and cigarette smoke, etc.; therefore, everyone and particularly susceptible children may be exposed to FA. FA is also widely used in industrial and medical settings and as a sterilizing agent, disinfectant, and preservative. Therefore, employees may be highly exposed to it in there settings. Of particular concern to the authors are anatomists and medical students, who can be highly exposed to formaldehyde vapor during dissection sessions. Formaldehyde is toxic over a range of doses; chances of exposure and subsequent harmful effects are increased as (room) temperature increases, because of FA's volatility. Many studies have been conducted to evaluate the effects of FA during systemic and respiratory exposures in rats. This review compiles that literature and emphasizes the neurotoxic effects of FA on neuronal morphology, behavior, and biochemical parameters. The review includes the results of some of the authors' work related to FA neurotoxicity, and such neurotoxic effects from FA exposure were experimentally demonstrated. Moreover, the effectiveness of some antioxidants such as melatonin, fish omega-3, and CAPE was observed in the treatment of the harmful effects of FA. Despite the harmful effects from FA exposure, it is commonly used in Turkey and elsewhere in dissection laboratories. Consequently, all anatomists must know and understand the effects of this toxic agent on organisms and the environment, and take precautions to avoid unnecessary exposure. The reviewed studies have indicated that FA has neurotoxic characteristics and systemic toxic effects. It is hypothesized that inhalation of FA, during the early postnatal period, is linked to some neurological diseases that occur in adults. Although complete prevention is impossible for laboratory workers and members of industries utilizing FA, certain precautions can be taken to decrease and/or prevent the toxic effects of FA.

http://www.ncbi.nlm.nih.gov/pubmed/?term=19957118

"The reviewed studies have indicated that Formaldehyde has neurotoxic characteristics and systemic toxic effects."

Journal Of Toxicology And Environmental Health Part A • 2010

Hepatitis B vaccination of male neonates and autism diagnosis NHIS 1997-2002

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Abstract

Universal hepatitis B vaccination was recommended for U.S. newborns in 1991; however, safety findings are mixed. The association between hepatitis B vaccination of male neonates and parental report of autism diagnosis was determined. This cross-sectional study used weighted probability samples obtained from National Health Interview Survey 1997-2002 data sets. Vaccination status was determined from the vaccination record. Logistic regression was used to estimate the odds for autism diagnosis associated with neonatal hepatitis B vaccination among boys age 3-17 years, born before 1999, adjusted for race, maternal education, and two-parent household. Boys vaccinated as neonates had threefold greater odds for autism diagnosis compared to boys never vaccinated or vaccinated after the first month of life. Non-Hispanic white boys were 64% less likely to have autism diagnosis relative to nonwhite boys. Findings suggest that U.S. male neonates vaccinated with the hepatitis B vaccine prior to 1999 (from vaccination record) had a threefold higher risk for parental report of autism diagnosis compared to boys not vaccinated as neonates during that same time period. Nonwhite boys bore a greater risk.

http://www.ncbi.nlm.nih.gov/pubmed/?term=21058170

“Findings suggest that U.S. male neonates vaccinated with the hepatitis B vaccine prior to 1999 (from vaccination record) had a threefold higher risk for parental report of autism diagnosis compared to boys not vaccinated as neonates during that same time period. Nonwhite boys bore a greater risk.”

Acta Neurobiologiea Experimentalis • 2010

Influence of pediatric vaccines on amygdala growth and opioid ligand binding in rhesus macaque infants: A pilot study

Author information

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Abstract

This longitudinal, case-control pilot study examined amygdala growth in rhesus macaque infants receiving the complete US childhood vaccine schedule (1994-1999). Longitudinal structural and functional neuroimaging was undertaken to examine central effects of the vaccine regimen on the developing brain. Vaccine-exposed and saline-injected control infants underwent MRI and PET imaging at approximately 4 and 6 months of age, representing two specific timeframes within the vaccination schedule. Volumetric analyses showed that exposed animals did not undergo the maturational changes over time in amygdala volume that was observed in unexposed animals. After controlling for left amygdala volume, the binding of the opioid antagonist [(11)C]diprenorphine (DPN) in exposed animals remained relatively constant over time, compared with unexposed animals, in which a significant decrease in [(11)C]DPN binding occurred. These results suggest that maturational changes in amygdala volume and the binding capacity of [(11)C]DPN in the amygdala was significantly altered in infant macaques receiving the vaccine schedule. The macaque infant is a relevant animal model in which to investigate specific environmental exposures and structural/functional neuroimaging during neurodevelopment.

http://www.ncbi.nlm.nih.gov/pubmed/?term=20628439

“This longitudinal, case-control pilot study examined amygdala growth in rhesus macaque infants receiving the complete US childhood vaccine schedule (1994-1999). These results suggest that maturational changes in amygdala volume and the binding capacity of [(11)C]DPN in the amygdala was significantly altered in infant macaques receiving the vaccine schedule.”

“The decrease in the collapse pressure of the monolayer film caused by coated nanoparticles, in vitro, was associated with an acute pulmonary toxicity in vivo.”

American Association Of Pharmaceutical Sciences • September 2010

Pulmonary Toxicity of Polysorbate-80-coated Inhalable Nanoparticles; In vitro and In vivo Evaluation

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CONCLUSION

The presented in vitro model for studying the surface pressure-area isotherms is an early screening tool to assess the biophysical compatibility of selected drug carriers with lung surfactant films. The decrease in the collapse pressure of the monolayer film caused by coated NPs, in vitro, was associated with an acute pulmonary toxicity in vivo. This in vivo toxicity was not observed when uncoated nanoparticles were used. Therefore, the dosage from toxicity of colloidal carriers intended for pulmonary delivery is mainly determined by their final composition rather than their individual components. More investigations are required to set different cut-off points for the collapse pressure to correlate them with different stages of pulomary toxicity in vivo. The outcomes of this study should not be generalized for all surfactants or bi-block polymers. Other surfactants with different hydrophilic-lipophilic properties might interact differently with lung surfactant films. This method may be useful to establish upper deposition limits for inhalable dry powders.

http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2895437/

Proceedings Of The National Academy Of Sciences Of The USA • September 2010

Triton X-100 concentration effects on membrane permeability of a single HeLa cell by scanning electrochemical microscopy (SECM)

Author information

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Abstract

Changes in HeLa cell morphology, membrane permeability, and viability caused by the presence of Triton X-100 (TX100), a nonionic surfactant, were studied by scanning electrochemical microscopy (SECM). No change in membrane permeability was found at concentrations of 0.15 mM or lower during an experimental period of 30 to 60 min. Permeability of the cell membrane to the otherwise impermeable, highly charged hydrophilic molecule ferrocyanide was seen starting at concentrations of TX100 of about 0.17 mM. This concentration level of TX100 did not affect cell viability. Based on a simulation model, the membrane permeability for ferrocyanide molecules passing though the live cell membrane was 6.5 ± 2.0 × 10(-6) m/s. Cells underwent irreversible permeabilization of the membrane and structural collapse when the TX100 concentration reached the critical micelle concentration (CMC), in the range of 0.19 to 0.20 mM. The impermeability of ferrocyanide molecules in the absence of surfactant was also used to determine the height and diameter of a single living cell with the aid of the approach curve and probe scan methods in SECM.

http://www.ncbi.nlm.nih.gov/pubmed/?term=20837548

“Permeability of the cell membrane to the otherwise impermeable, highly charged hydrophilic molecule ferrocyanide was seen starting at concentrations of TX100 of about 0.17 mM. Cells underwent irreversible permeabilization of the membrane and structural collapse when the TX100 concentration reached the critical micelle concentration (CMC), in the range of 0.19 to 0.20 mM.”

Proceedings Of The National Academy Of Science • September 2010

Triton X-100 concentration effects on membrane permeability of a single HeLa cell by scanning electrochemical microscopy (SECM)

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ABSTRACT

Changes in HeLa cell morphology, membrane permeability, and viability caused by the presence of Triton X-100 (TX100), a nonionic surfactant, were studied by scanning electrochemical microscopy (SECM). No change in membrane permeability was found at concentrations of 0.15 mM or lower during an experimental period of 30 to 60 min. Permeability of the cell membrane to the otherwise impermeable, highly charged hydrophilic molecule ferrocyanide was seen starting at concentrations of TX100 of about 0.17 mM. This concentration level of TX100 did not affect cell viability. Based on a simulation model, the membrane permeability for ferrocyanide molecules passing though the live cell membrane was 6.5 ± 2.0 × 10-6 m/s. Cells underwent irreversible permeabilization of the membrane and structural collapse when the TX100 concentration reached the critical micelle concentration (CMC), in the range of 0.19 to 0.20 mM. The impermeability of ferrocyanide molecules in the absence of surfactant was also used to determine the height and diameter of a single living cell with the aid of the approach curve and probe scan methods in SECM.

DISCUSSION

When the concentration of TX100 is below the CMC range (i.e. 0.17 mM and less) the surfactant may act as a permeabilizing agent depending on the dose and duration of exposure to cells. This is a good range for transfection of the cell with an added agent, but prolonged exposure to cells even at these low concentrations can lead to some cell death. When concentrations of TX100 in the CMC range, > 0.18 mM, are used, the cell membrane disintegrated causing a collapse of the entire cell structure and cell death within a few minutes.

Full Report

http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2947864/

“When concentrations of TX100 in the CMC range, > 0.18 mM, are used, the cell membrane disintegrated causing a collapse of the entire cell structure and cell death within a few minutes.”

Yao Xue Xue Bao • Acta Pharmaceutica Sinica • October 2010

Polysorbate-80 modified neurotoxin nanoparticle with its transport and cytotoxicity against blood-brain barrier

Author information

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Abstract

This study was aimed at the transport across blood-brain barrier (BBB) of polysorbate-80 modified neurotoxin loaded polybutylcyanoacrylate nanoparticle (P-80-NT-NP) and its cytotoxicity. An in vitro model of BBB using rat brain microvascular endothelial cells (rBMECs) was established. The cytotoxicity of P-80-NT-NP was measured by the MTT assays, where neurotoxin (NT), nanoparticle (NP), neurotoxin nanoparticle (NT-NP) as control, and the permeability of P-80-NT-NP was determined by using of Millicell insert coculture with rBMECs and fluorescence spectrophotometry. MTT results showed that NT, NP, NT-NP and P-80-NT-NP were avirulent to rBMECs when the concentration of NT was lower than 200 ng x mL(-1). But the cytotoxicity of NP, NT-NP and P-80-NT-NP would be augmented accordingly as concentration increased ($P < 0.01$), causing obvious reductions of cell survival rate, with no significant difference between them ($P > 0.05$). When the concentration of NT was 150 ng x mL(-1), the permeability on rBMECs of P-80-NT-NP and NT-NP were both significantly higher than that of NT ($P < 0.01$), and the permeability of P-80-NT-NP was greater than that of NT-NP ($P < 0.05$). In conclusion, polysorbate-80 modified neurotoxin nanoparticles can transport across the BBB, while concentration of NT is greater than 200 ng x mL(-1), P-80-NT-NP has a little cytotoxicity against rBMECs.

http://www.ncbi.nlm.nih.gov/pubmed/21348312

“... polysorbate-80 modified

neurotoxin nanoparticles

can transport across the Blood Brain Barrier ...”

Vaccine • January 2011

Diphtheria-tetanus-pertussis vaccine administered simultaneously with measles vaccine is associated with increased morbidity and poor growth in girls A randomised trial from Guinea-Bissau

Author information

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Abstract

BACKGROUND
Combined vaccination with diphtheria-tetanus-pertussis (DTP) and measles vaccine (MV) has been associated with increased mortality in observational studies. Among children missing MV and a dose of DTP and oral polio vaccine (OPV), we conducted a randomised trial of providing MV+DTP+OPV simultaneously, as currently recommended, or MV+OPV only, and examined the effect on morbidity and growth. We hypothesised that the MV+OPV group would experience less morbidity and grow better. Due to previous observations of sex differences in the non-specific effects of vaccinations, we analysed all data stratified by sex.

METHODS
At the Bandim Health Project in Guinea-Bissau, 568 children who were due to receive MV and who were missing either DTP3 or DTP booster were enrolled in the study. A subgroup of 332 children was followed intensively to register adverse events and infections in the first month after vaccination. A subgroup of 276 children was followed every third month for a year to monitor growth. All children were followed for one year for infectious diseases, consultations, and hospitalisations.

RESULTS
As expected, adverse events were more common in the MV+DTP+OPV group; diarrhoea and use of medication were increased among girls but not among boys (both p=0.02, test of interaction between DTP and sex). Febrile disease with vesicular rash, as well as consultations and hospitalisations tended to be more common in the MV+DTP+OPV group than in the MV+OPV group; the hazard ratio (HR) for febrile disease with vesicular rash was 1.86 (1.00; 3.47). The strongest tendencies for more febrile diseases and hospitalisations in the MV+DTP+OPV group were found in girls. Overall, growth did not differ by randomisation group. However, results differed by sex. Girls in the MV+DTP+OPV group had a consistent pattern of worse z-scores for weight, height, and mid-upper-arm-circumference (MUAC) than girls in the MV+OPV group. The effect was opposite for boys, with boys in the MV+OPV group faring worse than those in the MV+DTP+OPV group, the interaction test for sex and DTP being significant for weight at 6 and 9 months, for MUAC at 12 months and for weight-for-height at 3 and 9 months after randomisation.

CONCLUSION
This is the first randomised trial of the non-specific effects of DTP and supports that these effects may be sex-differential and of clinical and anthropometric importance. Combined vaccination with DTP+MV+OPV may be detrimental for girls.

http://www.ncbi.nlm.nih.gov/pubmed/21093496

“This is the first randomised trial of the non-specific effects of DTP and supports that these effects may be sex-differential and of clinical and anthropometric importance. Combined vaccination with DTP+MV+OPV may be detrimental for girls.”

Nucleic Acids Research • January 2011

Protegen:
a web-based protective antigen database and analysis system

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Abstract

Protective antigens are specifically targeted by the acquired immune response of the host and are able to induce protection in the host against infectious and non-infectious diseases. Protective antigens play important roles in vaccine development, as biological markers for disease diagnosis, and for analysis of fundamental host immunity against diseases. Protegen is a web-based central database and analysis system that curates, stores and analyzes protective antigens. Basic antigen information and experimental evidence are curated from peer-reviewed articles. More detailed gene/protein information (e.g. DNA and protein sequences, and COG classification) are automatically extracted from existing databases using internally developed scripts. Bioinformatics programs are also applied to compute different antigen features, such as protein weight and pI, and subcellular localizations of bacterial proteins. Presently, 590 protective antigens have been curated against over 100 infectious diseases caused by pathogens and non-infectious diseases (including cancers and allergies). A user-friendly web query and visualization interface is developed for interactive protective antigen search. A customized BLAST sequence similarity search is also developed for analysis of new sequences provided by the users. To support data exchange, the information of protective antigens is stored in the Vaccine Ontology (VO) in OWL format and can also be exported to FASTA and Excel files. Protegen is publically available at http://www.violinet.org/protegen.

Full Report

http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3013795/

“Protegen is a web-based central database and analysis system that curates, stores and analyzes protective antigens. Presently, 590 protective antigens have been curated against over 100 infectious diseases caused by pathogens and non-infectious diseases (including cancers and allergies).”

Journal Of Autoimmunity • February 2011

Autoimmune or auto-inflammatory syndrome induced by adjuvants (ASIA): old truths and a new syndrome?

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Abstract

There has been considerable interest in the role of environmental factors and the induction of autoimmunity and the ways by which they facilitate loss of tolerance. Clearly both genetic and environmental factors are incriminated, as evidenced by the lack of concordance in identical twins and the relatively recent identification of the shared epitope in rheumatoid arthritis. In this issue a new syndrome called 'Asia'-autoimmune/auto-inflammatory syndrome induced by adjuvants has been proposed. It is an intriguing issue and one that is likely to be provocative and lead to further biologic and molecular investigations.

http://www.ncbi.nlm.nih.gov/pubmed/21051205

"In this issue a new syndrome called 'Asia'-autoimmune/auto-inflammatory syndrome induced by adjuvants has been proposed. It is an intriguing issue and one that is likely to be provocative and lead to further biologic and molecular investigations."

Journal Of Autoimmunity • February 2011

‘ASIA’ autoimmune/inflammatory syndrome induced by adjuvants

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Abstract

The role of various environmental factors in the pathogenesis of immune mediated diseases is well established. Of which, factors entailing an immune adjuvant activity such as infectious agents, silicone, aluminium salts and others were associated with defined and non-defined immune mediated diseases both in animal models and in humans. In recent years, four conditions: siliconosis, the Gulf war syndrome (GWS), the macrophagic myofasciitis syndrome (MMF) and post-vaccination phenomena were linked with previous exposure to an adjuvant. Furthermore, these four diseases share a similar complex of signs and symptoms which further support a common denominator. Thus, we review herein the current data regarding the role of adjuvants in the pathogenesis of immune mediated diseases as well as the amassed data regarding each of these four conditions. Relating to the current knowledge we would like to suggest to include these comparable conditions under a common syndrome entitled ASIA, “Autoimmune (Auto-inflammatory) Syndrome Induced by Adjuvants”.

http://www.ncbi.nlm.nih.gov/pubmed/20708902

“Relating to the current knowledge we would like to suggest to include these comparable conditions under a common syndrome entitled ASIA, “Autoimmune (Auto-inflammatory) Syndrome Induced by Adjuvants”.”

“By means of a study including 300 unexplained sudden unexpected deaths (uSUD),

a 16-fold risk increase [in death] after the 4th dose could be detected with a power of at least 90 per cent.

A general 2-fold risk increase after vaccination could be detected with a power of 80 per cent.”

Statistics In Medicine • March 2011

A modified self-controlled case series method to examine association between multidose vaccinations and death

Author information

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Abstract

The self-controlled case series method (SCCS) was developed to analyze the association between a time-varying exposure and an outcome event. We consider penta- or hexavalent vaccination as the exposure and unexplained sudden unexpected death (uSUD) as the event. The special situation of multiple exposures and a terminal event requires adaptation of the standard SCCS method. This paper proposes a new adaptation, in which observation periods are truncated according to the vaccination schedule. The new method exploits known minimum spacings between successive vaccine doses. Its advantage is that it is very much simpler to apply than the method for censored, perturbed or curtailed post-event exposures recently introduced. This paper presents a comparison of these two SCCS methods by simulation studies and an application to a real data set. In the simulation studies, the age distribution and the assumed vaccination schedule were based on real data. Only small differences between the two SCCS methods were observed, although 50 per cent of cases could not be included in the analysis with the SCCS method with truncated observation periods. By means of a study including 300 uSUD, a 16-fold risk increase after the 4th dose could be detected with a power of at least 90 per cent. A general 2-fold risk increase after vaccination could be detected with a power of 80 per cent. Reanalysis of data from cases of the German case-control study on sudden infant death (GeSID) resulted in slightly higher point estimates using the SCCS methods than the odds ratio obtained by the case-control analysis.

http://www.ncbi.nlm.nih.gov/pubmed/21337361

Mutation Research • March 2011

Genotoxicity biomarkers in occupational exposure to formaldehyde the case of histopathology laboratories

Author information

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Abstract

Formaldehyde, classified by the IARC as carcinogenic in humans and experimental animals, is a chemical agent that is widely used in histopathology laboratories. The exposure to this substance is epidemiologically linked to cancer and to nuclear changes detected by the cytokinesis-block micronucleus test (CBMN). This method is extensively used in molecular epidemiology, since it provides information on several biomarkers of genotoxicity, such as micronuclei (MN), which are biomarkers of chromosomes breakage or loss, nucleoplasmic bridges (NPB), common biomarkers of chromosome rearrangement, poor repair and/or telomere fusion, and nuclear buds (NBUD), biomarkers of elimination of amplified DNA. The aim of this study is to compare the frequency of genotoxicity biomarkers, provided by the CBMN assay in peripheral lymphocytes and the MN test in buccal cells, between individuals occupationally exposed and non-exposed to formaldehyde and other environmental factors, namely tobacco and alcohol consumption. The sample comprised two groups: 56 individuals occupationally exposed to formaldehyde (cases) and 85 unexposed individuals (controls), from whom both peripheral blood and exfoliated epithelial cells of the oral mucosa were collected in order to measure the genetic endpoints proposed in this study. The mean level of TWA(8h) was 0.16±0.11 ppm (<detection limit until 0.51 ppm) and the mean of ceiling values was 1.14±0.74 ppm (0.18-2.93 ppm). All genotoxicity biomarkers showed significant increases in exposed workers in comparison with controls (Mann-Whitney test, $p<0.002$) and the analysis of confounding factors showed that there were no differences between genders. As for age, only the mean MN frequency in lymphocytes was found significantly higher in elderly people among the exposed groups ($p=0.006$), and there was also evidence of an interaction between age and gender with regards to that biomarker in those exposed. Smoking habits did not influence the frequency of the biomarkers, whereas alcohol consumption only influenced the MN frequency in lymphocytes in controls ($p=0.011$), with drinkers showing higher mean values. These results provide evidence of the association between occupational exposure to formaldehyde and the presence of genotoxicity biomarkers.

http://www.ncbi.nlm.nih.gov/pubmed/?term=21256246

“These results provide evidence of the association between occupational exposure to formaldehyde and the presence of genotoxicity biomarkers.”

Medical Journal of Australia • April 2011
Medicine and the law

Vaccination, consent and multidose vials

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Abstract

• Multidose vials (MDVs) for injectable therapeutic agents, including vaccines, pose a risk of infection to injected patients as a result of contamination of the vials.

• The Australian Government Department of Health and Ageing (DoHA) distributed the vaccine against pandemic (H1N1) 2009 influenza in MDVs. The distribution was accompanied by consent forms.

• The consent forms provided an inadequate basis for a discussion with patients about the risks associated with the use of MDVs.

• The High Court of Australia has previously held that medical practitioners who fail to explain the material risks of medical procedures to their patients might be held liable in negligence for any adverse sequelae of the procedures, even if the risks are very low.

• Medical practitioners, nurses, medical indemnity insurers and the DoHA should prepare now for the probable future use of MDVs by developing a consent form that would provide a solid foundation for a discussion of material risks with patients seeking vaccination.

Full Report

https://www.mja.com.au/system/files/issues/194_08_180411/dia10882_fm.pdf

"The consent forms provided an inadequate basis for a discussion with patients about the risks associated with the use of Multi-dose Vials."

Evidence Based Complementary Alternative Medicine • April 2011

Revisiting the Sham: Is It all Smoke and Mirrors?

Author information

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Abstract

The misuse of sham controls in examining the efficacy or effectiveness of Complementary and Alternative Medicine has created numerous problems. The theoretical justification for incorporating a sham is questionable. The sham does not improve our control of bias and leads to relativistic data that, in most instances, has no appropriate interpretation with regards to treatment efficacy. Even the concept of a sham or placebo control in an efficacy trial is inherently paradoxical. Therefore, it is prudent to re-examine how we view sham controls in the context of medical research. Extreme caution should be used in giving weight to any sham-controlled study claiming to establish efficacy or safety.

Full Report

http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3137704/

Clinical And Experimental Pharmacology And Physiology • April 2011

Formaldehyde induces neurotoxicity to PC12 cells involving inhibition of paraoxonase-1 expression and activity

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Abstract

1. Formaldehyde (FA) has been found to cause toxicity to neurons. However, its neurotoxic mechanisms have not yet been clarified. Increasing evidence has shown that oxidative damage is one of the most critical effects of formaldehyde exposure. Paraoxonase-1 (PON-1) is a pivotal endogenous anti-oxidant. Thus, we hypothesized that FA-mediated downregulation of PON1 is associated with its neurotoxicity.

2. In the present work, we used PC12 cells to study the neurotoxicity of FA and explore whether PON-1 is implicated in FA-induced neurotoxicity.

3. We found that FA has potent cytotoxic and apoptotic effects on PC12 cells. FA induces an accumulation of intracellular reactive oxygen species along with downregulation of Bcl-2 expression, as well as increased cytochrome c release. FA significantly suppressed the expression and activity of PON-1 in PC12 cells. Furthermore, H(2)S, an endogenous anti-oxidant gas, antagonizes FA-induced cytotoxicity as well as 2-hydroxyquinoline, a specific inhibitor of PON-1, which also induces cytotoxicity to PC12 cells.

4. The results of the present study provide, for the first time, evidence that the inhibitory effect on PON-1 expression and activity is involved in the neurotoxicity of FA, and suggest a promising role of PON-1 as a novel therapeutic strategy for FA-mediated toxicity.

http://www.ncbi.nlm.nih.gov/pubmed/21261675

“The results of the present study provide, for the first time, evidence that the inhibitory effect on Paraoxonase-1 expression and activity is involved in the neurotoxicity of Formaldehyde ...”

British Journal of Dermatology • May 2011

Biologic-induced urticaria due to polysorbate 80: usefulness of prick test

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Report Available For Purchase Only:
http://onlinelibrary.wiley.com/doi/10.1111/j.1365-2133.2011.10220.x/abstract

Virology Journal • June 2011

Genetic drift evolution under vaccination pressure among H5N1 Egyptian isolates

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Abstract

Background

The highly pathogenic H5N1 is a major avian pathogen that intensively affects the poultry industry in Egypt even in spite of the adoption of vaccination strategy. Antigenic drift is among the strategies the influenza virus uses to escape the immune system that might develop due to the pressure of extensive vaccination. H5N1 mutates in an intensified manner and is considered a potential candidate for the possible next pandemic with all the catastrophic consequences such an eventuality will entail.

Methods

H5N1 was isolated from the pooled organ samples of four different affected flocks in specific pathogen free embryonated chicken eggs (SPF-ECE). A reverse transcriptase polymerase chain reaction (RT-PCR) was performed to the haemagglutingin and neuraminidase. Sequencing of the full length haemagglutingin was performed. Sequence analyses of the isolated strains were performed and compared to all available H5N1 from Egyptian human and avian strains in the flu database. Changes in the different amino acid that may be related to virus virulence, receptor affinity and epitope configuration were assigned and matched with all available Egyptian strains in the flu database.

Results

One out of the four strains was found to be related to the B2 Egyptian lineage, 2 were related to A1 lineage and the 4th was related to A2 lineage. Comparing data obtained from the current study by other available Egyptian H5N1 sequences remarkably demonstrates that amino acid changes in the immune escape variants are remarkably restricted to a limited number of locations on the HA molecule during antigenic drift. Molecular diversity in the HA gene, in relevance to different epitopes, were not found to follow a regular trend, suggesting abrupt cumulative sequence mutations. However a number of amino acids were found to be subjected to high mutation pressure.

Conclusion

The current data provides a comprehensive view of HA gene evolution among H5N1 subtype viruses in Egypt. Egyptian H5N1-AIVs are constantly undergoing genetic changes and reveal a complex pattern of drifts. These findings raise the concerns about the value of using influenza vaccines in correlation with the development of antigenic drift in influenza epidemics.

Full Report

http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3146449/

“The current data provides a comprehensive view of HA gene evolution among H5N1 subtype viruses in Egypt. Egyptian H5N1-AIVs are constantly undergoing genetic changes and reveal a complex pattern of drifts. These findings raise the concerns about the value of using influenza vaccines in correlation with the development of antigenic drift in influenza epidemics.”

Surgery Neurology International • July 2011

Immunoexcitotoxicity as a central mechanism in chronic traumatic encephalopathy —A unifying hypothesis

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Abstract

Some individuals suffering from mild traumatic brain injuries, especially repetitive mild concussions, are thought to develop a slowly progressive encephalopathy characterized by a number of the neuropathological elements shared with various neurodegenerative diseases. A central pathological mechanism explaining the development of progressive neurodegeneration in this subset of individuals has not been elucidated. Yet, a large number of studies indicate that a process called immunoexcitotoxicity may be playing a central role in many neurodegenerative diseases including chronic traumatic encephalopathy (CTE). The term immunoexcitotoxicity was first coined by the lead author to explain the evolving pathological and neurodevelopmental changes in autism and the Gulf War Syndrome, but it can be applied to a number of neurodegenerative disorders. The interaction between immune receptors within the central nervous system (CNS) and excitatory glutamate receptors trigger a series of events, such as extensive reactive oxygen species/reactive nitrogen species generation, accumulation of lipid peroxidation products, and prostaglandin activation, which then leads to dendritic retraction, synaptic injury, damage to microtubules, and mitochondrial suppression. In this paper, we discuss the mechanism of immunoexcitotoxicity and its link to each of the pathophysiological and neurochemical events previously described with CTE, with special emphasis on the observed accumulation of hyperphosphorylated tau.

[Although this report discusses traumatic brain injury the data discussed fits in perfectly with and coincides with vaccine-induced brain injury and is included for that reason]

Full Report

http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3157093/

Vaccine • August 2011

Pandemic influenza H1N1 2009 infection in Victoria, Australia: no evidence for harm or benefit following receipt of seasonal influenza vaccine in 2009

Author information

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Abstract

Conflicting findings regarding the level of protection offered by seasonal influenza vaccination against pandemic influenza H1N1 have been reported. We performed a test-negative case control study using sentinel patients from general practices in Victoria to estimate seasonal influenza vaccine effectiveness against laboratory proven infection with pandemic influenza. Cases were defined as patients with an influenza-like illness who tested positive for influenza while controls had an influenza-like illness but tested negative. We found no evidence of significant protection from seasonal vaccine against pandemic influenza virus infection in any age group. Age-stratified point estimates, adjusted for pandemic phase, ranged from 44% in persons aged less than 5 years to -103% (odds ratio=2.03) in persons aged 50-64 years. Vaccine effectiveness, adjusted for age group and pandemic phase, was 3% (95% CI -48 to 37) for all patients. Our study confirms the results from our previous interim report, and other studies, that failed to demonstrate benefit or harm from receipt of seasonal influenza vaccine in patients with confirmed infection with pandemic influenza H1N1 2009.

http://www.ncbi.nlm.nih.gov/pubmed/?term=21473950

“Our study confirms the results from our previous interim report, and other studies, that failed to demonstrate benefit or harm from receipt of seasonal influenza vaccine ...”

Pharmazie • September 2011

Stability of the non-ionic surfactant polysorbate 80 investigated by HPLC-MS and charged aerosol detector

Author information

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Abstract

An analytical method using HPLC coupled with a charged aerosol detector (CAD) and a mass selective detector (MSD) was developed to characterize the non-ionic surfactant polysorbate 80 (PS 80). The molecular structure and heterogeneous composition due to isomers and various lengths of PEG-chains make it difficult to develop sensitive and specific analytical methods. Hence, there is only limited knowledge about the stability and purity of this compound. Polysorbate 80 does not possess any chromophore, thus UV detection is not applicable. Therefore, CAD and MSD have been used for determination. The aim of this study was to characterize polysorbate 80 and to examine its stability at pH 1.0 and 37 degrees C simulating harsh gastric conditions. It was shown that this surfactant is liable to degradation under these conditions. Within 8 h monoesters of PS 80 were hydrolyzed to an extent of 9.5% (+/- 3.0%), whereas incubation in water did not result in any detectable degradation. Furthermore, we demonstrated that HPLC-MS is a suitable technique to investigate ethoxylated compounds like polysorbates.

http://www.ncbi.nlm.nih.gov/pubmed/?term=22026121

“The aim of this study was to characterize polysorbate 80 and to examine its stability at pH 1.0 and 37 degrees C simulating harsh gastric conditions. It was shown that this surfactant is liable to degradation under these conditions.”

Human And Experimental Toxicology • September 2011

Infant mortality rates regressed against number of vaccine doses routinely given: Is there a biochemical or synergistic toxicity?

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Abstract

The infant mortality rate (IMR) is one of the most important indicators of the socio-economic well-being and public health conditions of a country. The US childhood immunization schedule specifies 26 vaccine doses for infants aged less than 1 year—the most in the world—yet 33 nations have lower IMRs. Using linear regression, the immunization schedules of these 34 nations were examined and a correlation coefficient of $r = 0.70$ ($p < 0.0001$) was found between IMRs and the number of vaccine doses routinely given to infants. Nations were also grouped into five different vaccine dose ranges: 12–14, 15–17, 18–20, 21–23, and 24–26. The mean IMRs of all nations within each group were then calculated. Linear regression analysis of unweighted mean IMRs showed a high statistically significant correlation between increasing number of vaccine doses and increasing infant mortality rates, with $r = 0.992$ ($p = 0.0009$). Using the Tukey-Kramer test, statistically significant differences in mean IMRs were found between nations giving 12–14 vaccine doses and those giving 21–23, and 24–26 doses. A closer inspection of correlations between vaccine doses, biochemical or synergistic toxicity, and IMRs is essential.

Conclusion

The US childhood immunization schedule requires 26 vaccine doses for infants aged less than 1 year, the most in the world, yet 33 nations have better IMRs. Using linear regression, the immunization schedules of these 34 nations were examined and a correlation coefficient of 0.70 ($p < 0.0001$) was found between IMRs and the number of vaccine doses routinely given to infants. When nations were grouped into five different vaccine dose ranges (12–14, 15–17, 18–20, 21–23, and 24–26), 98.3% of the total variance in IMR was explained by the unweighted linear regression model. These findings demonstrate a counter-intuitive relationship: nations that require more vaccine doses tend to have higher infant mortality rates.

Efforts to reduce the relatively high US IMR have been elusive. Finding ways to lower preterm birth rates should be a high priority. However, preventing premature births is just a partial solution to reduce infant deaths. A closer inspection of correlations between vaccine doses, biochemical or synergistic toxicity, and IMRs, is essential. All nations—rich and poor, advanced and developing—have an obligation to determine whether their immunization schedules are achieving their desired goals.

http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3170075/

“These findings demonstrate a counter-intuitive relationship: nations that require more vaccine doses tend to have higher infant mortality rates.”

BMC Immunology • October 2011

Immune enhancement by novel vaccine adjuvants in autoimmune-prone NZB/W F1 mice: relative efficacy and safety

Author information

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Abstract

BACKGROUND

Vaccines have profoundly impacted global health although concerns persist about their potential role in autoimmune or other adverse reactions. To address these concerns, vaccine components like immunogens and adjuvants require critical evaluation not only in healthy subjects but also in those genetically averse to vaccine constituents. Evaluation in autoimmune-prone animal models of adjuvants is therefore important in vaccine development. The objective here was to assess the effectiveness of experimental adjuvants: two phytol-derived immunostimulants PHIS-01 (phytanol) and PHIS-03 (phytanyl mannose), and a new commercial adjuvant from porcine small intestinal submucosa (SIS-H), relative to a standard adjuvant alum. Phytol derivatives are hydrophobic, oil-in water diterpenoids, while alum is hydrophilic, and SIS is essentially a biodegradable and collagenous protein cocktail derived from extracellular matrices.

RESULTS

We studied phthalate -specific and cross-reactive anti-DNA antibody responses, and parameters associated with the onset of autoimmune disorders. We determined antibody isotype and cytokine/chemokine milieu induced by the above experimental adjuvants relative to alum. Our results indicated that the phytol-derived adjuvant PHIS-01 exceeded alum in enhancing anti-phthalate antibody without much cross reactivity with ds-DNA. Relatively, SIS and PHIS-03 proved less robust, but they were also less inflammatory. Interestingly, these adjuvants facilitated isotype switching of anti-hapten, but not of anti-DNA response. The current study reaffirms our earlier reports on adjuvanticity of phytol compounds and SIS-H in non autoimmune-prone BALB/c and C57BL/6 mice. These adjuvants are as effective as alum also in autoimmune-prone NZB/WF1 mice, and they have little deleterious effects.

CONCLUSION

Although all adjuvants tested impacted cytokine/chemokine milieu in favor of Th1/Th2 balance, the phytol compounds fared better in reducing the onset of autoimmune syndromes. However, SIS is least inflammatory among the adjuvants evaluated.

http://www.ncbi.nlm.nih.gov/pubmed/?term=22024358

“Evaluation in autoimmune-prone animal models of adjuvants is therefore important in vaccine development.”

Archives In Neurology • October 2011

Postvaccination Miller Fisher Syndrome

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Abstract

Background
Although postvaccination Guillain-Barré syndrome is commonly reported, there have only been 2 previously reported cases of postvaccination Miller Fisher syndrome, and none in association with the novel influenza A(H1N1) vaccine.

Objective
To describe a case of Miller Fisher syndrome following receipt of the seasonal influenza and novel influenza A(H1N1) vaccine.

Design
Case report and literature review.

Setting
Vancouver General Hospital.

Patient
A 77-year-old Chinese woman.

Results
The patient presented with ophthalmoplegia, ataxia, areflexia, and a sensory neuropathy within 2 weeks of immunization. Findings of parainfectious evaluation were unremarkable. Treatment with 2 courses of intravenous immunoglobulin led to clinical improvement. Her presentation and natural history of disease were similar to the 2 previously published cases.

Conclusions
We present the third case of postvaccination Miller Fisher syndrome in the literature and the first associated with the novel influenza A(H1N1) vaccine. The benefits of the development of vaccines and the ensuing modern immunization programs are overwhelmingly without question. Nevertheless, there is a growing public concern surrounding the potential for postvaccination adverse events, a sentiment that has dwelled since their nascence.1 In view of the recent novel influenza A(H1N1) pandemic and scramble toward developing new vaccines for mass worldwide immunization campaigns, a better understanding of these potential adverse events is vital. We present a case of Miller Fisher syndrome (MFS) following seasonal influenza and novel influenza A(H1N1) vaccination, as well as a review of the literature on postvaccination MFS.

http://archneur.jamanetwork.com/article.aspx?articleid=1107885&resultClick=3

“We present the third case of postvaccination Miller Fisher syndrome in the literature and the first associated with the novel influenza A(H1N1) vaccine.”

Clinical Reviews In Allergy And Immunology • October 2011

Macrophagic myofaciitis
a vaccine (alum) autoimmune-related disease

Author information

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Abstract

Macrophagic myofasciitis (MMF) is an immune-mediated condition first reported in 1998. MMF is characterized by post-vaccination systemic manifestations as well as local-stereotyped and immunologically active lesion in the site of inoculation (deltoid muscle). MMF systemic symptoms included myalgias, arthralgias, marked asthenia, muscle weakness, chronic fatigue, and fever. Recently, studies demonstrated that the local lesion is due to persistence for years at site of injection of an aluminum (Al(OH)3) adjuvant commonly used in human vaccines. Time elapsed from last immunization with an Al(OH)3-containing vaccine to muscle biopsy range from 3 months to 8 years; in rare cases, MMF may be diagnosed even 10 years post-vaccination. The discrepancy between the wide applications of aluminum hydroxide-containing vaccines and the very limited number of MMF cases reported may be resolved by observations suggesting that aluminum-containing vaccinations may trigger MMF in genetically susceptible subjects carrying the HLA-DRB1*01. Thus, MMF may be defined as an emerging novel condition that may be triggered by exposure to alum-containing vaccines, in patients with a specific genetic background, and this temporal association may be exhibited from a few months up to 10 years.

http://www.ncbi.nlm.nih.gov/pubmed/?term=20882368

“MMF may be defined as an emerging novel condition that may be triggered by exposure to alum-containing vaccines ... and this temporal association may be exhibited from a few months up to 10 years.”

Infectious Disease Clinics Of North America • December 2011

The common immunogenic etiology of chronic fatigue syndrome: from infections to vaccines via adjuvants to the ASIA syndrome

Author information

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Abstract

Chronic fatigue syndrome (CFS) is characterized by unexplained fatigue that lasts for at least 6 months with a constellation of other symptoms. Most cases start suddenly, and are usually accompanied by a flu-like illness. It is a symptom-based diagnosis of exclusion, the pathogenesis of which is unknown. Studies have examined and hypothesized about the possible biomedical and epidemiologic characteristics of the disease, including genetic predisposition, infections, endocrine abnormalities, and immune dysfunction and psychological and psychosocial factors. Recently, the AISA (autoimmune/inflammatory syndrome induced by adjuvants) syndrome was recognized, indicating the possible contribution of adjuvants and vaccines to the development of autoimmunity.

http://www.ncbi.nlm.nih.gov/pubmed/22054760

“Recently, the AISA (autoimmune/inflammatory syndrome induced by adjuvants) syndrome was recognized, indicating the possible contribution of adjuvants and vaccines to the development of autoimmunity.”

Medical Hypotheses • December 2011

Hypothesis: conjugate vaccines may predispose children to autism spectrum disorders

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Abstract

The first conjugate vaccine was approved for use in the US in 1988 to protect infants and young children against the capsular bacteria Haemophilus influenzae type b (Hib). Since its introduction in the US, this vaccine has been approved in most developed countries, including Denmark and Israel where the vaccine was added to their national vaccine programs in 1993 and 1994, respectively. There have been marked increases in the reported prevalence of autism spectrum disorders (ASDs) among children in the US beginning with birth cohorts in the late 1980s and in Denmark and Israel starting approximately 4-5 years later. Although these increases may partly reflect ascertainment biases, an exogenous trigger could explain a significant portion of the reported increases in ASDs. It is hypothesized here that the introduction of the Hib conjugate vaccine in the US in 1988 and its subsequent introduction in Denmark and Israel could explain a substantial portion of the initial increases in ASDs in those countries. The continuation of the trend toward increased rates of ASDs could be further explained by increased usage of the vaccine, a change in 1990 in the recommended age of vaccination in the US from 15 to 2 months, increased immunogenicity of the vaccine through changes in its carrier protein, and the subsequent introduction of the conjugate vaccine for Streptococcus pneumoniae. Although conjugate vaccines have been highly effective in protecting infants and young children from the significant morbidity and mortality caused by Hib and S. pneumoniae, the potential effects of conjugate vaccines on neural development merit close examination. Conjugate vaccines fundamentally change the manner in which the immune systems of infants and young children function by deviating their immune responses to the targeted carbohydrate antigens from a state of hypo-responsiveness to a robust B2 B cell mediated response. This period of hypo-responsiveness to carbohydrate antigens coincides with the intense myelination process in infants and young children, and conjugate vaccines may have disrupted evolutionary forces that favored early brain development over the need to protect infants and young children from capsular bacteria.

http://www.ncbi.nlm.nih.gov/pubmed/?term=21993250

“This period of hypo-responsiveness to carbohydrate antigens coincides with the intense myelination process in infants and young children, and conjugate vaccines may have disrupted evolutionary forces that favored early brain development over the need to protect infants and young children from capsular bacteria.”

Reumatismo • 2011

‘ASIA’ - Autoimmune/inflammatory syndrome induced by adjuvants: even and odd

Author information

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Reumatologia
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Abstract

Recently, Shoenfeld and Agmon-Levin described a potential new syndrome, namely ASIA - autoimmune/inflammatory syndrome induced by adjuvants, that comprises four medical conditions: siliconosis, the Gulf war syndrome, the macrophagic myofasciitis syndrome and post-vaccination phenomena, characterized by hyperactive immune responses accompanied by a similar complex of signs and symptoms. Most relevantly, these conditions share a linkage represented by adjuvants. This common soil may possibly induce autoimmune or auto-inflammatory diseases in humans as it was demonstrated in different animal models. Reconsidering under a unified umbrella this apparently detached condition is not only intriguing, but also provocative, and may help in unraveling novel pathogenetic mechanisms, preventive measures, and therapeutic targets.

http://www.ncbi.nlm.nih.gov/pubmed/21776441

“This common soil may possibly induce autoimmune or auto-inflammatory diseases in humans as it was demonstrated in different animal models.”

Public Health Report • 2011

Highlights of Historical Events Leading to National Surveillance of Vaccination Coverage in the United States

Author Information

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Abstract

The articles published in this special supplement of Public Health Reports provide examples of only some of the current efforts in the United States for evaluating vaccination coverage. So, how did we get here? The history of vaccination and assessment of vaccination coverage in the U.S. has its roots in the pre-Revolutionary War era. In many cases, development of vaccines, and attention devoted to the assessment of vaccination coverage, has grown from the impact of infectious disease on major world events such as wars. The purpose of this commentary is to provide a brief overview of the key historical events in the U.S. that influenced the development of vaccines and the efforts to track vaccination coverage, which laid the foundation for contemporary vaccination assessment efforts.

Full Report • Recommended Reading

http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3113425/

“The history of vaccination and assessment of vaccination coverage in the U.S. has its roots in the pre-Revolutionary War era.”

JAMA • January 2012

Serum Vaccine Antibody Concentrations in Children Exposed to Perfluorinated Compounds

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Abstract

Context

Perfluorinated compounds (PFCs) have emerged as important food contaminants. They cause immune suppression in a rodent model at serum concentrations similar to those occurring in the US population, but adverse health effects of PFC exposure are poorly understood.

Objective

To determine whether PFC exposure is associated with antibody response to childhood vaccinations.

Design, Setting, and Participants

Prospective study of a birth cohort from the National Hospital in the Faroe Islands. A total of 656 consecutive singleton births were recruited during 1997-2000, and 587 participated in follow-up through 2008.

Main Outcome Measures

Serum antibody concentrations against tetanus and diphtheria toxoids at ages 5 and 7 years.

Results

Similar to results of prior studies in the United States, the PFCs with the highest serum concentrations were perfluorooctane sulfonic acid (PFOS) and perfluorooctanoic acid (PFOA). Among PFCs in maternal pregnancy serum, PFOS showed the strongest negative correlations with antibody concentrations at age 5 years, for which a 2-fold greater concentration of exposure was associated with a difference of □39% (95% CI, □55% to □17%) in the diphtheria antibody concentration. PFCs in the child's serum at age 5 years showed uniformly negative associations with antibody levels, especially at age 7 years, except that the tetanus antibody level following PFOS exposure was not statistically significant. In a structural equation model, a 2-fold greater concentration of major PFCs in child serum was associated with a difference of □49% (95% CI, □67% to □23%) in the overall antibody concentration. A 2-fold increase in PFOS and PFOA concentrations at age 5 years was associated with odds ratios between 2.38 (95% CI, 0.89 to 6.35) and 4.20 (95% CI, 1.54 to 11.44) for falling below a clinically protective level of 0.1 IU/mL for tetanus and diphtheria antibodies at age 7 years.

Conclusion

Elevated exposures to PFCs were associated with reduced humoral immune response to routine childhood immunizations in children aged 5 and 7 years.

http://jama.jamanetwork.com/article.aspx?articleid=1104903&resultClick=3

"Elevated exposures to PFCs were associated with reduced humoral immune response to routine childhood immunizations in children aged 5 and 7 years."

Journal Of Pharmacology And Pharmacotherapeutics • January 2012

Diphtheria, pertussis (whooping cough), and tetanus vaccine induced recurrent seizures and acute encephalopathy in a pediatric patient: Possibly due to pertussis fraction

Author information

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Abstract

A 5-month-old male patient developed recurrent seizures and acute encephalopathy possibly due to first dose of diphtheria, pertussis (whooping cough), and tetanus (DPT) vaccine used for routine immunization. Postreaction computed tomography (CT) scan of brain, magnetic resonance imaging (MRI) of brain, and electroencephalogram were normal. Pertussis fraction of DPT vaccine is responsible for this reaction. It is suggested that acellular pertussis vaccine should be used instead of whole cell vaccine because it is associated with lower frequency of neurological complications, such as seizures, encephalopathy, and hypotensive episodes. However, acellular pertussis-containing vaccines are currently not affordable in most developing countries.

Full Report

http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3284047/

“It is suggested that acellular pertussis vaccine should be used instead of whole cell vaccine because it is associated with lower frequency of neurological complications, such as seizures, encephalopathy, and hypotensive episodes.”

Lupus • February 2012

Influenza vaccination can induce new-onset anticardiolipins but not B2-glycoprotein-I antibodies among patients with systemic lupus erythematosus

Author information

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Abstract

BACKGROUND
Antiphospholipid syndrome is characterized by autoantibodies against cardiolipins (aCL), lupus anticoagulant, and independent B2-glycoprotein (B2GPI). Controversy exists as to whether vaccination triggers the development of antiphospholipid antibodies (aPL) in patients with systemic lupus erythematosus (SLE).

METHODS
Patients with SLE (101) and matched controls (101) were enrolled from 2005-2009 and received seasonal influenza vaccinations. Sera were tested by ELISA for aCL at baseline, 2, 6, and 12 weeks after vaccination. Vaccine responses were ranked according to an overall anti-influenza antibody response index. Individuals with positive aCL were further tested for B2GPI antibodies.

RESULTS
Patients with SLE and healthy controls can develop new-onset aCL post vaccination, although at rates which do not differ between patients and controls (12/101 cases and 7/101 controls, OR 1.81, $p = 0.34$). New-onset moderate aCL are slightly enriched in African American SLE patients (5/36 cases; $p = 0.094$). The optical density measurements for aCL reactivity in patients were significantly higher than baseline at 2 weeks ($p < 0.05$), 6 weeks ($p < 0.05$), and 12 weeks ($p < 0.05$) post vaccination. No new B2GPI antibodies were detected among patients with new aCL reactivity. Vaccine response was not different between patients with and without new-onset aCL reactivity ($p = 0.43$).

CONCLUSIONS
This study shows transient increases in aCL, but not anti-B2GPI responses, after influenza vaccination.

http://www.ncbi.nlm.nih.gov/pubmed/?term=22235049

“Controversy exists as to whether vaccination triggers the development of antiphospholipid antibodies (aPL) in patients with systemic lupus erythematosus (SLE). This study shows transient increases in aCL, but not anti-B2GPI responses, after influenza vaccination.”

Lupus • February 2012

Autoimmune response following influenza vaccination in patients with autoimmune inflammatory rheumatic disease

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Abstract

Vaccines have undoubtedly brought overwhelming benefits to mankind and are considered safe and effective. Nevertheless, they can occasionally stimulate autoantibody production or even a recently defined syndrome known as autoimmune/inflammatory syndrome induced by adjuvants (ASIA). There is scarce data regarding autoimmune response after seasonal/influenza A (H1N1) vaccine in patients with autoimmune inflammatory rheumatic disease (AIRD). The objective of our study was therefore to determine autoimmune response in a large group of AIRD patients vaccinated against seasonal and/or H1N1 influenza. We conducted a prospective cohort study with a 6-month follow-up. Two-hundred and eighteen patients with AIRD (50 vaccinated against seasonal influenza, six against H1N1, 104 against both, 58 non-vaccinated controls) and 41 apparently healthy controls (nine vaccinated against seasonal influenza, three against H1N1, 18 against both, 11 non-vaccinated controls) were included. Blood samples were taken and screened for autoantibodies [antinuclear antibody (ANA), anti-extractable nuclear antigen (anti-ENA), anticardiolipin (aCL) IgG/IgM antibodies, anti-beta 2-glycoprotein I (anti-□2GPI)] at inclusion in the study, before each vaccination, 1 month after the last vaccination and 6 months after inclusion. For non-vaccinated participants (patients and healthy controls) blood samples were taken at the time of inclusion in the study and 6 months later. We report that after the administration of seasonal/H1N1 vaccine there were mostly transient changes in autoantibody production in AIRD patients and in healthy participants. However, a small subset of patients, especially ANA-positive patients, had a tendency towards anti-ENA development. Although no convincing differences between the seasonal and H1N1 vaccines were observed, our results imply that there might be a slight tendency of the H1N1 vaccine towards aCL induction. Although seasonal and H1N1 vaccines are safe and effective, they also have the potential to induce autoantibodies in selected AIRD patients and healthy adults. Follow-up of such individuals is proposed and further research is needed.

http://www.ncbi.nlm.nih.gov/pubmed/?term=22235050

“they [vaccines] can occasionally stimulate autoantibody production or even a recently defined syndrome known as autoimmune/inflammatory syndrome induced by adjuvants (ASIA).”

Lupus • February 2012

Aluminum as an adjuvant in Crohn's disease induction

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Abstract

Alum (AlK(SO(4))(2)) is an adjuvant commonly utilized in vaccines, and is a ubiquitous element used extensively in contemporary life. Food, air, water, waste, the earth's surface, and pharmaceuticals all represent pathways of aluminum (Al) exposure. Crohn's disease (CD) is a chronic relapsing intestinal inflammation in genetically susceptible individuals and is caused by yet unidentified environmental factors. Al is a potential factor for the induction of inflammation in CD, and its immune activities share many characteristics with the immune pathology of CD: many luminal bacterial or dietary compounds can be adsorbed to the metal surface and induce Th1 profile cytokines, shared cytokines/chemokines, co-stimulatory molecules, and intracellular pathways and stress-related molecular expression enhancement, affecting intestinal macrobiota, trans-mural granuloma formation, and colitis induction in an animal CD model. The inflammasome plays a central role in Al mode of action and in CD pathophysiology. It is suggested that Al adjuvant activity can fit between the aberrations of innate and adaptive immune responses occurring in CD. The CD mucosa is confronted with numerous inappropriate bacterial components adsorbed on the Al compound surface, constituting a pro-inflammatory supra-adjuvant. Al fits the diagnostic criteria of the newly described autoimmune/inflammatory syndrome induced by adjuvants. If a cause and effect relationship can be established, the consequences will greatly impact public health and CD prevention and management.

http://www.ncbi.nlm.nih.gov/pubmed/22235058

"The inflammasome plays a central role in Aluminum mode of action and in Crohn's Disease (CD) pathophysiology. It is suggested that Aluminum adjuvant activity can fit between the aberrations of innate and adaptive immune responses occurring in Crohn's Disease. The CD mucosa is confronted with numerous inappropriate bacterial components adsorbed on the Aluminum compound surface, constituting a pro-inflammatory supra-adjuvant. Aluminum fits the diagnostic criteria ..."

Lupus • February 2012

Adjuvant immunization induces high levels of pathogenic antiphospholipid antibodies in genetically prone mice: another facet of the ASIA syndrome

Author information

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Abstract

Adjuvants may induce autoimmune diseases in susceptible individuals, a phenomenon recently defined as autoimmune/inflammatory syndrome induced by adjuvants (ASIA). Patients with both antiphospholipid antibodies (aPL) and the genetic coagulopathy factor V Leiden (FVL) are frequently found. We therefore evaluated whether adjuvant can induce aPL in heterozygous FVL mice. aPL were measured in naïve mice and at 1 and 5 months after immunization with either complete or incomplete Freund's adjuvant (CFA, IFA) in FVL and control C57/B6 background mice. We defined antibody levels 3 SD above the mean of C57/B6 mice immunized with adjuvant as positive (specificity of 99%). For B(2)GPI-dependent aPL, 28.6% (6/21) of FVL mice 5 months after immunization with adjuvant (both IFA and CFA) were positive compared with 4.8% (1/22) of FVL mice 1 month after adjuvant and 0% of naïve FVL and C57/B6 mice (0/16, $p < 0.001$). aPL levels correlated with behavioral hyperactivity in the staircase test. FVL mice immunized with adjuvant did not develop B(2)GPI-independent aPL. We hypothesize that the FVL aPL association is not a coincidence, but that chronic coagulation defects combined with external inflammatory stimuli analogous to adjuvant may induce aPL and also antiphospholipid syndrome, thus supporting the notion of ASIA.

http://www.ncbi.nlm.nih.gov/pubmed/22235055

"Adjuvants may induce autoimmune diseases in susceptible individuals, a phenomenon recently defined as autoimmune/inflammatory syndrome induced by adjuvants (ASIA)."

Lupus • February 2012

Autoimmunity following hepatitis B vaccine as part of the spectrum of 'Autoimmune (Auto-inflammatory) Syndrome induced by Adjuvants' (ASIA): analysis of 93 cases

Author information

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Abstract

OBJECTIVES

In this study we analyzed the clinical and demographic manifestations among patients diagnosed with immune/autoimmune-mediated diseases post-hepatitis B vaccination. We aimed to find common denominators for all patients, regardless of different diagnosed diseases, as well as the correlation to the criteria of Autoimmune (Auto-inflammatory) Syndrome induced by Adjuvants (ASIA).

PATIENTS AND METHODS

We have retrospectively analyzed the medical records of 114 patients, from different centers in the USA, diagnosed with immune-mediated diseases following immunization with hepatitis-B vaccine (HBVv). All patients in this cohort sought legal consultation. Of these, 93/114 patients diagnosed with disease before applying for legal consultation were included in the study. All medical records were evaluated for demographics, medical history, number of vaccine doses, peri-immunization adverse events and clinical manifestations of diseases. In addition, available blood tests, imaging results, treatments and outcomes were recorded. Signs and symptoms of the different immune-mediated diseases were grouped according to the organ or system involved. ASIA criteria were applied to all patients.

RESULTS

The mean age of 93 patients was 26.5 ± 15 years; 69.2% were female and 21% were considered autoimmune susceptible. The mean latency period from the last dose of HBVv and onset of symptoms was 43.2 days. Of note, 47% of patients continued with the immunization program despite experiencing adverse events. Manifestations that were commonly reported included neuro-psychiatric (70%), fatigue (42%) mucocutaneous (30%), musculoskeletal (59%) and gastrointestinal (50%) complaints. Elevated titers of autoantibodies were documented in 80% of sera tested. In this cohort 80/93 patients (86%), comprising 57/59 (96%) adults and 23/34 (68%) children, fulfilled the required criteria for ASIA.

CONCLUSIONS

Common clinical characteristics were observed among 93 patients diagnosed with immune-mediated conditions post-HBVv, suggesting a common denominator in these diseases. In addition, risk factors such as history of autoimmune diseases and the appearance of adverse event(s) during immunization may serve to predict the risk of post-immunization diseases. The ASIA criteria were found to be very useful among adults with post-vaccination events. The application of the ASIA criteria to pediatric populations requires further study.

http://www.ncbi.nlm.nih.gov/pubmed/22235045

"Manifestations that were commonly reported included neuro-psychiatric (70%), fatigue (42%) mucocutaneous (30%), musculoskeletal (59%) and gastrointestinal (50%) complaints."

Lupus • February 2012

Macrophagic myofasciitis: characterization and pathophysiology

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Abstract

Aluminium oxyhydroxide (alum), a nanocrystalline compound forming agglomerates, has been used in vaccines for its immunological adjuvant effect since 1927. Alum is the most commonly used adjuvant in human and veterinary vaccines, but the mechanisms by which it stimulates immune responses remain incompletely understood. Although generally well tolerated, alum may occasionally cause disabling health problems in presumably susceptible individuals. A small proportion of vaccinated people present with delayed onset of diffuse myalgia, chronic fatigue and cognitive dysfunction, and exhibit very long-term persistence of alum-loaded macrophages at the site of previous intramuscular (i.m.) immunization, forming a granulomatous lesion called macrophagic myofasciitis (MMF). Clinical symptoms associated with MMF are paradigmatic of the recently delineated 'autoimmune/inflammatory syndrome induced by adjuvants' (ASIA). The stereotyped cognitive dysfunction is reminiscent of cognitive deficits described in foundry workers exposed to inhaled Al particles. Alum safety concerns will largely depend on whether the compound remains localized at the site of injection or diffuses and accumulates in distant organs. Animal experiments indicate that biopersistent nanomaterials taken up by monocyte-lineage cells in tissues, such as fluorescent alum surrogates, can first translocate to draining lymph nodes, and thereafter circulate in blood within phagocytes and reach the spleen, and, eventually, slowly accumulate in the brain.

http://www.ncbi.nlm.nih.gov/pubmed/?term=22235051

"Animal experiments indicate that biopersistent nanomaterials taken up by monocyte-lineage cells in tissues, such as fluorescent alum surrogates, can first translocate to draining lymph nodes, and thereafter circulate in blood within phagocytes and reach the spleen, and, eventually, slowly accumulate in the brain."

Lupus • February 2012

Gulf War syndrome as a part of the autoimmune (autoinflammatory) syndrome induced by adjuvant (ASIA)

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Abstract

Gulf War syndrome (GWS) is a multi-symptom condition comprising a variety of signs and symptoms described in the literature, which not been fully resolved. The various symptoms of the condition include muscle fatigue and tiredness, malaise, myalgia, impaired cognition, ataxia, diarrhoea, bladder dysfunction, sweating disturbances, headaches, fever, arthralgia, skin rashes, and gastrointestinal and sleep disturbances. In addition, excessive chemical sensitivity and odour intolerance is reported. The aetiology of the condition is unclear, but many reviews and epidemiological analyses suggest association with pyridostigmine bromide (PB), certain vaccination regimes, a variety of possible chemical exposures, including smoke from oil-well fires or depleted uranium from shells, as well as physical and psychological stress. Recently, Shoenfeld et al. suggested that four conditions--siliconosis, macrophagic myofaciitis (MMF), GWS and post-vaccination phenomena--that share clinical and pathogenic resemblances, may be incorporated into common syndrome called ‘Autoimmune (Autoinflammatory) Syndrome induced by Adjuvants’ (ASIA). Symptoms and signs of the four conditions described by Shoenfeld et al. show that at least eight out of ten main symptoms are in correlation in all four conditions. Namely, myalgia, arthralgias, chronic fatigue, neurological cognitive impairment, gastrointestinal symptoms, respiratory symptoms, skin manifestations and appearance of autoantibodies. Regardless of the aetiology of GWS, be it exposure to environmental factors or chemical drugs, vaccinations or the adjuvants in them, GWS fits well with the definition of ASIA and is included as part of ‘Shoenfeld’s syndrome’.

http://www.ncbi.nlm.nih.gov/pubmed/?term=22235052

“Recently, Shoenfeld et al. suggested that four conditions—siliconosis, macrophagic myofaciitis (MMF), GWS and post-vaccination phenomena—that share clinical and pathogenic resemblances, may be incorporated into common syndrome called ‘Autoimmune (Autoinflammatory) Syndrome induced by Adjuvants’ (ASIA). Symptoms and signs of the four conditions described by Shoenfeld et al. show that at least eight out of ten main symptoms are in correlation in all four conditions. Namely, myalgia, arthralgias, chronic fatigue, neurological cognitive impairment, gastrointestinal symptoms, respiratory symptoms, skin manifestations and appearance of autoantibodies.”

Lupus • February 2012

Vaccine model of antiphospholipid syndrome induced by tetanus vaccine

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Abstract

Successful induction of antiphospholipid syndrome (APS) in two different non-autoimmune prone mouse strains, BALB/c and C57BL/6, was achieved by tetanus toxoid (TTd) hyperimmunization using different adjuvants (glycerol or aluminium hydroxide), and different adjuvant pretreatments (glycerol or Complete Freund's Adjuvant (CFA)). APS had different manifestations of reproductive pathology in BALB/c and C57BL/6 mice: fetal resorption (as a consequence of extreme T-cell activation obtained in the course of pretreatment), and lowering of fecundity (as a consequence of polyclonal B-cell stimulation), respectively. In BALB/c mice fetal resorption coincided with glycerol and CFA pretreatments, while in C57BL/6 mice lowering of fecundity was most obvious in CFA-pretreated mice immunized with TTd in aluminium hydroxide. Both molecular mimicry and polyclonal B-cell activation occur in APS induction, with molecular mimicry effects being dominant in BALB/c mice, and polyclonal cell activation being dominant in C57BL/6 mice. Confirmation of molecular mimicry effects, which in the condition of T-cell stimulation generated fetal resorptions in the BALB/c strain, was achieved by passive infusion of monoclonal antibody (MoAb) T-26 specific for TTd and anti-□(2)-glycoprotein I obtained after TTd hyperimunization. High polyclonal B-cell activation in C57BL/6 mice prevented fetal resorption but induced fecundity lowering, as was the case in passive administration of MoAb T-26 in this mouse strain. Passive infusion of anti-idiotypic MoAb Y7 into C57BL/6 mice induced fetal resorptions and confirmed the above suggestion on the protective role of polyclonal B-cell stimulation in fetal resorptions.

http://www.ncbi.nlm.nih.gov/pubmed/?term=22235053

"Successful induction of antiphospholipid syndrome (APS) in two different non-autoimmune prone mouse strains ... was achieved by tetanus toxoid (TTd) hyperimmunization using different adjuvants (glycerol or aluminium hydroxide), and different adjuvant pretreatments (glycerol or Complete Freund's Adjuvant (CFA)."

Lupus • February 2012

Oily adjuvants and autoimmunity: now time for reconsideration?

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Abstract

Immunologists have relied heavily on oil-based adjuvants to generate antibodies or induce auto-allergic responses in experimental animals. These are rarely used today for human vaccination because of their persistent irritancies and propensity to cause ulcers at sites of injection. However oily materials with adjuvant properties abound in our modern environment, both personal and extraneous. Their inadvertent impact as cryptotoxins may contribute to the rising incidence of auto-allergic diseases in recent times. Experimentally, the potential adjuvanticity of various oils, fats and other lipids can be evaluated by their ability (or otherwise) to induce auto-allergic disease(s) in rats and mice with, or even without, the addition of a mycobacterial immunostimulant. Genetic factors have been recognized that determine an animal's susceptibility or resistance to these oil-induced immunopathies. So it may be profitable to further characterize these factors, first in animals and then perhaps in human populations, to help find ways to enhance natural resistance to those adjuvant-active oils that may be widely distributed in the personal environment, notably mineral oil(s). (The six tables in this article summarize some relevant facts and a few conjectures.) A caveat: This review is restricted to the adjuvant properties of some oils in the personal environment. It does not cover the mechanisms of adjuvanticity.

http://www.ncbi.nlm.nih.gov/pubmed/?term=22235056

"Immunologists have relied heavily on oil-based adjuvants to generate antibodies or induce auto-allergic responses in experimental animals. These are rarely used today for human vaccination because of their persistent irritancies and propensity to cause ulcers at sites of injection. However oily materials with adjuvant properties abound in our modern environment, both personal and extraneous. Their inadvertent impact as cryptotoxins may contribute to the rising incidence of auto-allergic diseases in recent times."

Lupus • February 2012

Induction of the ‘ASIA’ syndrome in NZB/NZWF1 mice after injection of complete Freund’s adjuvant (CFA)

Author information

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Abstract

Adjuvants, commonly used in vaccines, may be responsible for inducing autoimmunity and autoimmune diseases, both in humans and mice. The so-called ‘ASIA’ (Autoimmune/inflammatory Syndrome Induced by Adjuvants) syndrome has been recently described, which is caused by the exposure to a component reproducing the effect of adjuvants. The aim of our study was to evaluate the effect of injection of complete Freund’s adjuvant (CFA) in NZB/NZWF1 mice, a lupus-prone murine model. We injected 10 NZB/NZWF1 mice with CFA/PBS and 10 with PBS, three times, 3 weeks apart, and followed-up until natural death. CFA-injected mice developed both anti-double-stranded DNA and proteinuria earlier and at higher levels than the control group. Proteinuria-free survival rate and survival rate were significantly lower in CFA-treated mice than in the control mice ($p = 0.002$ and $p = 0.001$, respectively). Histological analyses showed a more severe glomerulonephritis in CFA-injected mice compared with the control mice. In addition, lymphoid hyperplasia in spleen and lungs, myocarditis, and vasculitis were observed in the former, but not in the latter group. In conclusion, the injection of CFA in NZB/NZWF1 mice accelerated autoimmune manifestations resembling ‘ASIA’ syndrome in humans.

http://www.ncbi.nlm.nih.gov/pubmed/22235054

“... lymphoid hyperplasia in spleen and lungs, myocarditis, and vasculitis were observed in the former, but not in the latter group. In conclusion, the injection of Complete Freund’s Adjuvant (CFA) [a vaccine ingredient] in NZB/NZWF1 mice accelerated autoimmune manifestations resembling ‘ASIA’ syndrome in humans.”

[complete Freund’s adjuvant is used in some vaccines]

“The design and reporting of safety outcomes in MMR vaccine studies,
both pre- and post-marketing, are largely inadequate. The evidence of adverse events following immunisation
with the MMR vaccine cannot be separated from its role in preventing the target diseases.”

Cochrane Database Of Systematic Reviews • February 2012

Vaccines for measles, mumps and rubella in children

Author information

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Abstract

BACKGROUND

Mumps, measles and rubella (MMR) are serious diseases that can lead to potentially fatal illness, disability and death. However, public debate over the safety of the trivalent MMR vaccine and the resultant drop in vaccination coverage in several countries persists, despite its almost universal use and accepted effectiveness.

OBJECTIVES

To assess the effectiveness and adverse effects associated with the MMR vaccine in children up to 15 years of age.

SEARCH METHODS

For this update we searched the Cochrane Central Register of Controlled Trials (CENTRAL) (The Cochrane Library 2011, Issue 2), which includes the Cochrane Acute Respiratory Infections Group’s Specialised Register, PubMed (July 2004 to May week 2, 2011) and Embase.com (July 2004 to May 2011).

SELECTION CRITERIA

We used comparative prospective or retrospective trials assessing the effects of the MMR vaccine compared to placebo, do nothing or a combination of measles, mumps and rubella antigens on healthy individuals up to 15 years of age.

DATA COLLECTION AND ANALYSIS

Two review authors independently extracted data and assessed methodological quality of the included studies. One review author arbitrated in case of disagreement.

MAIN RESULTS

We included five randomised controlled trials (RCTs), one controlled clinical trial (CCT), 27 cohort studies, 17 case-control studies, five time-series trials, one case cross-over trial, two ecological studies, six self controlled case series studies involving in all about 14,700,000 children and assessing effectiveness and safety of MMR vaccine. Based on the available evidence, one MMR vaccine dose is at least 95% effective in preventing clinical measles and 92% effective in preventing secondary cases among household contacts.Effectiveness of at least one dose of MMR in preventing clinical mumps in children is estimated to be between 69% and 81% for the vaccine prepared with Jeryl Lynn mumps strain and between 70% and 75% for the vaccine containing the Urabe strain. Vaccination with MMR containing the Urabe strain has demonstrated to be 73% effective in preventing secondary mumps cases. Effectiveness of Jeryl Lynn containing MMR in preventing laboratory-confirmed mumps cases in children and adolescents was estimated to be between 64% to 66% for one dose and 83% to 88% for two vaccine doses. We did not identify any studies assessing the effectiveness of MMR in preventing rubella.The highest risk of association with aseptic meningitis was observed within the third week after immunisation with Urabe-containing MMR (risk ratio (RR) 14.28; 95% confidence interval (CI) from 7.93 to 25.71) and within the third (RR 22.5; 95% CI 11.8 to 42.9) or fifth (RR 15.6; 95% CI 10.3 to 24.2) weeks after immunisation with the vaccine prepared with the Leningrad-Zagreb strain. A significant risk of association with febrile seizures and MMR exposure during the two previous weeks (RR 1.10; 95% CI 1.05 to 1.15) was assessed in one large person-time cohort study involving 537,171 children aged between three months and five year of age. Increased risk of febrile seizure has also been observed in children aged between 12 to 23 months (relative incidence (RI) 4.09; 95% CI 3.1 to 5.33) and children aged 12 to 35 months (RI 5.68; 95% CI 2.31 to 13.97) within six to 11 days after exposure to MMR vaccine. An increased risk of thrombocytopenic purpura within six weeks after MMR immunisation in children aged 12 to 23 months was assessed in one case-control study (RR 6.3; 95% CI 1.3 to 30.1) and in one small self controlled case series (incidence rate ratio (IRR) 5.38; 95% CI 2.72 to 10.62). Increased risk of thrombocytopenic purpura within six weeks after MMR exposure was also assessed in one other case-control study involving 2311 children and adolescents between one month and 18 years (odds ratio (OR) 2.4; 95% CI 1.2 to 4.7). Exposure to the MMR vaccine was unlikely to be associated with autism, asthma, leukaemia, hay fever, type 1 diabetes, gait disturbance, Crohn’s disease, demyelinating diseases, bacterial or viral infections.

AUTHORS’ CONCLUSIONS

The design and reporting of safety outcomes in MMR vaccine studies, both pre- and post-marketing, are largely inadequate. The evidence of adverse events following immunisation with the MMR vaccine cannot be separated from its role in preventing the target diseases.

http://www.ncbi.nlm.nih.gov/pubmed/22336803

“Herein, we report 10 cases of previously healthy subjects who developed GCA/PMR within 3 months of influenza vaccination (Inf-V). A Medline search uncovered an additional 11 isolated cases of GCA/PMR occurring after influenza vaccination Inf-V.”

[GCA stands for giant cell arteritis and PMR stands for polymyalgia rheumatica]

Lupus • February 2012

Giant cell arteritis and polymyalgia rheumatica after influenza vaccination: report of 10 cases and review of the literature

Author information

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Abstract

Giant cell arteritis (GCA) and polymyalgia rheumatica (PMR) are inflammatory rheumatic diseases common in people over the age of 50 years. Herein, we report 10 cases of previously healthy subjects who developed GCA/PMR within 3 months of influenza vaccination (Inf-V). A Medline search uncovered additional 11 isolated cases of GCA/PMR occurring after Inf-V. We discuss the role of individual susceptibility, the potential function of immune adjuvants as triggers of autoimmunity post-vaccination, and the correlation of our observation with the ‘ASIA’ syndrome, i.e. autoimmune/inflammatory syndrome induced by adjuvants and including post-vaccination phenomena.

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Lupus • February 2012

The spectrum of ASIA: ‘Autoimmune (Auto-inflammatory) Syndrome induced by Adjuvants’

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Abstract

Physicians are often puzzled by enigmatic medical conditions or the abrupt appearance of an immune-mediated disease. Such a story was recently presented to us by a young Sheikh. A Saudi Sheikh, who suffered at the age of 27 from joints pains, rash and serological evidence of anti-Ro antibodies, was diagnosed with probable systemic lupus erythematosus (SLE) at that time. He was treated with Plaquenil for a year, but as no signs of SLE were apparent, treatment was stopped and he remained disease free for the next 12 years. At the age of 39 years, 2 weeks after immunization with the flu vaccine, his disease reemerged. This time he presented with severe arthritis and pericarditis, which required treatment with high doses of steroids.

This patient’s story illustrates the acceleration of an autoimmune or immune-mediated condition following exposure to external stimuli. During the past year a new syndrome was introduced and termed ASIA, ‘Autoimmune (Auto-inflammatory) Syndrome induced by Adjuvants’.1 This syndrome assembles a spectrum of immune-mediated diseases triggered by an adjuvant stimulus.2 – 4 The use of medical adjuvants has become common practice and substances such as aluminum adjuvant are added to most human and animal vaccines, while the adjuvant silicone is extensively used for breast implants and cosmetic procedures. Furthermore, ‘hidden adjuvants’ such as infectious material or house molds have also been associated with different immune mediated conditions.1,5 The adjuvant effect has been recognized for years, and is broadly utilized to enhance desired antigen-specific immune responses.6 This effect is accomplished via mechanisms that impinge on both the innate and adaptive immune systems.6 – 9 Formerly, adjuvants were thought to pose little or no independent threat. Alas, studies of animal models and humans demonstrated the ability of some of them to inflict autoimmunity and immune-mediated diseases by themselves.2,10,11 Intriguingly, although exposure is common, adjuvant disease is relatively rare. It has been suggested that for a clinically overt adjuvant disease additional risk factors are required such as genetic susceptibilities or the co-exposure to other environmental factors.1

http://lup.sagepub.com/content/21/2/118.full

This special issue of Lupus is dedicated to ASIA and contains diverse articles from different geographical areas which provide a broad view of the clinical manifestations as well as the mechanisms related to the adjuvant effect.

Autism Research • April 2012

Disordered porphyrin metabolism: a potential biological marker for autism risk assessment

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Abstract

Autism (AUT) is a complex neurodevelopmental disorder that, together with Asperger's syndrome and Pervasive Developmental Disorder-Not Otherwise Specified (PDD-NOS), comprises the expanded classification of autistic spectrum disorder (ASD). The heterogeneity of ASD underlies the need to identify biomarkers or clinical features that can be employed to identify meaningful subtypes of ASD, define specific etiologies, and inform intervention and treatment options. Previous studies have shown that disordered porphyrin metabolism, manifested principally as significantly elevated urinary concentrations of pentacarboxyl (penta) and coproporphyrins, is commonly observed among some children with ASD. Here, we extend these observations by specifically evaluating penta and coproporphyrins as biological indicators of ASD among 76 male children comprising 30 with validated AUT, 14 with PDD-NOS, and 32 neurotypical (NT) controls. ASD children (AUT and PDD-NOS) had higher mean urinary penta ($P < 0.006$) and copro ($P < 0.006$) concentrations compared with same-aged NT children, each characterized by a number of extreme values. Using Receiver Operating Characteristic curve analysis, we evaluated the sensitivity and specificity of penta, copro, and their combined Z-scores in ASD detection. The penta sensitivity was 30% for AUT and 36% for PDD-NOS, with 94% specificity. The copro sensitivity was 33% and 14%, respectively, with 94% specificity. The combined Z-score measure had 33% and 21% sensitivity for AUT and PDD-NOS, respectively, with 100% specificity. These findings demonstrate that porphyrin measures are strong predictors of both AUT and PDD-NOS, and support the potential clinical utility of urinary porphyrin measures for identifying a subgroup of ASD subjects in whom disordered porphyrin metabolism may be a salient characteristic.

Full Report

http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3329579/

"These findings demonstrate that porphyrin measures are strong predictors of both AUT and PDD-NOS, and support the potential clinical utility of urinary porphyrin measures for identifying a subgroup of ASD subjects in whom disordered porphyrin metabolism may be a salient characteristic."

"Given all this, supporting the 'one-size fits all' vaccination program is neither reasonable nor ethical."

Vaccine • March 2012

Vaccination: Why the 'one size fits all' vaccination argument does not fit all!

By Lucija Tomljenovic, PhD

Imagine the next time you went to Walmart, Target or Sears that due to scientific research and government regulation your retailer only stocked one size of clothing – regardless of whether you are male or female, child or adult, and with no sensitivity to your cultural or ethnic background. Would you be happy? Would you accept it? Would you wear the clothes? The answer is clearly NO! What if the clothing manufacturer used a highly toxic dye in the clothing fabric and knew this dye could cause serious skin reactions in some people but they failed to declare this? Would that be acceptable to you? Yet that is exactly what the current approach to vaccines worldwide is – one size fits all and some "collateral damage" is acceptable for the sake of the alleged "greater good".

In the case of vaccines, the good news is that even those in the scientific community who are strong proponents of vaccinations, are coming to question the scientific legitimacy of "one-size fits all" vaccination practices. [1]

For example, Gregory Poland MD, Editor in Chief of the journal Vaccine and co-author of "The age-old struggle against the anti-vaccinationists" [2] and colleagues rightly ask whether:

...with the advances coming from the new biology of the 2st century. It is time to consider how might new genetic and molecular biology information inform vaccinology practices of the future? [1]

In light of this question Poland et al. conclude that "one-size fits all" approach for all vaccines and all persons should be abandoned. According to Poland, this conclusion applies to both vaccine efficacy, as well as safety.[1]

Regarding the safety, the widely held view that serious vaccine-related adverse reactions are rare needs revision, as current worldwide vaccination policies indeed operate on a "one-size fits all" assumption. This assumption persists despite the fact that historically, vaccine trials routinely exclude vulnerable individuals with a variety of pre-existing conditions (i.e., premature birth, personal or family history of developmental delay or neurologic disorders including epilepsy/seizures, hypersensitivity to vaccine constituents etc...). [3-7]

Because of such selection bias at the very base level of research, the occurrence of serious adverse reactions resulting from vaccinations is considerably underestimated.

Worse yet, such an outcome should be of concern to all who vaccinate in view of the documented scientific evidence describing cases of permanent neurodevelopmental disabilities and deaths following vaccination in children with underlying genetic/mitochondrial disorders and other susceptibilities, such as a family history of auto-immune diseases (i.e., asthma, diabetes, multiple sclerosis, etc...), allergies, or a compromised immune system. [8-10]

Poland's along with the other scientists' current data therefore have far broader implications for understanding vaccines, not only in terms of efficacy and the desired immune response, but also in terms of safety for those susceptible to adverse health outcomes and excluded from clinical trials --- but not from receipt!

Vulnerable individuals, both male and female, will neither have the same antibody response nor the same level of tolerance to serious adverse reactions as non-vulnerable individuals. [1, 11]

Before one considers vaccinating their child according to the current 'one size fits all' vaccination program, one should think about the fact that we all have a different genetic history, personal health history, current health status, nutritional status and exposures to level of environmental toxins – all of which may impact how an individual, or their child will respond to a vaccine. Given all this, supporting the 'one-size fits all' vaccination program is neither reasonable nor ethical.

References:

1. Poland, G.A., I.G. Ovsyannikova, and R.M. Jacobson, Vaccine immunogenetics: bedside to bench to population. Vaccine, 2008. 26(49): p. 6183-8.
2. Poland, G.A. and R.M. Jacobson, The age-old struggle against the antivaccinationists. N Engl J Med, 2011. 364(2): p. 97-9.
3. Kovel, A., et al., Safety and immunogenicity of acellular diphtheria-tetanus-pertussis and Haemophilus conjugate vaccines given in combination or at separate injection sites. J Pediatr, 1992. 120(1): p. 84-7.
4. Kaplan, S.L., et al., Immunogenicity and safety of Haemophilus influenzae type b-tetanus protein conjugate vaccine alone or mixed with diphtheria-tetanus-pertussis vaccine in infants. J Pediatr, 1994. 124(2): p. 323-7.
5. Li, G., et al., Safety and immunogenicity of a diphtheria, tetanus, acellular pertussis and Haemophilus influenzae Type b combination vaccine compared with separate administration of licensed equivalent vaccines in Chinese infants and toddlers for primary and booster immunization. Vaccine, 2010. 28(25): p. 4215-23.
6. Shinefield, H., et al., Evaluation of a quadrivalent measles, mumps, rubella and varicella vaccine in healthy children. Pediatr Infect Dis J, 2005. 24(8): p. 665-9.
7. Velu, V., et al., Comparative efficacy of two dosages of recombinant hepatitis B vaccine in healthy adolescents in India. Pediatr Infect Dis J, 2007. 26(11): p. 1038-41.
8. Poling, J.S., et al., Developmental regression and mitochondrial dysfunction in a child with autism. J Child Neurol, 2006. 21(2): p. 170-2.
9.Yang, Y., et al., Acute metabolic crisis induced by vaccination in seven Chinese patients. Pediatr Neurol, 2006. 35(2): p. 114-8.
10. Ottaviani, G., A.M. Lavezzi, and L. Matturri, Sudden infant death syndrome (SIDS) shortly after hexavalent vaccination: another pathology in suspected SIDS? Virchows Arch, 2006. 448(1): p. 100-4.
11. Thomas, C. and M. Moridani, Interindividual variations in the efficacy and toxicity of vaccines. Toxicology, 2009. 278(2): p. 204-10.

http://www.ncbi.nlm.nih.gov/pubmed/22119595

"103 vaccine adjuvants have been curated in Vaxjo.
Among these adjuvants, 98 have been used in 384 vaccines stored in VIOLIN against over 81 pathogens, cancers, or allergies. All these vaccine adjuvants are categorized and analyzed based on adjuvant types, pathogens used, and vaccine types."

Journal Of Biomedicine & Biotechnology • March 2012

Vaxjo: a web-based vaccine adjuvant database and its application for analysis of vaccine adjuvants and their uses in vaccine development

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Abstract

Vaccine adjuvants are compounds that enhance host immune responses to co-administered antigens in vaccines. Vaxjo is a web-based central database and analysis system that curates, stores, and analyzes vaccine adjuvants and their usages in vaccine development. Basic information of a vaccine adjuvant stored in Vaxjo includes adjuvant name, components, structure, appearance, storage, preparation, function, safety, and vaccines that use this adjuvant. Reliable references are curated and cited. Bioinformatics scripts are developed and used to link vaccine adjuvants to different adjuvanted vaccines stored in the general VIOLIN vaccine database. Presently, 103 vaccine adjuvants have been curated in Vaxjo. Among these adjuvants, 98 have been used in 384 vaccines stored in VIOLIN against over 81 pathogens, cancers, or allergies. All these vaccine adjuvants are categorized and analyzed based on adjuvant types, pathogens used, and vaccine types. As a use case study of vaccine adjuvants in infectious disease vaccines, the adjuvants used in Brucella vaccines are specifically analyzed. A user-friendly web query and visualization interface is developed for interactive vaccine adjuvant search. To support data exchange, the information of vaccine adjuvants is stored in the Vaccine Ontology (VO) in the Web Ontology Language (OWL) format.

http://www.ncbi.nlm.nih.gov/pubmed/?term=22505817

PLoS One • March 2012

AS03 adjuvanted AH1N1 vaccine associated with an abrupt increase in the incidence of childhood narcolepsy in Finland

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Abstract

BACKGROUND

Narcolepsy is a chronic sleep disorder with strong genetic predisposition causing excessive daytime sleepiness and cataplexy. A sudden increase in childhood narcolepsy was observed in Finland soon after pandemic influenza epidemic and vaccination with ASO3-adjuvanted Pandemrix. No increase was observed in other age groups.

METHODS

Retrospective cohort study. From January 1, 2009 to December 31, 2010 we retrospectively followed the cohort of all children living in Finland and born from January 1991 through December 2005. Vaccination data of the whole population was obtained from primary health care databases. All new cases with assigned ICD-10 code of narcolepsy were identified and the medical records reviewed by two experts to classify the diagnosis of narcolepsy according to the Brighton collaboration criteria. Onset of narcolepsy was defined as the first documented contact to health care because of excessive daytime sleepiness. The primary follow-up period was restricted to August 15, 2010, the day before media attention on post-vaccination narcolepsy started.

FINDINGS

Vaccination coverage in the cohort was 75%. Of the 67 confirmed cases of narcolepsy, 46 vaccinated and 7 unvaccinated were included in the primary analysis. The incidence of narcolepsy was 9.0 in the vaccinated as compared to 0.7/100,000 person years in the unvaccinated individuals, the rate ratio being 12.7 (95% confidence interval 6.1-30.8). The vaccine-attributable risk of developing narcolepsy was 1:16,000 vaccinated 4 to 19-year-olds (95% confidence interval 1:13,000-1:21,000).

CONCLUSIONS

Pandemrix vaccine contributed to the onset of narcolepsy among those 4 to 19 years old during the pandemic influenza in 2009-2010 in Finland. Further studies are needed to determine whether this observation exists in other populations and to elucidate potential underlying immunological mechanism. The role of the adjuvant in particular warrants further research before drawing conclusions about the use of adjuvanted pandemic vaccines in the future.

http://www.ncbi.nlm.nih.gov/pubmed/22470453

Full Report: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3314666/

“Pandemrix vaccine

contributed to the onset of narcolepsy

among those 4 to 19 years old during the

pandemic influenza in 2009-2010 in Finland.

The role of the adjuvant in particular warrants

further research before drawing conclusions about

the use of adjuvanted pandemic vaccines in the future.”

Clinical Reviews In Allergy & Immunology • April 2012

Guillain-Barré syndrome a classical autoimmune disease triggered by infection or vaccination

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Abstract

Guillain-Barré syndrome (GBS) is a rare autoimmune disorder, the incidence of which is estimated to be 0.6-4/100,000 person/year worldwide. Often, GBS occurs a few days or weeks after the patient has had symptoms of a respiratory or gastrointestinal microbial infection. The disorder is sub-acute developing over the course of hours or days up to 3 to 4 weeks. About a third of all cases of Guillain-Barré syndrome are preceded by Campylobacter jejuni infection. C. jejuni strains isolated from GBS patients have a lipooligosaccharide (LOS) with a GM1-like structure. Molecular mimicry between LOS and the peripheral nerves as a cause of GBS was demonstrated in animal models of human GBS. Following the "swine flu" virus vaccine program in the USA in 1976, an increase in incidence of GBS was observed and the calculated relative risk was 6.2. Later studies have found that influenza vaccines contained structures that can induce anti-GM1 (ganglioside) antibodies after inoculation into mice. More recent information has suggested that the occurrence of GBS after currently used influenza and other vaccines is rare. GBS involves genetic and environmental factors, may be triggered by infections or vaccinations, and predisposition can be predicted by analyzing some of these factors.

http://www.ncbi.nlm.nih.gov/pubmed/20890797

" Guillain-Barré syndrome involves genetic and environmental factors, may be triggered by infections or vaccinations, and predisposition can be predicted by analyzing some of these factors."

International Journal Of Cosmetic Science • April 2012

In vitro induction of apoptosis, necrosis and genotoxicity by cosmetic preservatives: application of flow cytometry as a complementary analysis by NRU

Author information

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Abstract

Preservatives are used in cosmetics to prevent microbial contamination; however, some preservatives are not free of allergenic and cytotoxic potential. Allergenicity and cytotoxicity potential values are major aspects of preservative safety, which determine limitations and maximum concentration dose in a cosmetic product. The purpose of this study was to investigate and compare the in vitro apoptosis, necrosis and genotoxicity-inducing potential of five different types of preservatives: Phenoxyethanol (PE), Propylparaben (PP), Methylparaben (MP), Benzyl Alcohol (BA) and Ethylhexyl Glycerine (EG). In vitro experiments were carried out on human dermal fibroblasts by a quantitative flow cytometry method, using specific cell markers (Annexin V, Propidium Iodide and H2AX). We compared the resulting cell viability by means of neutral red uptake (NRU) and established the IC(50) . Our results showed that PE, PP, MP and BA have similar cytotoxic mechanisms (high apoptosis and necrosis levels only at the test concentration of 1%), whereas EG showed only an apoptosis pathway. For genotoxicity, both parabens yielded the highest values. Results obtained by flow cytometry for necrosis were comparable to those produced by NRU; however, NRU does not distinguish apoptosis from necrosis. We propose that flow cytometry is a more sophisticated methodology for understanding the cytotoxic mechanisms of cosmetic preservatives and can be used to complement the NRU.

http://www.ncbi.nlm.nih.gov/pubmed/?term=22118339

“Our results showed that Phenoxyethanol [a vaccine ingredient] ... have similar cytotoxic mechanisms (high apoptosis and necrosis levels only at the test concentration of 1%) ...”

Dermatitis • May 2012

Hypersensitivity reactions to vaccine constituents: a case series and review of the literature

Author information

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Abstract

Vaccines are composed of immunogens, preservatives, adjuvants, antibiotics, and manufacturing by-products. Components of vaccines may rarely elicit adverse reactions in susceptible individuals, thus raising concerns regarding vaccine safety. In this report, we add to the medical literature 3 cases of cutaneous delayed-type hypersensitivity to the vaccine preservative aluminum. We provide a review of major constituents in vaccines that have elicited immediate-type or delayed-type hypersensitivity reactions and describe their clinical manifestations. We include a table of the Food and Drug Administration-approved vaccines, which lists the quantities of major components including ovalbumin (egg protein), gelatin, aluminum, neomycin, 2-phenoxyethanol, thimerosal, and formaldehyde. Our goals were to inform physicians on the variety of hypersensitivity reactions to common vaccines and to provide information on the choice of vaccines in patients with suspected hypersensitivity.

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“Our goals were to inform physicians on the variety of hypersensitivity reactions to common vaccines and to provide information on the choice of vaccines in patients with suspected hypersensitivity.”

BMJ Case Report • May 2012

Hypersensitivity reaction to human papillomavirus vaccine due to polysorbate 80

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Abstract

A 17-year-old girl reported generalised urticaria, eyelid angioedema, rhino-conjunctivitis, dyspnoea and wheezing 1 h after third intramuscular administration of quadrivalent human papilloma virus vaccine (Gardasil). She was treated with antihistamine, and corticosteroids with prompt relief of rhinitis and dyspnoea, while urticaria and angioedema lasted 24 h. Intradermal test with Gardasil, which contains polysorbate 80 (PS80), resulted positive, while skin tests with the bivalent vaccine were negative. Prick test performed with PS80 resulted positive in the patient and negative in ten healthy controls. The CD203 basophil activation test result was negative for PS80 at all the tested dilutions and specific IgE was not found. As flu vaccine was recommended, the authors skin tested two flu vaccine, one containing PS80 (Fluarix, GSK), which resulted positive and another flu vaccine with no adjuvant or preservative (Vaxigrip, Sanofi Pasteur MSD), which gave negative results. The patient then received Vaxigrip without adverse reactions.

Full Report:

http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3351639/

“... the authors skin tested two flu vaccine, one containing PS80 (Fluarix, GSK), which resulted positive and another flu vaccine with no adjuvant or preservative (Vaxigrip, Sanofi Pasteur MSD), which gave negative results.”

"With herd immunity to whooping cough,

DTP is associated with higher mortality for girls."

BMJ Open • May 2012

Testing the hypothesis that diphtheria–tetanus–pertussis vaccine has negative non-specific and sex-differential effects on child survival in high-mortality countries

Author Information

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Abstract

Background

Measles vaccines (MV) have sex-differential effects on mortality not explained by protection against measles infection.

Objective

The authors examined whether whole-cell diphtheria–tetanus–pertussis (DTP) vaccine has sex-differential and non-specific effects.

Data sources and eligibility

Following previous reviews and a new search, the effect of DTP on mortality up to the next vaccination was assessed in all studies where DTP was given after BCG or DTP was given after MV and there was prospective follow-up after ascertainment of vaccination status.

Setting

High-mortality countries in Africa and Asia.

Methods

The initial observation of negative effect of DTP generated six hypotheses, which were examined in all available studies and two randomised trials reducing the time of exposure to DTP.

Main outcome

Consistency between studies.

Results

In the first study, DTP had negative effects on survival in contrast to the beneficial effects of BCG and MV. This pattern was repeated in the six other studies available. Second, the two 'natural experiments' found significantly higher mortality for DTP-vaccinated compared with DTP-unvaccinated children. Third, the female–male mortality ratio was increased after DTP in all nine studies; in contrast, the ratio was decreased after BCG and MV in all studies. Fourth, the increased female mortality associated with high-titre measles vaccine was found only among children who had received DTP after high-titre measles vaccine. Fifth, in six randomised trials of early MV, female but not male mortality was increased if DTP was likely to be given after MV. Sixth, the mortality rate declined markedly for girls but not for boys when DTP-vaccinated children received MV. The authors reduced exposure to DTP as most recent vaccination by administering a live vaccine (MV and BCG) shortly after DTP. Both trials reduced child mortality.

Conclusions

These observations are incompatible with DTP merely protecting against the targeted diseases. With herd immunity to whooping cough, DTP is associated with higher mortality for girls. Randomised studies of DTP are warranted to measure the true impact on survival.

Full Report

http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3364456/

Apoptosis • May 2012

Hepatitis B vaccine induces apoptotic death in Hepa1-6 cells

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Abstract

Vaccines can have adverse side-effects, and these are predominantly associated with the inclusion of chemical additives such as aluminum hydroxide adjuvant. The objective of this study was to establish an in vitro model system amenable to mechanistic investigations of cytotoxicity induced by hepatitis B vaccine, and to investigate the mechanisms of vaccine-induced cell death. The mouse liver hepatoma cell line Hepa1-6 was treated with two doses of adjuvanted (aluminium hydroxide) hepatitis B vaccine (0.5 and 1 µg protein per ml) and cell integrity was measured after 24, 48 and 72 h. Hepatitis B vaccine exposure increased cell apoptosis as detected by flow cytometry and TUNEL assay. Vaccine exposure was accompanied by significant increases in the levels of activated caspase 3, a key effector caspase in the apoptosis cascade. Early transcriptional events were detected by qRT-PCR. We report that hepatitis B vaccine exposure resulted in significant upregulation of the key genes encoding caspase 7, caspase 9, Inhibitor caspase-activated DNase (ICAD), Rho-associated coiled-coil containing protein kinase 1 (ROCK-1), and Apoptotic protease activating factor 1 (Apaf-1). Upregulation of cleaved caspase 3,7 were detected by western blot in addition to Apaf-1 and caspase 9 expressions argues that cell death takes place via the intrinsic apoptotic pathway in which release of cytochrome c from the mitochondria triggers the assembly of a caspase activation complex. We conclude that exposure of Hepa1-6 cells to a low dose of adjuvanted hepatitis B vaccine leads to loss of mitochondrial integrity, apoptosis induction, and cell death, apoptosis effect was observed also in C2C12 mouse myoblast cell line after treated with low dose of vaccine (0.3, 0.1, 0.05 µg/ml). In addition In vivo apoptotic effect of hepatitis B vaccine was observed in mouse liver.

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"We conclude that exposure of Hepa1-6 cells to a low dose of adjuvanted hepatitis B vaccine leads to loss of mitochondrial integrity, apoptosis induction, and cell death, apoptosis effect was observed also in C2C12 mouse myoblast cell line after treated with low dose of vaccine (0.3, 0.1, 0.05 µg/ml). In addition In vivo apoptotic effect of hepatitis B vaccine was observed in mouse liver."

“We will discuss the possible mechanisms which pertain to ASIA (Shoenfeld syndrome).”

Lupus • June 2012

When APS (Hughes syndrome) met the autoimmune/inflammatory syndrome induced by adjuvants (ASIA)

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Abstract

Vaccination of healthy individuals is the most effective approach to protect the public from infections and prevent the spread of many infectious diseases all over the globe. Licensed vaccines are mostly safe, but in rare cases they may be associated with humoral response to self-antigens due to molecular mimicry, epitope spread, bystander activation or polyclonal triggering. Moreover, the clinical picture of autoimmune conditions following post-vaccination is rarer. Nevertheless, anecdotal case reports on the flare of autoimmune response with clinical manifestations were reported. Herein, we discuss this topic in relation to post-vaccination-induced antiphospholipid antibodies following tetanus toxoid vaccine, HBV and influenza associated in rare cases with antiphospholipid syndrome clinical manifestations. We will discuss the possible mechanisms which pertain to ASIA (Shoenfeld syndrome). Therefore, these all strengthen the importance of ASIA and should be kept in mind during clinical work and research.

Full Report

http://lup.sagepub.com/content/21/7/711.long

Environmental Health Perspectives • June 2012

Neurotoxic metal coexposures and neurodevelopment

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Abstract

Claus Henn et al. (2012) addressed a “real world scenario” of exposure to multiple neurotoxic metals in their unique and interesting study. They investigated manganese–lead coexposure and its association with neurodevelopmental deficiencies in Mexican children. Their rationale was that neurodevelopmental deficiencies of both metals together could be more severe than expected based on effects of exposure to each metal alone. Indeed, they observed a synergism between manganese and lead. Given the early age of the subjects (12 and 24 months of age), I suggest that some confounders not included in their model deserve consideration in regard to this study.

Claus Henn et al. (2012) collected information on duration of breast-feeding, but it seems that in their statistical analyses, they adjusted only for sex, gestational age, hemoglobin, maternal IQ (intelligence quotient), and maternal education. Other confounders, such as thimerosal (a compound containing ethylmercury that is used as a preservative in some vaccines) and breast-feeding, may influence neurodevelopment outcomes. In countries such as Mexico, children 12–24 months of age may be immunized with thimerosal-containing vaccines (TCVs) (WHO 2011). Because of opposite effects on the central nervous system, the combination of breast-feeding and ethylmercury may influence neurodevelopmental outcomes. Kramer et al. (2008) showed that children who were exclusively breast-fed had improved cognitive development. Indeed, Kostial et al. (1978) demonstrated that infant rats fed cow’s milk diets absorbed more lead and manganese, which are associated with a higher relative retention of mercury in the brain.

Blood levels of lead and manganese are indicators of ongoing exposure; however, ethylmercury has a short half-life and thus is unlikely to be concurrently measured in blood (Dórea et al. 2011). Nevertheless we can ascertain exposure from vaccination cards (Dórea et al. 2012; Marques et al. 2009). Following participants in the National Immunization Program of Mexico, the amount of ethylmercury from routine immunizations against hepatitis B (three doses), DTP (diphtheria, tetanus, and pertussis, three doses), and influenza can be estimated from records on vaccination cards. Additionally, during pregnancy, Mexican mothers may receive tetanus toxoid (TT) vaccines and other products, such as anti-RhoD immune globulins (given to Rh-negative mothers) that may contain thimerosal (Marques et al. 2009). These sources of prenatal and postnatal ethylmercury exposure should be considered significant sources of an additional neurotoxic coexposure—organic mercury.

Claus Henn et al. (2012) realized that information on the association of neurodevelopment and coexposure to multiple chemicals is limited; the scientific literature is even more scarce for the specific exposure to small amounts of ethylmercury derived from TCVs (Oken and Bellinger 2008), which are largely used in nonindustrialized countries. However, recent work has suggested that when studies with young children are properly adjusted for exposure to TCVs, subtle neurodevelopmental effects can be demonstrated (Dórea et al. 2012; Marques et al. 2009; Mrozek-Budzyn 2011a, 2011b). Therefore, the potential for interaction of ethylmercury, manganese, and lead provides an opportunity to expand our knowledge.

Factors related to maternal neurotoxic exposure and neurodevelopment (e.g., breast-feeding) are significant in studies of children’s exposure to ethylmercury (Marques et al. 2009). The study design used by Claus Henn et al. (2012) could provide further information on this timely issue and also provide direction for future studies of contaminants and confounders that affect neurodevelopment.

“Claus Henn et al. (2012) realized that information on the association of neurodevelopment and coexposure to multiple chemicals is limited; the scientific literature is even more scarce for the specific exposure to small amounts of ethyl mercury derived from Thimerosal containing vaccines, which are largely used in nonindustrialized countries.”

Full Report

http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3385458/

Biometals • June 2012

A case of multiple sclerosis improvement following removal of heavy metal intoxication: lessons learnt from Matteo's case

Author information

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Abstract

Multiple sclerosis (MS) is a chronic progressive disease of the central nervous system (CNS) provoking disability and neurological symptoms. The exact causes of MS are unknown, even if it is characterized by focal inflammatory lesions in CNS accompanied by autoimmune reaction against myelin. Indeed, many drugs able to modulate the immune response of patients have been used to treat MS. More recently, toxic metals have been proposed as possible causes of neurodegenerative diseases. The objective of this study is to investigate in vivo the impact of heavy metal intoxication in MS progression. We studied the case of a patient affected by MS, who has been unsuccessfully treated for some years with current therapies. We examined his levels of toxic heavy metals in the urine, following intravenous "challenge" with the chelating agent calcium disodium ethylene diamine tetraacetic acid (EDTA).The patient displayed elevated levels of aluminium, lead and mercury in the urine. Indeed, he was subjected to treatment with EDTA twice a month. Under treatment, the patient revealed in time improved symptoms suggestive of MS remission. The clinical data correlated with the reduction of heavy metal levels in the urine to normal range values. Our case report suggests that levels of toxic metals can be tested in patients affected by neurodegenerative diseases as MS.

http://www.ncbi.nlm.nih.gov/pubmed/22438029/

"More recently, toxic metals have been proposed as possible causes of neurodegenerative diseases."

“Being protected against influenza, trivalent inactivated influenza vaccine recipients may lack temporary non-specific immunity that protected against other respiratory viruses.”

Clinical Infectious Disease • June 2012

Increased risk of noninfluenza respiratory virus infections associated with receipt of inactivated influenza vaccine

Author information

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Abstract

We randomized 115 children to trivalent inactivated influenza vaccine (TIV) or placebo. Over the following 9 months, TIV recipients had an increased risk of virologically-confirmed non-influenza infections (relative risk: 4.40; 95% confidence interval: 1.31-14.8). Being protected against influenza, TIV recipients may lack temporary non-specific immunity that protected against other respiratory viruses.

Full Report

http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3404712/

Zhongguo Zhong Yao Za Zhi
Chinese Journal Of Chinese Materia Medica • July 2012

Comparative study on pseudoanaphylactoid reactions induced by medicinal tween 80 and injectable tween 80

Author information

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Abstract

OBJECTIVE

To investigate the safety of different level of tween 80 by comparing the degree of pseudoanaphylactoid reactions (PR) induced by medicinal tween 80 and injectable tween 80.

METHOD

The analysis of vascular permeability of the mice ears: ICR mouse were divided into different test groups, the mice were intravenously injected with solutions of medicinal tween 80 and injectable tween 80 with 0.2%, 1% and 5% concentration, positive control Compound 48/80 and 5% glucose injection. All test substances were mixed with 0.4% Evans blue. The reaction and vascular permeability of the ears were observed and measured 30 min after injection. The analysis of vascular permeability of the rat's skin: the rats were intravenous injected with 0. 6% Evans blue normal saline solution first, 10 minutes later, the same substances were intradermal administrated into the back of rats. The rats were sacrificed and the diameter of locus ceruleus and the content of Evans blue leak out were measured 20 min after injection.

RESULT

Medicinal tween 80 and injectable tween 80 with 5% concentration caused obvious vascular hyper permeability in ICR mice, but the degree of vascular hyperpermeability caused by injectable tween 80 was lighter than by medicinal tween 80. Other tween 80 didn't cause obvious vascular hyper permeability in the ears of mouse. The solution of different concentration of tween 80 caused obvious locus ceruleus reaction in rat's back. As for the content Evans blue leak out, there was no statistical significance between each group except positive control Compound 48/80 group.

CONCLUSION

Tween 80 can cause obvious vascular hyper permeability and the effect is dose dependent, which indicated that tween 80 can cause PR. On the other hand, injectable tween 80 is more security than medicinal tween 80, the dosage of tween 80 should be still controlled strictly so that to decrease the incidence of PR.

http://www.ncbi.nlm.nih.gov/pubmed/23019864

"Tween 80 can cause obvious vascular hyper permeability and the effect is dose dependent, which indicated that Tween 80 can cause PR [pseudoanaphylactoid reactions].

Current Opinion In Rheumatology • July 2012

Infections and vaccines in the etiology of antiphospholipid syndrome

Author information

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Abstract

PURPOSE OF REVIEW
To present scientific evidence supporting the infectious origin for the antiphospholipid syndrome (APS) by molecular mimicry between pathogens, infection and vaccination with ß2-glycoprotein I (ß2-GPI) molecule.

RECENT FINDINGS
APS is characterized by the presence of pathogenic autoantibodies against ß2-GPI. The infection etiology of APS was well established. Likewise, a link between vaccination such as tetanus toxoid may trigger antibodies targeting tetanus toxoid and ß2-GPI, due to molecular mimicry between the two molecules. During the years, the pathogenic potential of anti-tetanus toxoid antibodies cross reactive with ß2-GPI were found to be pathogenic in animal models, inducing experimental APS.

SUMMARY
Accumulated evidence supports that the presence of anti-ß2-GPI antibodies is associated with a history of infections and the main mechanism to explain this correlation is molecular mimicry. The relationship between tetanus toxoid vaccination and APS reveals a novel view on the autoimmune/autoinflammatory syndrome induced by adjuvants (ASIA).

http://www.ncbi.nlm.nih.gov/pubmed/?term=22617823

“The relationship between tetanus toxoid vaccination and Anti-Phospholipid Syndrome reveals a novel view on the autoimmune/autoinflammatory syndrome induced by adjuvants (ASIA).

Blood • July 2012

The significance of autoantibodies against ß2-glycoprotein I

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Abstract

The antiphospholipid syndrome (APS) is defined by the persistent presence of antiphospholipid antibodies in patients with a history of thrombosis and/or pregnancy morbidity, including fetal loss. APS is an autoimmune disease with a confusing name because the pathologic auto-antibodies are shown to be directed against the plasma protein ß(2)-glycoprotein I and not against phospholipids. In fact, auto-antibodies that recognize phospholipids themselves are not associated with thrombosis but with infectious diseases. One of the intriguing questions is why autoantibodies against ß(2)-glycoprotein I are so commonly found in both patients and the healthy. Several potential mechanisms have been suggested to explain the increased thrombotic risk in patients with these autoantibodies. In this overview, we will summarize our knowledge on the etiology of the autoantibodies, and we will discuss the evidence that identify autoantibodies against ß(2)-glycoprotein I as the culprit of APS.

http://www.ncbi.nlm.nih.gov/pubmed/?term=22553312

“... we will summarize our knowledge on the etiology of the autoantibodies, and we will discuss the evidence that identify autoantibodies against ß(2)-glycoprotein I as the culprit of Antiphospholipid Syndrome.”

Food And Chemical Toxicology • September 2012

Fragrance material review on 2-phenoxyethanol

Author information

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Abstract

A toxicologic and dermatologic review of 2-phenoxyethanol when used as a fragrance ingredient is presented. 2-Phenoxyethanol is a member of the fragrance structural group Aryl Alkyl Alcohols and is a primary alcohol. The AAAs are a structurally diverse class of fragrance ingredients that includes primary, secondary, and tertiary alkyl alcohols covalently bonded to an aryl (Ar) group, which may be either a substituted or unsubstituted benzene ring. The common structural element for the AAA fragrance ingredients is an alcohol group -C-(R1)(R2)OH and generically the AAA fragrances can be represented as an Ar-C-(R1)(R2)OH or Ar-Alkyl-C-(R1)(R2)OH group. This review contains a detailed summary of all available toxicology and dermatology papers that are related to this individual fragrance ingredient and is not intended as a stand-alone document. Available data for 2-phenoxyethanol were evaluated then summarized and includes physical properties, acute toxicity, skin irritation, mucous membrane (eye) irritation, skin sensitization, elicitation, phototoxicity, photoallergy, toxicokinetics, repeated dose, and reproductive toxicity data. A safety assessment of the entire Aryl Alkyl Alcohols will be published simultaneously with this document; please refer to Belsito et al. (2012) for an overall assessment of the safe use of this material and all Aryl Alkyl Alcohols in fragrances.

http://www.ncbi.nlm.nih.gov/pubmed/?term=22036980

Editors Note: 2-Phenoxyethanol MSDS States:

This substance is toxic to kidneys, nervous system, liver.

Link for 2-Phenoxyethanol MSDS

http://www.sciencelab.com/msds.php?msdsid=9926486

“Available data for 2-phenoxyethanol [a vaccine ingredient used in some vaccines] were evaluated then summarized and includes physical properties, acute toxicity, skin irritation, mucous membrane (eye) irritation, skin sensitization, elicitation, phototoxicity, photoallergy, toxicokinetics, repeated dose, and reproductive toxicity data.”

Human Experimental Toxicology • October 2012

Relative trends in hospitalizations and mortality among infants by the number of vaccine doses and age, based on the Vaccine Adverse Event Reporting System (VAERS) 1990-2010

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Abstract

In this study, the Vaccine Adverse Event Reporting System (VAERS) database, 1990-2010, was investigated; cases that specified either hospitalization or death were identified among 38,801 reports of infants. Based on the types of vaccines reported, the actual number of vaccine doses administered, from 1 to 8, was summed for each case. Linear regression analysis of hospitalization rates as a function of (a) the number of reported vaccine doses and (b) patient age yielded a linear relationship with r(2) = 0.91 and r(2) = 0.95, respectively. The hospitalization rate increased linearly from 11.0% (107 of 969) for 2 doses to 23.5% (661 of 2817) for 8 doses and decreased linearly from 20.1% (154 of 765) for children aged <0.1 year to 10.7% (86 of 801) for children aged 0.9 year. The rate ratio (RR) of the mortality rate for 5-8 vaccine doses to 1-4 vaccine doses is 1.5 (95% confidence interval (CI), 1.4-1.7), indicating a statistically significant increase from 3.6% (95% CI, 3.2-3.9%) deaths associated with 1-4 vaccine doses to 5.5% (95% CI, 5.2-5.7%) associated with 5-8 vaccine doses. The male-to-female mortality RR was 1.4 (95% CI, 1.3-1.5). Our findings show a positive correlation between the number of vaccine doses administered and the percentage of hospitalizations and deaths. Since vaccines are given to millions of infants annually, it is imperative that health authorities have scientific data from synergistic toxicity studies on all combinations of vaccines that infants might receive. Finding ways to increase vaccine safety should be the highest priority.

Full Report

http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3547435/

“Our findings show a positive correlation between the number of vaccine doses administered and the percentage of hospitalizations and deaths. Since vaccines are given to millions of infants annually, it is imperative that health authorities have scientific data from synergistic toxicity studies on all combinations of vaccines that infants might receive.”

[complex and unknown synergies]

“Despite widespread pertussis immunization in childhood, there are an estimated 50 million cases and 300,000 deaths due to pertussis globally each year.”

Expert Review Of Vaccines • November 2012

Re-emergence of pertussis: what are the solutions?

Author information

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Abstract

Whooping cough, due to Bordetella pertussis and Bordetella parapertussis, is an important cause of childhood morbidity and mortality. Despite widespread pertussis immunization in childhood, there are an estimated 50 million cases and 300,000 deaths due to pertussis globally each year. Infants who are too young to be vaccinated, children who are partially vaccinated and fully-vaccinated persons with waning immunity are especially vulnerable to disease. Since pertussis is one of the vaccine-preventable diseases on the rise, additional vaccine approaches are needed. These approaches include vaccination of newborns, additional booster doses for older adolescents and adults, and immunization of pregnant women with existing vaccines. Innovative new vaccines are also being studied. Each of these options will be discussed and their potential impact on pertussis control assessed.

http://www.ncbi.nlm.nih.gov/pubmed/23249233

American Journal Of Perinatology • November 2012

Breast-feeding and responses to infant vaccines: constitutional and environmental factors

Author information

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Abstract

Neonates and nursing infants are special with regard to immune development and vulnerability to infectious diseases. Although breast-feeding is essential to modulate and prime immune defenses, vaccines (an interventional prophylaxis) are crucial to prevent and control infectious diseases. During nursing, the type of feeding influences infants' natural defenses (including gut colonization) and their response to vaccines, both through cell-mediated immunity and specific antibody production. Given the variety and combination of vaccine components (antigens and excipients, preservative thimerosal, and aluminum adjuvants) and route of administration, there is a need to examine the role of infant feeding practices in intended and nonintended outcomes of vaccination. Maternal factors related to milk constituents (nutrients and pollutants) and feeding practices can affect response to vaccines. Collectively, studies that compared type of feeding (or used breast-feeding-adjusted statistical models) showed significant influence on some vaccines taken during infancy. Nurslings deprived of the full benefit of breast-feeding could have altered immune responses affecting vaccine outcome. In the absence of studies elucidating neurodevelopment (including excitoxicity) and immunotoxicity issues, vaccination practices should promote and support breast-feeding.

http://www.ncbi.nlm.nih.gov/pubmed/22773284

"Maternal factors related to milk constituents (nutrients and pollutants) and feeding practices can affect response to vaccines. Collectively, studies that compared type of feeding (or used breast-feeding-adjusted statistical models) showed significant influence on some vaccines taken during infancy. Nurslings deprived of the full benefit of breast-feeding could have altered immune responses affecting vaccine outcome."

PLoS One • December 2012

Comparison of Shedding Characteristics of Seasonal Influenza Virus (Sub)Types and Influenza A(H1N1)pdm09 Germany, 2007–2011

Conclusion

Asymptomatic/subclinical infections occur infrequently, but may be associated with substantial amounts of viral shedding. Presymptomatic shedding may arise in one third of cases, and shedding characteristics appear to be independent of (seasonal or pandemic) (sub)type, age, antiviral therapy or vaccination; however the power to find moderate differences was limited.

In summary, our study addresses several important questions on clinical manifestation, duration of infectiousness, viral shedding patterns, including shedding before symptom onset and in asymptomatic/subclinical patients, as well as the effect of vaccination and antiviral therapy on viral shedding. Important single results include the finding that children do not seem to be infected asymptomatically, that shedding one day before symptom onset may occur in one third of influenza patients, that asymptomatic/subclinical influenza patients occur rarely, but viral load (and probably infectiousness) may be substantial, and vaccinated influenza patients do not show different shedding patterns compared to non-vaccinated cases with ILI. Overall results do not show marked differences between seasonal influenza (sub)types and influenza A(H1N1)pdm09.

Full Report

http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3519848/

“Asymptomatic/subclinical infections occur infrequently, but may be associated with substantial amounts of viral shedding. Presymptomatic shedding may arise in one third of cases, and shedding characteristics appear to be independent of (seasonal or pandemic) (sub)type, age, antiviral therapy or vaccination...”

“The effectiveness of influenza vaccines is still controversial ...”

Vaccine • December 2012

Adjuvants in influenza vaccines

Author information

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Abstract

The effectiveness of influenza vaccines is still controversial, and the role of adjuvants in such vaccines is briefly reviewed in this paper. Inactivated whole virus vaccines may include components that function as adjuvants, meaning that additive adjuvants are often not required. MF59 and AS03 showed higher adjuvanticity than aluminum salts in several clinical studies. Recent research has suggested that immune cell recruitment is the main mechanism underlying adjuvant actions in general, and that aluminum salts induce this recruitment via inflammation at the injected site. The aspect of how oil-based adjuvants, such as MF59 and AS03, recruit immune cells remains to be clarified.

http://www.ncbi.nlm.nih.gov/pubmed/?term=23084848

Journal Of Inorganic Biochemistry • December 2012

Detection of human papillomavirus (HPV) L1 gene DNA possibly bound to particulate aluminum adjuvant in the HPV vaccine Gardasil

Author information

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Abstract

Medical practitioners in nine countries submitted samples of Gardasil (Merck & Co.) to be tested for the presence of human papillomavirus (HPV) DNA because they suspected that residual recombinant HPV DNA left in the vaccine might have been a contributing factor leading to some of the unexplained post-vaccination side effects. A total of 16 packages of Gardasil were received from Australia, Bulgaria, France, India, New Zealand, Poland, Russia, Spain and the United States. A nested polymerase chain reaction (PCR) method using the MY09/MY11 degenerate primers for initial amplification and the GP5/GP6-based nested PCR primers for the second amplification were used to prepare the template for direct automated cycle DNA sequencing of a hypervariable segment of the HPV L1 gene which is used for manufacturing of the HPV L1 capsid protein by a DNA recombinant technology in vaccine production. Detection of HPV DNA and HPV genotyping of all positive samples were finally validated by BLAST (Basic Local Alignment Search Tool) analysis of a 45-60 bases sequence of the computer-generated electropherogram. The results showed that all 16 Gardasil samples, each with a different lot number, contained fragments of HPV-11 DNA, or HPV-18 DNA, or a DNA fragment mixture from both genotypes. The detected HPV DNA was found to be firmly bound to the insoluble, proteinase-resistant fraction, presumably of amorphous aluminum hydroxyphosphate sulfate (AAHS) nanoparticles used as adjuvant. The clinical significance of these residual HPV DNA fragments bound to a particulate mineral-based adjuvant is uncertain after intramuscular injection, and requires further investigation for vaccination safety.

http://www.ncbi.nlm.nih.gov/pubmed/23078778

“Medical practitioners in nine countries submitted samples of Gardasil (Merck & Co.) to be tested for the presence of human papillomavirus (HPV) DNA because they suspected that residual recombinant HPV DNA left in the vaccine might have been a contributing factor leading to some of the unexplained post-vaccination side effects. A total of 16 packages of Gardasil were received from Australia, Bulgaria, France, India, New Zealand, Poland, Russia, Spain and the United States.

The results showed that all 16 Gardasil samples, each with a different lot number, contained fragments of HPV-11 DNA, or HPV-18 DNA, or a DNA fragment mixture from both genotypes. The detected HPV DNA was found to be firmly bound to the insoluble, proteinase-resistant fraction, presumably of amorphous aluminum hydroxyphosphate sulfate (AAHS) nanoparticles used as adjuvant. The clinical significance of these residual HPV DNA fragments bound to a particulate mineral-based adjuvant is uncertain after intramuscular injection ...”

Autoimmunity in connection with a metal implant: a case of autoimmune/autoinflammatory syndrome induced by adjuvants

Author information

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Abstract

Autoimmune/autoinflammatory syndrome induced by adjuvants (ASIA) has been recently proposed by Shoenfeld and Agmon-Levin as a new entity that comprises several conditions: the macrophagic-myofasciitis syndrome, the Gulf War syndrome, silicosis and post-vaccination phenomena, autoimmunity related to infectious fragments, hormones, aluminum, silicone, squalene oil, and pristane. We report the case of a 23-year-old woman who developed serial episodes of high fever, extreme fatigue, transient thrombocytopenia, multiple cervical adenopathies, hepatosplenomegaly, anemia, neutropenia, severe proteinuria and urine sediment abnormalities, elevated serum ferritin levels, and transient low positive antinuclear antibodies 1 year after she had a nickel-titanium chin implant for cosmetic reasons. The clinical picture simulated a variety of probable diseases: systemic lupus erythematosus, Kikuchi-Fujimoto syndrome, adult onset Still’s disease, antiphospholipid syndrome, and hemophagocytic syndrome, among others, so she underwent an extensive medical investigation including two lymph node biopsies. She received treatment accordingly with steroids, methotrexate, and mofetil mycophenolate, with initial improvement of her symptoms, which recurred every time the dose was reduced. Two and a half years later the patient decided to retire the chin implant and afterwards all her systemic symptoms have disappeared. She remains in good health, without recurrence of any symptom and off medications until today. Albeit this patient fulfills proposed major ASIA criteria, to our knowledge it would be the first description of systemic features of autoinflammation in connection with a metal implant.

http://www.ncbi.nlm.nih.gov/pubmed/26000140

“We report the case of a 23-year-old woman who developed serial episodes of high fever, extreme fatigue, transient thrombocytopenia, multiple cervical adenopathies, hepatosplenomegaly, anemia, neutropenia, severe proteinuria and urine sediment abnormalities, elevated serum ferritin levels, and transient low positive antinuclear antibodies 1 year after she had a nickel-titanium chin implant for cosmetic reasons.

Two and a half years later the patient decided to retire the chin implant and afterwards all her systemic symptoms have disappeared.”

PLoS One • December 2012

Comparison of Shedding Characteristics of Seasonal Influenza Virus (Sub)Types and Influenza A(H1N1) Germany, 2007–2011

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Joerg Doellinger, Christian Braun, Walter Haas, Gérard Krause, Udo Buchhol

Abstract

Background

Influenza viral shedding studies provide fundamental information for preventive strategies and modelling exercises. We conducted a prospective household study to investigate viral shedding in seasonal and pandemic influenza between 2007 and 2011 in Berlin and Munich, Germany.

Methods

Study physicians recruited index patients and their household members. Serial nasal specimens were obtained from all household members over at least eight days and tested quantitatively by qRT-PCR for the influenza virus (sub)type of the index patient. A subset of samples was also tested by viral culture. Symptoms were recorded daily.

Results

We recruited 122 index patients and 320 household contacts, of which 67 became secondary household cases. Among all 189 influenza cases, 12 were infected with seasonal/prepandemic influenza A(H1N1), 19 with A(H3N2), 60 with influenza B, and 98 with A(H1N1)pdm09. Nine (14%) of 65 non-vaccinated secondary cases were asymptomatic/subclinical (0 (0%) of 21 children, 9 (21%) of 44 adults; p=0.03). Viral load among patients with influenza-like illness (ILI) peaked on illness days 1, 2 or 3 for all (sub)types and declined steadily until days 7–9. Clinical symptom scores roughly paralleled viral shedding dynamics. On the first day prior to symptom onset 30% (12/40) of specimens were positive. Viral load in 6 asymptomatic/subclinical patients was similar to that in ILI-patients. Duration of infectiousness as measured by viral culture lasted approximately until illness days 4–6. Viral load did not seem to be influenced by antiviral therapy, age or vaccination status.

Conclusion

Asymptomatic/subclinical infections occur infrequently, but may be associated with substantial amounts of viral shedding. Presymptomatic shedding may arise in one third of cases, and shedding characteristics appear to be independent of (seasonal or pandemic) (sub)type, age, antiviral therapy or vaccination; however the power to find moderate differences was limited.

Full Report

http://journals.plos.org/plosone/article?id=10.1371/journal.pone.0051653

“Asymptomatic/subclinical infections occur infrequently, but may be associated with substantial amounts of viral shedding. Presymptomatic shedding may arise in one third of cases, and shedding characteristics appear to be independent of (seasonal or pandemic) (sub)type, age, antiviral therapy or vaccination ...”

Der Unfallchirurg • December 2012

Persistent swelling after flushing of an abscess with Octenisept

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Abstract

We report the case of a long-lasting cutaneous side effect after inappropriate use of Octenisept® solution (containing octenidine and phenoxyethanol). Following lavage of an abscess in the inguinal region, a painful erythematous induration mimicking cellulitis persisted for several months. Manual lymphatic drainage considerably improved the symptoms. Octenisept® shows considerable tissue toxicity in vivo including - but not restricted to - blood vessel damage. Deterioration of endothelial cells followed by oedema and continued tissue damage can be seen histologically. Despite the fact that there is a circular letter issued by the manufacturer as well as a boxed warning on the bottles, the awareness to avoid this misuse of Octenisept® is still lacking.

http://www.ncbi.nlm.nih.gov/pubmed/?term=22101779

“Octenisept® solution (containing octenidine and phenoxyethanol) ... shows considerable tissue toxicity in vivo including - but not restricted to - blood vessel damage. Deterioration of endothelial cells followed by oedema and continued tissue damage can be seen histologically.”

[phenoxyethanol is a vaccine ingredient]

American Journal Of Perinatology • 2012

Breast-Feeding and Responses to Infant Vaccines: Constitutional and Environmental Factors

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Abstract

Neonates and nursing infants are special with regard to immune development and vulnerability to infectious diseases. Although breast-feeding is essential to modulate and prime immune defenses, vaccines (an interventional prophylaxis) are crucial to prevent and control infectious diseases. During nursing, the type of feeding influences infants' natural defenses (including gut colonization) and their response to vaccines, both through cell-mediated immunity and specific antibody production. Given the variety and combination of vaccine components (antigens and excipients, preservative thimerosal, and aluminum adjuvants) and route of administration, there is a need to examine the role of infant feeding practices in intended and nonintended outcomes of vaccination. Maternal factors related to milk constituents (nutrients and pollutants) and feeding practices can affect response to vaccines. Collectively, studies that compared type of feeding (or used breast-feeding-adjusted statistical models) showed significant influence on some vaccines taken during infancy. Nurslings deprived of the full benefit of breast-feeding could have altered immune responses affecting vaccine outcome. In the absence of studies elucidating neurodevelopment (including excitoxicity) and immunotoxicity issues, vaccination practices should promote and support breast-feeding.

https://www.thieme-connect.com/DOI/DOI?10.1055/s-0032-1316442

"Nurslings deprived of the full benefit of breast-feeding could have altered immune responses affecting vaccine outcome."

Journal of Autoimmunity • January 2013

Autoimmune/inflammatory syndrome induced by adjuvants (ASIA) 2013: Unveiling the pathogenic, clinical and diagnostic aspects

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Abstract

In 2011 a new syndrome termed 'ASIA Autoimmune/Inflammatory Syndrome Induced by Adjuvants' was defined pointing to summarize for the first time the spectrum of immune-mediated diseases triggered by an adjuvant stimulus such as chronic exposure to silicone, tetramethylpentadecane, pristane, aluminum and other adjuvants, as well as infectious components, that also may have an adjuvant effect. All these environmental factors have been found to induce autoimmunity by themselves both in animal models and in humans: for instance, silicone was associated with siliconosis, aluminum hydroxide with post- vaccination phenomena and macrophagic myofasciitis syndrome. Several mechanisms have been hy- pothesized to be involved in the onset of adjuvant-induced autoimmunity; a genetic favorable back- ground plays a key role in the appearance on such vaccine-related diseases and also justifies the rarity of these phenomena. This paper will focus on protean facets which are part of ASIA, focusing on the roles and mechanisms of action of different adjuvants which lead to the autoimmune/inflammatory response. The data herein illustrate the critical role of environmental factors in the induction of autoimmunity. Indeed, it is the interplay of genetic susceptibility and environment that is the major player for the initiation of breach of tolerance.

Final remarks

Despite the huge amount of money invested in studying vaccines, there are few observational studies and virtually no randomized clinical trials documenting the effect on mortality of any of the existing vaccines. One recent paper found an increased hospitalization rate with the increase of the number of vaccine doses and a mortality rate ratio for 5e8 vaccine doses to 1e4 vaccine doses of 1.5, indicating a statistically significant increase of deaths associated with higher vaccine doses. Since vaccines are given to millions of infants annually, it is imperative that health authorities have scientific data from synergistic toxicity studies on all combinations of vaccines that infants might receive to improve vaccine safety [194].

Moreover, from one side the non-specific beneficial effects of vaccines on survival can be underestimated, on the other side the negative effect of other vaccines may not be captured by current studies [195]. As a matter of fact, in case of vaccine-associated autoimmune phenomena latency periods between the vaccine administration and the appearance of clinical symptoms can be longer (months or years after vaccination) than the time interval commonly established in most vaccine risk assessment studies [196].

Full Report

http://www.2ndchance.info/onesize4all-Perricone2013.pdf

"Despite the huge amount of money invested in studying vaccines, there are few observational studies and virtually no randomized clinical trials documenting the effect on mortality of any of the existing vaccines. One recent paper found an increased hospitalization rate with the increase of the number of vaccine doses and a mortality rate ratio for 5e8 vaccine doses to 1e4 vaccine doses of 1.5, indicating a statistically significant increase of deaths associated with higher vaccine doses."

PLoS One • January 2013

A novel mechanism of formaldehyde neurotoxicity: inhibition of hydrogen sulfide generation by promoting overproduction of nitric oxide

Author information

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Abstract

BACKGROUND

Formaldehyde (FA) induces neurotoxicity by overproduction of intracellular reactive oxygen species (ROS). Increasing studies have shown that hydrogen sulfide (H(2)S), an endogenous gastransmitter, protects nerve cells against oxidative stress by its antioxidant effect. It has been shown that overproduction of nitric oxide (NO) inhibits the activity of cystathionine-beta-synthase (CBS), the predominant H(2)S-generating enzyme in the central nervous system.

OBJECTIVE

We hypothesize that FA-caused neurotoxicity involves the deficiency of this endogenous protective antioxidant gas, which results from excessive generation of NO. The aim of this study is to evaluate whether FA disturbs H(2)S synthesis in PC12 cells, and whether this disturbance is associated with overproduction of NO.

PRINCIPAL FINDINGS

We showed that exposure of PC12 cells to FA causes reduction of viability, inhibition of CBS expression, decrease of endogenous H(2)S production, and NO production. CBS silencing deteriorates FA-induced decreases in endogenous H(2)S generation, neurotoxicity, and intracellular ROS accumulation in PC12 cells; while ADMA, a specific inhibitor of NOS significantly attenuates FA-induced decreases in endogenous H(2)S generation, neurotoxicity, and intracellular ROS accumulation in PC12 cells.

CONCLUSION/SIGNIFICANCE

Our data indicate that FA induces neurotoxicity by inhibiting the generation of H(2)S through excess of NO and suggest that strategies to manipulate endogenous H(2)S could open a suitable novel therapeutic avenue for FA-induced neurotoxicity.

Full Report

http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3554621/

“Our data indicate that Formaldehyde induces neurotoxicity by inhibiting the generation of hydrogen sulfide through excess of nitric oxide ...”

Brain, Behavior And Immunity • February 2013

Altered immune pathway activity under exercise challenge in Gulf War Illness: an exploratory analysis

Author information

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Abstract

Though potentially linked to the basic physiology of stress response we still have no clear understanding of Gulf War Illness (GWI), a debilitating illness presenting with a complex constellation of immune, endocrine and neurological symptoms. Here we compared male GWI (n=20) with healthy veterans (n=22) and subjects with chronic fatigue syndrome/myalgic encephalomyelitis (CFS/ME) (n=7). Blood was drawn during a Graded eXercise Test (GXT) prior to exercise, at peak effort (VO2 max) and 4-h post exercise. Affymetrix HG U133 plus 2.0 microarray gene expression profiling in peripheral blood mononuclear cells (PBMCs) was used to estimate activation of over 500 documented pathways. This was cast against ELISA-based measurement of 16 cytokines in plasma and flow cytometric assessment of lymphocyte populations and cytotoxicity. A 2-way ANOVA corrected for multiple comparisons (q statistic <0.05) indicated significant increases in neuroendocrine-immune signaling and inflammatory activity in GWI, with decreased apoptotic signaling. Conversely, cell cycle progression and immune signaling were broadly subdued in CFS. Partial correlation networks linking pathways with symptom severity via changes in immune cell abundance, function and signaling were constructed. Central to these were changes in IL-10 and CD2+ cell abundance and their link to two pathway clusters. The first consisted of pathways supporting neuronal development and migration whereas the second was related to androgen-mediated activation of NF-□B. These exploratory results suggest an over-expression of known exercise response mechanisms as well as illness-specific changes that may involve an overlapping stress-potentiated neuro-inflammatory response.

http://www.ncbi.nlm.nih.gov/pubmed/23201588

“These exploratory results suggest an over-expression of known exercise response mechanisms as well as illness-specific changes that may involve an overlapping stress-potentiated neuro-inflammatory response.”

Biomedical Research International • February 2013

Vaccine adverse events reported during the first ten years (1998-2008) after introduction in the state of Rondonia, Brazil

Author information

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Abstract

Despite good safety records, vaccines given to young children can cause adverse events. We investigated the reported adverse events following immunization (AEFI) of vaccines given to children of less than seven years of age during the first ten years (1998 to 2008) in the state of Rondonia, Brazil. We worked with the events related to BCG (Bacillus Calmett-Guérin), HB (hepatitis B), DTwP/Hib (diphtheria-tetanus-pertussis+Hemophillus influenza b), DTP (diphtheria-tetanus-pertussis), MMR (mumps, measles, rubella), and YF (yellow fever) vaccines because they were part of the recommended scheme. The number of doses of vaccines given was 3,231,567 with an average of AEFI of 57.2/year during the studied period. DTwP/Hib was responsible for 298 (57.8%), DTP 114 (22.9%), HB 31 (6%), MMR 28 (5.4%), BCG 24 (4.7%), and YF 20 (3.9%) of the reported AEFI. The combination of the AEFI for DTwP/Hib vaccines showed the highest number of systemic (61.4%) and local events (33.8%). Young children (≤1-year old) were more susceptible to AEFI occurring in the 6 hours (54.2%) following vaccine uptake. This study suggests significant differences in reactogenicity of vaccines and that despite limitations of the AEFI Brazilian registry system we cannot ignore underreporting and should use the system to expand our understanding of adverse events and effects.

http://www.ncbi.nlm.nih.gov/pubmed/23509790

“This study suggests significant differences in reactogenicity of vaccines ...”

Biomolecular Concepts • February 2013

The meaning of aluminium exposure on human health and aluminium-related diseases

Crisponi G, Fanni D, Gerosa C, Nemolato S,
Nurchi VM, Crespo-Alonso M, Lachowicz JI, Faa G.

Abstract

The aim of this review is to attempt to answer extremely important questions related to aluminium-related diseases. Starting from an overview on the main sources of aluminium exposure in everyday life, the principal aspects of aluminium metabolism in humans have been taken into consideration in an attempt to enlighten the main metabolic pathways utilised by trivalent metal ions in different organs. The second part of this review is focused on the available evidence concerning the pathogenetic consequences of aluminium overload in human health, with particular attention to its putative role in bone and neurodegenerative human diseases.

http://www.ncbi.nlm.nih.gov/pubmed/25436567

“ The second part of this review is focused on the available evidence concerning the pathogenetic consequences of aluminium overload in human health, with particular attention to its putative role in bone and neurodegenerative human diseases.”

Biomedical Research International • February 2013

Vaccine Adverse Events Reported during the First Ten Years (1998–2008) after Introduction in the State of Rondonia, Brazil

Author Information

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Abstract

Despite good safety records, vaccines given to young children can cause adverse events. We investigated the reported adverse events following immunization (AEFI) of vaccines given to children of less than seven years of age during the first ten years (1998 to 2008) in the state of Rondonia, Brazil. We worked with the events related to BCG (Bacillus Calmett-Guérin), HB (hepatitis B), DTwP/Hib (diphtheria-tetanus-pertussis+Hemophillus influenza b), DTP (diphtheria-tetanus-pertussis), MMR (mumps, measles, rubella), and YF (yellow fever) vaccines because they were part of the recommended scheme. The number of doses of vaccines given was 3,231,567 with an average of AEFI of 57.2/year during the studied period. DTwP/Hib was responsible for 298 (57.8%), DTP 114 (22.9%), HB 31 (6%), MMR 28 (5.4%), BCG 24 (4.7%), and YF 20 (3.9%) of the reported AEFI. The combination of the AEFI for DTwP/Hib vaccines showed the highest number of systemic (61.4%) and local events (33.8%). Young children (≤1-year old) were more susceptible to AEFI occurring in the 6 hours (54.2%) following vaccine uptake. This study suggests significant differences in reactogenicity of vaccines and that despite limitations of the AEFI Brazilian registry system we cannot ignore underreporting and should use the system to expand our understanding of adverse events and effects.

http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3586457/

“... despite limitations of the AEFI Brazilian registry system we cannot ignore underreporting ...”

Annals Of Medical & Health Sciences Research • July 2013

Are the Currently Existing Anti-Human Papillomavirus Vaccines Appropriate for the Developing World?

Author Information

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Abstract

Cervical cancer prevention is expected to be achieved by vaccination of girls 2-3 years before sexual debut, and cervical smear cytology follow-up. The existing human papillomavirus (HPV) vaccines target the low-risk 6 and 11, and the high-risk 16 and 18 subtypes, the most common agents of ano-genital pre-invasive and invasive lesions. We conducted the review by searching PubMed using the terms “HPV,” “HPV subtypes,” “developing world,” and “HPV-vaccine” to retrieve articles published between 2000 and 2011. We focused on studies that were relevant to the developing world. The proposed vaccination policy is currently unachievable in the developing world because of the cost of the vaccine, the lack of adequate cytology and follow-up infrastructures. Moreover, the subtypes of HPV involved in cervical pathology, their associations, and natural history (clearance and persistence rates) differ from the industrialized world. Therefore, the current bivalent and quadrivalent anti-HPV vaccines are unlikely to achieve their target in the developing world. It follows from published data that there is an obligation of the pharmaceutical industry and of the public-health policy makers not to embark on mass vaccination campaigns without thorough information and investigation of the local relevance.

Full Report

http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3793430/

“The proposed vaccination policy is currently unachievable in the developing world because of the cost of the vaccine, the lack of adequate cytology and follow-up infrastructures. Moreover, the subtypes of HPV involved in cervical pathology, their associations, and natural history (clearance and persistence rates) differ from the industrialized world.”

EMBO Reports • March 2013

Scientific dissent and public policy. Is targeting dissent a reasonable way to protect sound policy decisions?

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The temptation to silence dissenters whose non-mainstream views negatively affect public policies is powerful. However, silencing dissent, no matter how scientifically unsound it might be, can cause the public to mistrust science in general. Dissent is crucial for the advancement of science. Disagreement is at the heart of peer review and is important for uncovering unjustified assumptions, flawed methodologies and problematic reasoning.

Full Report

http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3589084

“Dissent is crucial for the advancement of science. Disagreement is at the heart of peer review and is important for uncovering unjustified assumptions, flawed methodologies and problematic reasoning.”

Vaccine • March 2013

Review of the United States universal varicella vaccination program: Herpes zoster incidence rates, cost-effectiveness, and vaccine efficacy based primarily on the Antelope Valley Varicella Active Surveillance Project data

Author information

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Abstract

In a cooperative agreement starting January 1995, prior to the FDA's licensure of the varicella vaccine on March 17, the Centers for Disease Control and Prevention (CDC) funded the Los Angeles Department of Health Services' Antelope Valley Varicella Active Surveillance Project (AV-VASP). Since only varicella case reports were gathered, baseline incidence data for herpes zoster (HZ) or shingles was lacking. Varicella case reports decreased 72%, from 2834 in 1995 to 836 in 2000 at which time approximately 50% of children under 10 years of age had been vaccinated. Starting in 2000, HZ surveillance was added to the project. By 2002, notable increases in HZ incidence rates were reported among both children and adults with a prior history of natural varicella. However, CDC authorities still claimed that no increase in HZ had occurred in any US surveillance site. The basic assumptions inherent to the varicella cost-benefit analysis ignored the significance of exogenous boosting caused by those shedding wild-type VZV. Also ignored was the morbidity associated with even rare serious events following varicella vaccination as well as the morbidity from increasing cases of HZ among adults. Vaccine efficacy declined below 80% in 2001. By 2006, because 20% of vaccinees were experiencing breakthrough varicella and vaccine-induced protection was waning, the CDC recommended a booster dose for children and, in 2007, a shingles vaccination was approved for adults aged 60 years and older. In the prelicensure era, 95% of adults experienced natural chickenpox (usually as children)-these cases were usually benign and resulted in long-term immunity. Varicella vaccination is less effective than the natural immunity that existed in prevaccine communities. Universal varicella vaccination has not proven to be cost-effective as increased HZ morbidity has disproportionately offset cost savings associated with reductions in varicella disease. Universal varicella vaccination has failed to provide long-term protection from VZV disease.

http://www.ncbi.nlm.nih.gov/pubmed/22659447

"In the prelicensure era, 95% of adults experienced natural chickenpox (usually as children)-these cases were usually benign and resulted in long-term immunity. Varicella vaccination is less effective than the natural immunity that existed in prevaccine communities. Universal varicella vaccination has not proven to be cost-effective as increased HZ morbidity has disproportionately offset cost savings associated with reductions in varicella disease. Universal varicella vaccination has failed to provide long-term protection from VZV disease."

Frontiers In Cellular And Infection Microbiology • March 2013

Vaccine delivery using nanoparticles

Anthony E. Gregory,1,* Richard Titball,1 and Diane Williamson2

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Abstract

Vaccination has had a major impact on the control of infectious diseases. However, there are still many infectious diseases for which the development of an effective vaccine has been elusive. In many cases the failure to devise vaccines is a consequence of the inability of vaccine candidates to evoke appropriate immune responses. This is especially true where cellular immunity is required for protective immunity and this problem is compounded by the move toward devising sub-unit vaccines. Over the past decade nanoscale size (<1000 nm) materials such as virus-like particles, liposomes, ISCOMs, polymeric, and non-degradable nanospheres have received attention as potential delivery vehicles for vaccine antigens which can both stabilize vaccine antigens and act as adjuvants. Importantly, some of these nanoparticles (NPs) are able to enter antigen-presenting cells by different pathways, thereby modulating the immune response to the antigen. This may be critical for the induction of protective Th1-type immune responses to intracellular pathogens. Their properties also make them suitable for the delivery of antigens at mucosal surfaces and for intradermal administration. In this review we compare the utilities of different NP systems for the delivery of sub-unit vaccines and evaluate the potential of these delivery systems for the development of new vaccines against a range of pathogens.

Many of the NP delivery systems mentioned in this review are capable of eliciting both cellular and humoral immune responses. However, an efficient and protective vaccine is likely to induce a combination of both responses and should be tailored to the pathogen in question accordingly. Whilst these delivery vehicles may present as an exciting prospect for future vaccination strategies, it is also worth noting their potential drawbacks, particulary those associated with cytotoxicity. Since NPs have a relatively short history in medicine they do not have a longstanding safety profile in human use. It is therefore essential that further research is carried out in NP toxicity to fully address these questions if they are to be accepted as an alternative method for the delivery of novel vaccines and are licensed more widely for human use.

Full Report

http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3607064/

“Whilst these delivery vehicles may present as an exciting prospect for future vaccination strategies, it is also worth noting their potential drawbacks, particulary those associated with cytotoxicity.”

“This is the new wind blowing within the branches of autoimmunity ...”

BMC Medicine • April 2013

Novel pebbles in the mosaic of autoimmunity

Perricone C, Agmon-Levin N, Shoenfeld Y.

Abstract

Almost 25 years ago, the concept of the ‘mosaic of autoimmunity’ was introduced to the scientific community, and since then this concept has continuously evolved, with new pebbles being added regularly. We are now looking at an era in which the players of autoimmunity have changed names and roles. In this issue of BMC Medicine, several aspects of autoimmunity have been addressed, suggesting that we are now at the forefront of autoimmunity science. Within the environmental factors generating autoimmunity are now included unsuspected molecules such as vitamin D and aluminum. Some adjuvants such as aluminum are recognized as causal factors in the development of the autoimmune response. An entirely new syndrome, the autoimmune/inflammatory syndrome induced by adjuvants (ASIA), has been recently described. This is the new wind blowing within the branches of autoimmunity, adding knowledge to physicians for helping patients with autoimmune disease.

http://www.ncbi.nlm.nih.gov/pubmed/23557479

Virus Genes • April 2013

Genetic characterization of HA gene of low pathogenic H9N2 influenza viruses isolated in Israel during 2006-2012 periods

Author information

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Abstract

H9N2 influenza viruses are isolated in Israel since 2000 and became endemic. From November 2006 to the beginning of 2012, many H9N2 viruses were identified, all belonged to the Asian G1-like lineage represented by A/qu/Hong Kong/G1/97 (H9N2). In the present study, 66 isolates were selected for their hemagglutinin gene characterization. Most H9N2 isolates were distributed between two main groups, identified as the 4th and 5th introductions. The 5th introduction, was represented by a compact cluster containing viruses isolated in 2011-2012; the 4th introduction was subdivided into two subgroups, A and B, each containing at least two clusters, which can be identified as A-1, A-2, B-1, and B2, respectively. Genetic analysis of the deduced HA proteins of viruses, belonging to the 4th and 5th introductions, revealed amino acid variations in 79 out of 542 positions. All isolates had typical low pathogenicity motifs at the hemagglutinin (HA) cleavage site. Most viruses had leucine at position 216 in a receptor binding pocket that enables the virus to bind successfully with the cellular receptors intrinsic to mammals, including humans. It was shown that the differences between the HA proteins of viruses used for vaccine production and local field isolates increased in parallel with the duration and intensity of vaccine use, illustrating the genetic diversity of the H9N2 viruses in Israel.

http://www.ncbi.nlm.nih.gov/pubmed/23271448

“... the differences between the HA proteins of viruses used for vaccine production and local field isolates increased in parallel with the duration and intensity of vaccine use, illustrating the genetic diversity of the H9N2 viruses in Israel.”

Cell Biology And Toxicology • April 2013

How aluminum, an intracellular ROS generator promotes hepatic and neurological diseases: the metabolic tale

Author information

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Abstract

Metal pollutants are a global health risk due to their ability to contribute to a variety of diseases. Aluminum (Al), a ubiquitous environmental contaminant is implicated in anemia, osteomalacia, hepatic disorder, and neurological disorder. In this review, we outline how this intracellular generator of reactive oxygen species (ROS) triggers a metabolic shift towards lipogenesis in astrocytes and hepatocytes. This Al-evoked phenomenon is coupled to diminished mitochondrial activity, anerobiosis, and the channeling of a-ketoacids towards anti-oxidant defense. The resulting metabolic reconfiguration leads to fat accumulation and a reduction in ATP synthesis, characteristics that are common to numerous medical disorders. Hence, the ability of Al toxicity to create an oxidative environment promotes dysfunctional metabolic processes in astrocytes and hepatocytes. These molecular events triggered by Al-induced ROS production are the potential mediators of brain and liver disorders.

http://www.ncbi.nlm.nih.gov/pubmed/23463459

“The resulting metabolic reconfiguration leads to fat accumulation and a reduction in ATP synthesis, characteristics that are common to numerous medical disorders.

Hence, the ability of Al toxicity to create an oxidative environment promotes dysfunctional metabolic processes in astrocytes and hepatocytes. These molecular events triggered by Al-induced ROS production are the potential mediators of brain and liver disorders.”

“The incidence of narcolepsy was 25 times higher after the vaccination compared with the time period before. The children in the postvaccination group had a lower age at onset and a more sudden onset than that generally seen.”

Neurology • April 2013

Increased childhood incidence of narcolepsy in western Sweden after H1N1 influenza vaccination

Author information

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Abstract

OBJECTIVES

To assess the incidence of narcolepsy between January 2000 and December 2010 in children in western Sweden and its relationship to the Pandemrix vaccination, and to compare the clinical and laboratory features of these children.

METHODS

The children were identified from all local and regional pediatric hospitals, child rehabilitation centers, outpatient pediatric clinics, and regional departments of neurophysiology. Data collection was performed with the aid of a standardized data collection form, from medical records and telephone interviews with patients and parents. The laboratory and investigational data were carefully scrutinized.

RESULTS

We identified 37 children with narcolepsy. Nine of them had onset of symptoms before the H1N1 vaccination and 28 had onset of symptoms in relationship to the vaccination. The median age at onset was 10 years. All patients in the postvaccination group were positive for human leukocyte antigen (HLA)-DQB1*0602. Nineteen patients in the postvaccination group, compared with one in the prevaccination group, had a clinical onset that could be dated within 12 weeks.

CONCLUSION

Pandemrix vaccination is a precipitating factor for narcolepsy, especially in combination with HLA-DQB1*0602. The incidence of narcolepsy was 25 times higher after the vaccination compared with the time period before. The children in the postvaccination group had a lower age at onset and a more sudden onset than that generally seen.

http://www.ncbi.nlm.nih.gov/pubmed/?term=23486871

Expert Reviews Of Clinical Immunology • April 2013

Autoimmune/inflammatory syndrome induced by adjuvants (Shoenfeld's syndrome): clinical and immunological spectrum

Author information

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Abstract

An adjuvant is a substance that enhances the antigen-specific immune response, induces the release of inflammatory cytokines, and interacts with Toll-like receptors and the NALP3 inflammasome. The immunological consequence of these actions is to stimulate the innate and adaptive immune response. The activation of the immune system by adjuvants, a desirable effect, could trigger manifestations of autoimmunity or autoimmune disease. Recently, a new syndrome was introduced, autoimmune/inflammatory syndrome induced by adjuvants (ASIA), that includes postvaccination phenomena, macrophagic myofasciitis, Gulf War syndrome and siliconosis. This syndrome is characterized by nonspecific and specific manifestations of autoimmune disease. The main substances associated with ASIA are squalene (Gulf War syndrome), aluminum hydroxide (postvaccination phenomena, macrophagic myofasciitis) and silicone with siliconosis. Mineral oil, guaiacol and iodine gadital are also associated with ASIA. The following review describes the wide clinical spectrum and pathogenesis of ASIA including defined autoimmune diseases and nonspecific autoimmune manifestations, as well as the outlook of future research in this field.

http://www.ncbi.nlm.nih.gov/pubmed/23557271

"The activation of the immune system by adjuvants, a desirable effect, could trigger manifestations of autoimmunity or autoimmune disease. Recently, a new syndrome was introduced, autoimmune/inflammatory syndrome induced by adjuvants (ASIA), that includes postvaccination phenomena, macrophagic myofasciitis, Gulf War syndrome and siliconosis."

PLoS One • April 2013

Altered response to A(H1N1)pnd09 vaccination in pregnant women: a single blinded randomized controlled trial

Author information

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Abstract

BACKGROUND

Pregnant women were suspected to be at particular risk when H1N1pnd09 influenza became pandemic in 2009. Our primary objective was to compare the immune responses conferred by MF59®-adjuvanted vaccine (Focetria®) in H1N1pnd09-naïve pregnant and non-pregnant women. The secondary aims were to compare influences of dose and adjuvant on the immune response.

METHODS

The study was nested in the Copenhagen Prospective Studies on Asthma in Childhood (COPSAC2010) pregnancy cohort in 2009-2010 and conducted as a single-blinded block-randomised [1□1□1] controlled clinical trial in pregnant women after gestational week 20: (1) 7.5 µg H1N1pnd09 antigen with MF59-adjuvant (Pa7.5 µg); (2) 3.75 µg antigen half MF59-adjuvanted (Pa3.75 µg); (3) 15 µg antigen unadjuvanted (P15 µg); and in non-pregnant women receiving (4) 7.5 µg antigen full adjuvanted (NPa7.5 µg). Blood samples were collected at baseline, 3 weeks, 3 and 10 months after vaccination, adverse events were recorded prospectively.

RESULTS

58 pregnant women were allocated to Pa7.5 µg and 149 non-pregnant women were recruited to NPa7.5 µg. The sero-conversion rate was significantly increased in non-pregnant (NPa7.5 µg) compared with pregnant (Pa7.5 µg) women (OR=2.48 [1.03-5.95], p=0.04) and geometric mean titers trended towards being higher, but this difference was not statistically significant (ratio 1.27 [0.85-1.93], p=0.23). The significant titer increase rate showed no difference between pregnant (Pa7.5 µg) and non-pregnant (NPa7.5 µg) groups (OR=0.49 [0.13-1.85], p=0.29).

CONCLUSION

Our study suggests the immune response to the 7.5 µg MF59-adjuvanted Focetria® H1N1pnd09 vaccine in pregnant women may be diminished compared with non-pregnant women.

http://www.ncbi.nlm.nih.gov/pubmed/23637733

“Our study suggests the immune response to the 7.5 µg MF59-adjuvanted Focetria® H1N1pnd09 vaccine in pregnant women may be diminished compared with non-pregnant women.”

"Prevalence of CD and UC increased 2-fold to 3-fold among VA users between 1998 and 2009."

Inflammatory Bowel Diseases • April 2013

The incidence and prevalence of inflammatory bowel disease among U.S. veterans: A national cohort study

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Abstract

Background: Temporal trends in incidence and prevalence of Crohn's disease (CD) and ulcerative colitis (UC) in the United States have been reported only in regional populations. The Veterans Affairs (VA) health care system encompasses a national network of clinical care facilities. The aim of this study was to identify temporal trends in the incidence and prevalence of CD and UC among VA users using national VA data sets. Methods: Veterans with CD and UC were identified during fiscal years 1998 to 2009 in the national VA outpatient and inpatient files. Incident and prevalent cases were identified by diagnosis code, and age-standardized and gender-standardized annual prevalence and incidence rates were estimated using the VA 1998 population as the standard population. Results: The total of unique incident cases were 16,842 and 26,272 for CD and UC, respectively; 94% were men. The average annual age-standardized and gender-standardized incidence rate of CD was 33 per 100,000 VA users (range, 27-40), whereas the average for UC was 50 per 100,000 VA users (range, 36-65). In 2009, the age-standardized and gender-standardized point prevalence rate of CD was 287 per 100,000 VA users, whereas the point prevalence of UC was 413 per 100,000 VA users. Conclusions: Prevalence of CD and UC increased 2-fold to 3-fold among VA users between 1998 and 2009. The incidence of UC decreased among VA users from 1998 to 2004 but has remained stable from 2005 to 2009. The incidence of CD has remained stable during the observed time period.

http://www.ncbi.nim.nih.gov/pubmed/23448789

Clinical Infectious Disease • May 2013

Influenza vaccine effectiveness in the community and the household

Author information

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Abstract

Background
There is a recognized need to determine influenza vaccine effectiveness on an annual basis and a long history of studying respiratory illnesses in households.

Methods
We recruited 328 households with 1441 members, including 839 children, and followed them during the 2010-2011 influenza season. Specimens were collected from subjects with reported acute respiratory illnesses and tested by real-time reverse transcriptase polymerase chain reaction. Receipt of influenza vaccine was defined based on documented evidence of vaccination in medical records or an immunization registry. The effectiveness of 2010-2011 influenza vaccination in preventing laboratory-confirmed influenza was estimated using Cox proportional hazards models adjusted for age and presence of high-risk condition, and stratified by prior season (2009-2010) vaccination status.

Results
Influenza was identified in 78 (24%) households and 125 (9%) individuals; the infection risk was 8.5% in the vaccinated and 8.9% in the unvaccinated (P = .83). Adjusted vaccine effectiveness in preventing community-acquired influenza was 31% (95% confidence interval [CI], -7% to 55%). In vaccinated subjects with no evidence of prior season vaccination, significant protection (62% [95% CI, 17%-82%]) against community-acquired influenza was demonstrated. Substantially lower effectiveness was noted among subjects who were vaccinated in both the current and prior season. There was no evidence that vaccination prevented household transmission once influenza was introduced; adults were at particular risk despite vaccination.

Influenza Vaccine Effectiveness
(From Full Report Linked Below)

Adjusted vaccine effectiveness in preventing community-acquired influenza was 31% (95% confidence interval [CI], □7 to 55); point estimates were lowest in young children and modestly higher in adults. Stratified analyses indicated substantial differences in vaccine effectiveness based on whether or not seasonal influenza vaccine had been received the prior season (interaction term: P = .014). Among subjects with documented evidence of prior season vaccination, estimates of current season vaccine effectiveness were low overall and in each of the age groups examined. In contrast, for those subjects without evidence of prior season vaccine receipt, effectiveness estimates were higher for all age groups and statistically significant overall (62% [95% CI, 17%–82%]).

In adjusted analyses for all ages combined, effectiveness estimates were highest against influenza type B (48% [95% CI, □5% to 75%]), and lower for A (pH1N1) (26% [95% CI, □68% to 67%]) and A (H3N2) (10% [95% CI, □74% to 54%]). In analyses stratified by prior season vaccination status, estimates were substantially higher for those subjects without evidence of prior season vaccine receipt.

Conclusions
Vaccine effectiveness estimates were lower than those demonstrated in other observational studies carried out during the same season. The unexpected findings of lower effectiveness with repeated vaccination and no protection given household exposure require further study.

http://www.ncbi.nlm.nih.gov/pubmed/?term=23413420

Full Report

http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3693492/

“Influenza was identified in 78 (24%) households and 125 (9%) individuals; the infection risk was 8.5% in the vaccinated and 8.9% in the unvaccinated (P = .83). Adjusted vaccine effectiveness in preventing community-acquired influenza was 31% (95% confidence interval [CI], -7% to 55%).

In vaccinated subjects with no evidence of prior season vaccination, significant protection (62% [95% CI, 17%-82%]) against community-acquired influenza was demonstrated. Substantially lower effectiveness was noted among subjects who were vaccinated in both the current and prior season. There was no evidence that vaccination prevented household transmission once influenza was introduced; adults were at particular risk despite vaccination.”

Human And Experimental Toxicology • May 2013

Comparison of VAERS fetal-loss reports during three consecutive influenza seasons: was there a synergistic fetal toxicity associated with the two-vaccine 2009/2010 season?

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Abstract

The aim of this study was to compare the number of inactivated-influenza vaccine-related spontaneous abortion and stillbirth (SB) reports in the Vaccine Adverse Event Reporting System (VAERS) database during three consecutive flu seasons beginning 2008/2009 and assess the relative fetal death reports associated with the two-vaccine 2009/2010 season. The VAERS database was searched for reports of fetal demise following administration of the influenza vaccine/vaccines to pregnant women. Utilization of an independent surveillance survey and VAERS, two-source capture-recapture analysis estimated the reporting completeness in the 2009/2010 flu season. Capture-recapture demonstrated that the VAERS database captured about 13.2% of the total 1321 (95% confidence interval (CI): 815-2795) estimated reports, yielding an ascertainment-corrected rate of 590 fetal-loss reports per million pregnant women vaccinated (or 1 per 1695). The unadjusted fetal-loss report rates for the three consecutive influenza seasons beginning 2008/2009 were 6.8 (95% CI: 0.1-13.1), 77.8 (95% CI: 66.3-89.4), and 12.6 (95% CI: 7.2-18.0) cases per million pregnant women vaccinated, respectively. The observed reporting bias was too low to explain the magnitude increase in fetal-demise reporting rates in the VAERS database relative to the reported annual trends. Thus, a synergistic fetal toxicity likely resulted from the administration of both the pandemic (A-H1N1) and seasonal influenza vaccines during the 2009/2010 season.

Full Report

http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3888271/

“Thus, a synergistic fetal toxicity likely resulted from the administration of both the pandemic (A-H1N1) and seasonal influenza vaccines during the 2009/2010 season.”

“While young infants represent the major target population for vaccination,
effective immunization in this age group remains a challenge. Many parameters of innate immune responses
differ quantitatively and qualitatively from newborns to infants and adults,
revealing a highly regulated developmental program.”

Vaccine • May 2013

Immune response to vaccine adjuvants during the first year of life

Ofer Levya, Stanislas Gorielyb, Tobias R. Kollmannc

Abstract

Subunit vaccine formulations often include adjuvants that primarily stimulate innate immune cells. While young infants represent the major target population for vaccination, effective immunization in this age group remains a challenge. Many parameters of innate immune responses differ quantitatively and qualitatively from newborns to infants and adults, revealing a highly regulated developmental program. Herein, we discuss the potential implications of innate immune ontogeny for the activity of adjuvants contained in licensed infant vaccines, as well as future directions for rational design of adjuvanted vaccines for this age group.

- We comprehensively reviewed mechanisms of action of licensed adjuvants.
- We examined the changes of adjuvant responses with age in early life.
- We juxtaposed the current knowledge with safety considerations.
- We point to the need for targeted investigations of adjuvant activity early in life.

http://www.sciencedirect.com/science/article/pii/S0264410X12014624

Scandinavian Journal Of Clinical And Laboratory Investigations • May 2013

Leukocyte transcript alterations in West-African girls following a booster vaccination with diphtheria-tetanus-pertussis vaccine

Author information

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Abstract

Background. Observational studies from low-income countries have shown that the vaccination against diphtheria, tetanus and pertussis (DTP) is associated with excess female mortality due to infectious diseases. Methods. To investigate possible changes in gene expression after DTP vaccination, we identified a group of nine comparable West African girls, from a biobank of 356 children, who were due to receive DTP booster vaccine at age 18 months. As a pilot experiment we extracted RNA from blood samples before, and 6 weeks after, vaccination to analyze the coding transcriptome in leukocytes using expression microarrays, and ended up with information from eight girls. The data was further analyzed using dedicated array pathway and network software. We aimed to study whether DTP vaccination introduced a systematic alteration in the immune system in girls. Results. We found very few transcripts to alter systematically. Those that did mainly belonged to the Interferon (IFN) signalling pathway. We scrutinized this pathway as well as the Interleukin (IL) pathways. Two out of eight showed a down-regulated IFN pathway and two showed an up-regulated IFN pathway. The two with down-regulated IFN pathway had also down-regulated IL-6 pathway. In the study of networks, two of the girls stood out as not having the inflammatory response as top altered network. Conclusion. The transcriptome changes following DTP booster vaccination were subtle, but although the material was small, it was possible to identify sub groups that deviate from each other, mainly in the IFN response.

http://www.ncbi.nlm.nih.gov/pubmed/?term=23668887

“Two out of eight showed a down-regulated IFN [Interferon] pathway and two showed an up-regulated IFN [Interferon] pathway.”

BMC Medicine • May 2013

Video Q&A: what is ASIA? An interview with Yehuda Shoenfeld

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Introduction

Professor Yehuda Shoenfeld is the founder and head of the Zabludowicz Center for Autoimmune Diseases at the Sheba Medical Center, which is affiliated to the Sackler Faculty of Medicine at Tel-Aviv University, Israel. He is also the Incumbent of the Laura Schwarz-Kipp Chair for Research of Autoimmune Diseases at Tel-Aviv University. His clinical and scientific works focus on autoimmune and rheumatic diseases, and he has been the recipient of multiple awards, including a Life Contribution Prize in Internal Medicine in Israel, 2012.

In recent years, Professor Shoenfeld noted that four conditions: siliconosis, Gulf War syndrome (GWS), macrophagicmyofasciitis syndrome (MMF) and post-vaccination phenomena were linked with previous exposure to an adjuvant, and that the patients also presented with similar clinical symptoms. In 2011, this led Professor Shoenfeld to suggest these comparable conditions should be grouped under a common syndrome entitled ‘ASIA’, for ‘Autoimmune (Autoinflammatory) Syndrome Induced by Adjuvants’.

In this Q&A we talk to Professor Shoenfeld about ASIA, and discuss his recommendations regarding further research in the field.

Full Report

http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3662178/

Video Interview

https://www.youtube.com/watch?v=0n12pWMfHhs

“In this Q&A we talk to Professor Shoenfeld about ASIA, and discuss his recommendations regarding further research in the field.”

PLoS One • June 2013

Exercise challenge in Gulf War Illness reveals two subgroups with altered brain structure and function

Author information

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Abstract

Nearly 30% of the approximately 700,000 military personnel who served in Operation Desert Storm (1990-1991) have developed Gulf War Illness, a condition that presents with symptoms such as cognitive impairment, autonomic dysfunction, debilitating fatigue and chronic widespread pain that implicate the central nervous system. A hallmark complaint of subjects with Gulf War Illness is post-exertional malaise; defined as an exacerbation of symptoms following physical and/or mental effort. To study the causal relationship between exercise, the brain, and changes in symptoms, 28 Gulf War veterans and 10 controls completed an fMRI scan before and after two exercise stress tests to investigate serial changes in pain, autonomic function, and working memory. Exercise induced two clinical Gulf War Illness subgroups. One subgroup presented with orthostatic tachycardia (n=10). This phenotype correlated with brainstem atrophy, baseline working memory compensation in the cerebellar vermis, and subsequent loss of compensation after exercise. The other subgroup developed exercise induced hyperalgesia (n=18) that was associated with cortical atrophy and baseline working memory compensation in the basal ganglia. Alterations in cognition, brain structure, and symptoms were absent in controls. Our novel findings may provide an understanding of the relationship between the brain and post-exertional malaise in Gulf War Illness.

http://www.ncbi.nlm.nih.gov/pubmed/23798990

“Nearly 30% of the approximately 700,000 military personnel who served in Operation Desert Storm (1990-1991) have developed Gulf War Illness, a condition that presents with symptoms such as cognitive impairment, autonomic dysfunction, debilitating fatigue and chronic widespread pain that implicate the central nervous system.”

Methods In Molecular Biology • June 2013

Databases and in silico tools for vaccine design

Author information

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Abstract

In vaccine design, databases and in silico tools play different but complementary roles. Databases collect experimentally verified vaccines and vaccine components, and in silico tools provide computational methods to predict and design new vaccines and vaccine components. Vaccine-related databases include databases of vaccines and vaccine components. In the USA, the Food and Drug Administration (FDA) maintains a database of licensed human vaccines, and the US Department of Agriculture keeps a database of licensed animal vaccines. Databases of vaccine clinical trials and vaccines in research also exist. The important vaccine components include vaccine antigens, vaccine adjuvants, vaccine vectors, and -vaccine preservatives. The vaccine antigens can be whole proteins or immune epitopes. Various in silico vaccine design tools are also available. The Vaccine Investigation and Online Information Network (VIOLIN; http://www.violinet.org) is a comprehensive vaccine database and analysis system. The VIOLIN database includes various types of vaccines and vaccine components. VIOLIN also includes Vaxign, a Web-based in silico vaccine design program based on the reverse vaccinology strategy. Vaccine information and resources can be integrated with Vaccine Ontology (VO). This chapter introduces databases and in silico tools that facilitate vaccine design, especially those in the VIOLIN system.

http://www.ncbi.nlm.nih.gov/pubmed/23568467

“Vaxign, a Web-based in silico vaccine design program based on the reverse vaccinology strategy.”

Romanian Journal Of Internal Medicine • July 2013

ASIA or Shoenfeld's syndrome— an autoimmune syndrome induced by adjuvants

Cojocaru M, Chico□ B.

Abstract

Recently, reports have suggested grouping different autoimmune conditions that are triggered by external stimuli as a single syndrome called autoimmune syndrome induced by adjuvants (ASIA). This syndrome is characterized by the appearance of myalgia, myositis, muscle weakness, arthralgia, arthritis, chronic fatigue, sleep disturbances, cognitive impairment and memory loss, and the possible emergence of a demyelinating autoimmune disease caused by systemic exposure after vaccines and adjuvants. As there are no markers for ASIA, the authors intend to present ASIA, or Shoenfeld's syndrome, as an autoimmune syndrome induced by adjuvants.

http://www.ncbi.nlm.nih.gov/pubmed/24620624

"This syndrome is characterized by the appearance of myalgia, myositis, muscle weakness, arthralgia, arthritis, chronic fatigue, sleep disturbances, cognitive impairment and memory loss, and the possible emergence of a demyelinating autoimmune disease caused by systemic exposure after vaccines and adjuvants."

Immunology Research • July 2013

Adverse events following immunization with vaccines containing adjuvants

Author information

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Abstract

A traditional infectious disease vaccine is a preparation of live attenuated, inactivated or killed pathogen that stimulates immunity. Vaccine immunologic adjuvants are compounds incorporated into vaccines to enhance immunogenicity. Adjuvants have recently been implicated in the new syndrome named ASIA autoimmune/inflammatory syndrome induced by adjuvants. The objective describes the frequencies of post-vaccination clinical syndrome induced by adjuvants. We performed a cross-sectional study; adverse event following immunization was defined as any untoward medical occurrence that follows immunization 54 days prior to the event. Data on vaccinations and other risk factors were obtained from daily epidemiologic surveillance. Descriptive statistics were done using means and standard deviation, and odds ratio adjusted for potential confounding variables was calculated with SPSS 17 software. Forty-three out of 120 patients with moderate or severe manifestations following immunization were hospitalized from 2008 to 2011. All patients fulfilled at least 2 major and 1 minor criteria suggested by Shoenfeld and Agmon-Levin for ASIA diagnosis. The most frequent clinical findings were pyrexia 68%, arthralgias 47%, cutaneous disorders 33%, muscle weakness 16% and myalgias 14%. Three patients had diagnosis of Guillain-Barre syndrome, one patient had Adult-Still's disease 3 days after vaccination. A total of 76% of the events occurred in the first 3 days post-vaccination. Two patients with previous autoimmune disease showed severe adverse reactions with the reactivation of their illness. Minor local reactions were present in 49% of patients. Vaccines containing adjuvants may be associated with an increased risk of autoimmune/inflammatory adverse events following immunization.

http://www.ncbi.nlm.nih.gov/pubmed/23576057

“Vaccines containing adjuvants may be associated with an increased risk of autoimmune/inflammatory adverse events following immunization.”

"... a form of the autoimmune/autoinflammatory syndrome induced by adjuvants (ASIA syndrome)

in commercial sheep, linked to the repetitive inoculation of aluminum-containing adjuvants through vaccination.

The syndrome shows an acute phase that affects less than 0.5% of animals in a given herd ..."

[a syndrome that affects 5,000 per each 1 million]

Immunology Research • July 2013

Autoimmune/autoinflammatory syndrome induced by adjuvants (ASIA syndrome) in commercial sheep

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Abstract

We describe a form of the autoimmune/autoinflammatory syndrome induced by adjuvants (ASIA syndrome) in commercial sheep, linked to the repetitive inoculation of aluminum-containing adjuvants through vaccination. The syndrome shows an acute phase that affects less than 0.5% of animals in a given herd, it appears 2-6 days after an adjuvant-containing inoculation and it is characterized by an acute neurological episode with low response to external stimuli and acute meningoencephalitis, most animals apparently recovering afterward. The chronic phase is seen in a higher proportion of flocks, it can follow the acute phase, and it is triggered by external stimuli, mostly low temperatures. The chronic phase begins with an excitatory phase, followed by weakness, extreme cachexia, tetraplegia and death. Gross lesions are related to a cachectic process with muscular atrophy, and microscopic lesions are mostly linked to a neurodegenerative process in both dorsal and ventral column of the gray matter of the spinal cord. Experimental reproduction of ovine ASIA in a small group of repeatedly vaccinated animals was successful. Detection of Al(III) in tissues indicated the presence of aluminum in the nervous tissue of experimental animals. The present report is the first description of a new sheep syndrome (ovine ASIA syndrome) linked to multiple, repetitive vaccination and that can have devastating consequences as it happened after the compulsory vaccination against bluetongue in 2008. The ovine ASIA syndrome can be used as a model of other similar diseases affecting both human and animals. A major research effort is needed in order to understand its complex pathogenesis.

http://www.ncbi.nlm.nih.gov/pubmed/?term=23579772

American Journal of Homeopathic Medicine • Autumn 2013

Hidden in Plain Sight: Vaccines as a Major Risk Factor for Chronic Disease

Richard Moskowitz, MD

Abstract

The science and politics of vaccination in this country are examined, with a careful look at the rationale for mandatory vaccination, benefits, and harms, and illustrated by case examples showing injury, yet problematic medical-legal recognition.

Thirty-five years of medical practice have convinced me that all vaccines carry a significant risk of chronic disease that is inherent in the vaccination process and in fact central to how they work. Yet the growing concerns of parents and legislators and the media reports about them seldom elicit anything beyond automatic, scornful denials by medical and public health authorities alike. Reflecting on this discrepancy, the focal point of this essay, has also helped me appreciate how much the invisibility actually heightens the risk, and how intimately these phenomena are connected, like mirror-images of the same reality, so that it is wisest to study them together.

Since I am mainly a clinician, I will begin with a story. It concerns a twelve-year-old boy whom I know of solely from his mother's letter, but her words are so heartfelt and so congruent with the rest of my experience that I cannot doubt their veracity:

My son Adam was healthy until his first MMR shot at 15 months. Within 2 weeks he had flu and cold symptoms, which persisted for 6 weeks. Then his eyes became puffy, and he was hospitalized with nephrotic syndrome. A renal biopsy showed "focal sclerosing glomerulonephritis," but the illness didn't respond to steroids. I asked if it could be related to the vaccine, but they told me it couldn't, and we accepted that. Over the next 4 years he was hospitalized repeatedly, and missed many months of school, but finally went into remission, seeming normal and healthy and staying off all medications for about 5 years.

When he turned 10, his pediatrician recommended a booster, saying that a rise in measles cases made it dangerous for him not to be protected. I checked the PDR and other sources but found no contraindication for kidney disease and no listing of nephrosis as a possible adverse reaction, so I agreed to it. In less than 2 weeks he relapsed, with 4+ protein in his urine, swelling, and weight gain, signs that we recognized immediately. He got worse even on Prednisone, and was admitted in hypertensive crisis, with blood in his urine, fluid in his lungs,*and massive weight gain. On Cytoxan, massive doses of Prednisone, and three other drugs, he slowly improved, but missed another 7 months of school.

It's been 2 years since that horrible episode, and he still needs Captopril daily for high blood pressure, and spills 4+ protein every day. The doctor says he sustained major kidney damage, will always need medication to control his blood pressure, and will worsen as he grows older, necessitating a transplant eventually. This time I was convinced that his condition was related to the vaccine, but still the doctors didn't take me seriously, and told me it was a coincidence.

I began searching for information, and even contacted the manufacturer of the vaccine. Finally they sent me two case reports of nephrotic syndrome following the MMR vaccine. It's very difficult for lay people to get information, or even ask questions, since we don't use the correct medical terms and are made to feel stupid. Please tell me if my ideas are reasonable.

I don't think my son could tolerate another episode, and I think he'd have normal blood pressure and kidney function today if not for that second vaccination. I also have a great concern for other children who develop nephritic syndrome some weeks after receiving MMR and whose doctors never make the connection. They could all be at great risk if revaccinated. I realize that this letter has taken up a great deal of your time, and I'd appreciate any help you can give me. If we were closer, I'd make an appointment to see you in person, so please feel free to charge me. Thank you.

Full Text

http://www.whale.to/vaccine/moskowitz.html

Advisory Commission on Childhood Vaccines • September 2013

Updating the Vaccine Injury Table: Guillain-Barré Syndrome (GBS) and Seasonal Influenza Vaccines

Ahmed Calvo, M.D., M.P.H.
Medical Officer
National Vaccine Injury Compensation Program (VICP)

Summary

The report leaves us understanding that the strength of evidence and association is high between (2009) H1N1 vaccines and Guillain Barre Syndrome.

Full Report

http://www.hrsa.gov/vaccinecompensation/updatevaccineinjurytable2013.pdf

Current Alzheimer Research • November 2013

Military risk factors for cognitive decline, dementia and Alzheimer's disease

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Abstract

Delayed neurological health consequences of environmental exposures during military service have been generally underappreciated. The rapidly expanding understanding of Alzheimer's disease (AD) pathogenesis now makes it possible to quantitate some of the likely long-term health risks associated with military service. Military risk factors for AD include both factors elevated in military personnel such as tobacco use, traumatic brain injury (TBI), depression, and post-traumatic stress disorder (PTSD) and other nonspecific risk factors for AD including, vascular risk factors such as obesity and obesity-related diseases (e.g., metabolic syndrome), education and physical fitness. The degree of combat exposure, Vietnam era Agent Orange exposure and Gulf War Illness may also influence risk for AD. Using available data on the association of AD and specific exposures and risk factors, the authors have conservatively estimated 423,000 new cases of AD in veterans by 2020, including 140,000 excess cases associated with specific military exposures. The cost associated with these excess cases is approximately $5.8 billion to $7.8 billion. Mitigation of the potential impact of military exposures on the cognitive function of veterans and management of modifiable risk factors through specifically designed programs will be instrumental in minimizing the impact of AD in veterans in the future decades.

http://www.ncbi.nlm.nih.gov/pubmed/23906002

"... the authors have conservatively estimated 423,000 new cases of AD in veterans by 2020, including 140,000 excess cases associated with specific military exposures. The cost associated with these excess cases is approximately $5.8 billion to $7.8 billion."

Journal Of Inorganic Biochemistry • November 2013

Distinctive clinical features in arthro-myalgic patients with and without aluminum hydroxyde-induced macrophagic myofasciitis: an exploratory study

Author information

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Abstract

Macrophagic myofasciitis (MMF) is a specific histological lesion assessing the persistence of vaccine-derived aluminum oxyhydroxide in muscle tissue, at a site of previous immunization. Long-lasting MMF is usually detected in patients with arthromyalgias, chronic fatigue, and stereotyped cognitive dysfunction. MMF diagnosis requires muscle biopsy, an invasive procedure not suitable for the routine investigation of all patients with musculoskeletal pain. To help decision making in routine practice, we designed a retrospective analysis of 130 consecutive arthro-myalgic patients, previously immunized with aluminum-containing vaccines, in whom deltoid muscle biopsy was performed for diagnostic purposes. According to biopsy results, the patients were ascribed to either the MMF or the non-MMF group. MMF was diagnosed in 32.3% of the patients. MMF and non-MMF groups were similar according to both the injected vaccines and the delay between vaccination and biopsy. MMF patients had less frequent fibromyalgia than non-MMF patients (≥11 fibromyalgic tender points in 16.6 vs 55.5%, $p < 0.04$), and more often abnormal evoked potentials suggestive of CNS demyelination (38.5 vs 5.7%, $p < 0.01$). Predictive bioclinical scores based on simple variables such as the number of fibromyalgic tender points, arthralgias, and spinal pain, had sensitivity ranging from 50 to 88.1% and specificity from 36.4 to 76.1%.

In Conclusion

(i) most aluminum-containing vaccine receivers do not have long-lasting MMF in their muscle, but the prevalence of MMF among patients with arthromyalgia following immunization is substantial; (ii) patients with MMF have more CNS dysfunction and less fibromyalgic tender points than non-MMF patients; (iii) predictive scores may help to identify patients at high vs low risk of MMF.

http://www.ncbi.nlm.nih.gov/pubmed/?term=23921285

“most aluminum-containing vaccine receivers do not have long-lasting MMF in their muscle, but the prevalence of MMF among patients with arthromyalgia following immunization is substantial ... patients with MMF have more CNS dysfunction ...”

Deutsches Arzteblatt International • November 2013

Targeted vaccine selection in influenza vaccination

Author information

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Abstract

BACKGROUND

The main target groups for influenza vaccination are the elderly, the chronically ill, infants, and toddlers. Influenza vaccines are needed that suit the immunological particularities of each of these age and risk groups. Recent years have seen the approval of influenza vaccines that are more immunogenic than before, but whose use in Germany is limited by the restriction of reimbursement to a small number of vaccines.

METHODS

The Medline database was selectively searched for pertinent literature.

RESULTS

The suboptimal immunogenicity of conventional influenza vaccines that contain inactivated viral cleavage products and subunits can be markedly improved by the use of squalene-based adjuvant systems, by the integration of viral antigens in virosomal particles, or by intradermal administration. The vaccination of elderly persons with a vaccine containing the adjuvant MF59 was found to lower the risk of hospitalization for influenza or pneumonia by 25% compared to vaccination with a trivalent inactivated vaccine (TIV). On the other hand, the adjuvant ASO3 was found to be associated with an up to 17-fold increase in the frequency of narcolepsy among 4- to 18-year-olds. In a prospective study, a virosomal vaccine lowered the frequency of laboratory-confirmed influenza in vaccinated children by 88% compared to unvaccinated children (2 versus 18 cases per 1000 individuals). A live, attenuated influenza vaccine lowered the rate of disease in children up to age 7 by 48% compared to a TIV (4.2% versus 8.1%).

CONCLUSION

The newer vaccines possess improved efficacy when used for primary and booster immunization in certain age and risk groups, and they are superior in this respect to conventional vaccines based on viral cleavage products and subunits. The risk/benefit profiles of all currently available vaccines vary depending on the age group or risk group in which they are used.

http://www.ncbi.nlm.nih.gov/pubmed/24314622

From the full report:

“... the adjuvant ASO3 [squalene] was found to be associated with an up to 17-fold increase in the frequency of narcolepsy among 4- to 18-year-olds.”

Eurosurveillance, Volume 18 • December 2013
Rapid communications

Case Of Vaccine-Associated Measles Five Weeks Post-Immunization, British Columbia, Canada, October 2013

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We describe a case of vaccine-associated measles in a two-year-old patient from British Columbia, Canada, in October 2013, who received her first dose of measles-containing vaccine 37 days prior to onset of prodromal symptoms. Identification of this delayed vaccine-associated case occurred in the context of an outbreak investigation of a measles cluster.

Based on our review of the literature, this report documents the first case of MMR vaccine-associated measles, 37 days post-immunisation, well beyond 21 days and the routine 30 days post-MMR immunisation period used by the Canadian adverse event following immunization (AEFI) surveillance system.

Measles-containing vaccines are used globally, have been part of the British Columbia immunisation schedule since 1969, and have an impressive record of safety validated by careful, ongoing AEFI surveillance. Rash and/or mild clinical illness following MMR vaccine are not uncommon [7]. Clinically significant vaccine-associated illness is rare, but when it occurs it is indistinguishable from wild-type measles, except by genotyping [8]. Detection of vaccine virus has been documented up to 14 days post-immunisation by RT-PCR, and up to 16 days by immunofluorescence microscopy of urine sediment [9-12]. Complications from vaccine-associated measles have been documented in both immune-competent and compromised individuals [13,14]. Of note, only one case report of transmission from vaccine-associated measles has been identified [15,16].

Possible explanations for this prolonged shedding of measles vaccine virus include interference with the immune response by host or vaccine factors. Immunoglobulin administration early in the incubation period has been reported to extend the time to onset of symptoms, but in this child there was no such history and no known immunosuppressive illness [5]. The two-fold rise between acute and convalescent measles-specific IgG suggests the vaccine-mediated immune response had been underway prior to the onset of symptoms. Investigations clarified that there were no shipping, handling or cold-chain deviations for the specific vaccine used, and that it was administered by a public health nurse trained in immunisations. The potential immunological impact of the older age of the child at the time of receiving the first dose of MMR vaccine, 33 months versus the typical 12-15 months of age, and the co-administration of meningococcal C and pneumococcal conjugate vaccines are areas for future investigation.

“We describe a case of vaccine-associated measles in a two-year-old patient from British Columbia, Canada, in October 2013, who received her first dose of measles-containing vaccine 37 days prior to onset of prodromal symptoms. Identification of this delayed vaccine-associated case occurred in the context of an outbreak investigation of a measles cluster. Possible explanations for this prolonged shedding of measles vaccine virus include interference with the immune response by host or vaccine factors.”

Full Report

http://www.eurosurveillance.org/ViewArticle.aspx?ArticleId=20649

American Journal Of Obstetrics & Gynecology • December 2013

The fetal inflammatory response syndrome is a risk factor for morbidity in preterm neonates

Author information

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Abstract

OBJECTIVE

The aim of this study was to show and discuss an association between fetal inflammatory response syndrome (FIRS) and an adverse neonatal outcome defined as combined severe neonatal morbidity and mortality in preterm neonates hospitalized in our neonatal intensive care unit.

STUDY DESIGN

This was an observational study including all preterm neonates hospitalized in our neonatal intensive care unit over a 21 month period. FIRS was defined as cord blood interleukin (IL)-6 greater than 11 pg/mL. Main outcome parameter was an adverse neonatal outcome defined as hospital mortality and/or the presence of any of 5 prespecified morbidities (bronchopulmonary dysplasia, periventricular leukomalacia, intraventricular hemorrhage, and early- or late-onset sepsis).

RESULTS

Fifty-seven of 176 preterm infants hospitalized during the study period (32%) had an adverse neonatal outcome and 62 of these 176 infants (35%) had FIRS with median IL-6 values of 51.8 pg/mL (range, 11.2 to >1000 pg/mL). In a regression analysis, FIRS was significantly associated with adverse neonatal outcome ($P < .001$) and with the single outcome parameters, intraventricular hemorrhage and early-onset sepsis ($P = .006$ and $P = .018$, respectively). In the bivariate analysis, FIRS was associated with death and bronchopulmonary dysplasia ($P = .004$ and $P < .001$, respectively). IL-6 correlated with adverse neonatal outcome ($r = 0.411$, $P < .001$). When comparing the correlation in neonates less than 32 weeks' gestational age ($r = 0.481$, $P < .001$) with neonates 32 weeks or longer ($r = 0.233$, $P = .019$), the difference was nearly significant ($P = .065$).

CONCLUSION

FIRS is a risk factor for adverse neonatal outcome in preterm infants. In particular, the combination of IL-6 greater than 11 pg/mL and low gestational age increased the risk for severe neonatal morbidity or death.

http://www.ncbi.nlm.nih.gov/pubmed/?term=23994220

[hospitals do not routinely check interleukin (IL)-6 cord blood prior to vaccination, although they could]

Journal Of Autoimmunity • December 2013

Autoimmune/inflammatory syndrome induced by adjuvants (ASIA) 2013: Unveiling the pathogenic, clinical and diagnostic aspects

Author information

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Abstract

In 2011 a new syndrome termed 'ASIA Autoimmune/Inflammatory Syndrome Induced by Adjuvants' was defined pointing to summarize for the first time the spectrum of immune-mediated diseases triggered by an adjuvant stimulus such as chronic exposure to silicone, tetramethylpentadecane, pristane, aluminum and other adjuvants, as well as infectious components, that also may have an adjuvant effect. All these environmental factors have been found to induce autoimmunity by themselves both in animal models and in humans: for instance, silicone was associated with siliconosis, aluminum hydroxide with post-vaccination phenomena and macrophagic myofasciitis syndrome. Several mechanisms have been hypothesized to be involved in the onset of adjuvant-induced autoimmunity; a genetic favorable background plays a key role in the appearance on such vaccine-related diseases and also justifies the rarity of these phenomena. This paper will focus on protean facets which are part of ASIA, focusing on the roles and mechanisms of action of different adjuvants which lead to the autoimmune/inflammatory response. The data herein illustrate the critical role of environmental factors in the induction of autoimmunity. Indeed, it is the interplay of genetic susceptibility and environment that is the major player for the initiation of breach of tolerance.

http://www.ncbi.nlm.nih.gov/pubmed/24238833

"In 2011 a new syndrome termed 'ASIA Autoimmune/Inflammatory Syndrome Induced by Adjuvants' was defined pointing to summarize for the first time the spectrum of immune-mediated diseases triggered by an adjuvant stimulus such as chronic exposure to silicone, tetramethylpentadecane, pristane, aluminum and other adjuvants, as well as infectious components, that also may have an adjuvant effect."

Current Medicinal Chemistry • 2013

Autoimmune (auto-inflammatory) syndrome induced by adjuvants (ASIA)— animal models as a proof of concept

Author information

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Abstract

ASIA syndrome, "Autoimmune (Auto-inflammatory) Syndromes Induced by Adjuvants" includes at least four conditions which share a similar complex of signs and symptoms and have been defined by hyperactive immune responses: siliconosis, macrophagic myofasciitis syndrome, Gulf war syndrome and post-vaccination phenomena. Exposure to adjuvants has been documented in these four medical conditions, suggesting that the common denominator to these syndromes is a trigger entailing adjuvant activity. An important role of animal models in proving the ASIA concept has been established. Experimentally animal models of autoimmune diseases induced by adjuvants are currently widely used to understand the mechanisms and etiology and pathogenesis of these diseases and might thus promote the development of new diagnostic, predictive and therapeutic methods. In the current review we wish to unveil the variety of ASIA animal models associated with systemic and organ specific autoimmune diseases induced by adjuvants. We included in this review animal models for rheumatoid arthritis-like disease, for systemic lupus erythematosus-like disease, autoimmune thyroid disease-like disease, antiphospholipid syndrome, myocarditis and others. All these models support the concept of ASIA, as the Autoimmune (Auto-inflammatory) Syndrome Induced by Adjuvants.

http://www.ncbi.nlm.nih.gov/pubmed/23992328

"We included in this review animal models for rheumatoid arthritis-like disease, for systemic lupus erythematosus-like disease, autoimmune thyroid disease-like disease, antiphospholipid syndrome, myocarditis and others. All these models support the concept of ASIA, as the Autoimmune (Auto-inflammatory) Syndrome Induced by Adjuvants."

"... vaccine-induced Febrile Seizures could be a problem, particularly in genetically predisposed children."

Expert Review of Vaccines • 2013

Vaccines and febrile seizures

Abstract

Vaccine administration is the second leading cause of febrile seizures (FS). FS occurrence in children is a serious concern because it leads to public apprehension of vaccinations. This review discusses the clinical implications of FS, its potential link to vaccinations and its impact on official recommendations for vaccinations in children. Vaccines such as the pertussis antigen-containing vaccine, the measles-containing vaccine and the influenza vaccine have been linked to FS. However, FS events are very rare and are not usually associated with downstream complications or severe neurologic diseases. Considering their significant health benefits, vaccinations have not been restricted in the pediatric population. Nevertheless, vaccine-induced FS could be a problem, particularly in genetically predisposed children. Therefore, post-marketing surveillance studies are required to accurately assess the incidence of FS and identify individuals who are particularly susceptible to FS after vaccination.

http://www.tandfonline.com/doi/abs/10.1586/14760584.2013.814781

Human Vaccines And Immunotherapeutics • 2014

Mortality among recipients of the Merck V710 Staphylococcus aureus vaccine after postoperative S. aureus infections: an analysis of possible contributing host factors

Author information

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Abstract

In a blinded randomized trial, preoperative receipt of the Merck V710 Staphylococcus aureus vaccine was associated with a higher mortality rate than placebo in patients who later developed postoperative S. aureus infections. Of the tested patients, all 12 V710 recipients (but only 1 of 13 placebo recipients) with undetectable serum IL2 levels prior to vaccination and surgery died after postoperative S. aureus infection. The coincidence of 3 factors (low prevaccination IL-2 levels, receipt of V710, and postoperative S. aureus infection) appeared to substantially increase mortality in our study population after major cardiothoracic surgery. Furthermore, 9 of the 10 V710 recipients with undetectable preoperative IL17a levels and postoperative S. aureus infections died. Although the current study is hypothesis-generating and the exact pathophysiology remains speculative, these findings raise concern that immune predispositions may adversely impact the safety and efficacy of staphylococcal vaccines actively under development. The potential benefits of an effective vaccine against S. aureus justify continued but cautious pursuit of this elusive goal.

http://www.ncbi.nlm.nih.gov/pubmed/?term=25483690

“In a blinded randomized trial, preoperative receipt of the Merck V710 Staphylococcus aureus vaccine was associated with a higher mortality rate than placebo in patients who later developed postoperative S. aureus infections. Of the tested patients, all 12 V710 recipients (but only 1 of 13 placebo recipients) with undetectable serum IL2 levels prior to vaccination and surgery died after postoperative S. aureus infection.”

Human Vaccines & Immunotherapeutics • 2014

Hepatitis B vaccine adverse events in China: risk control and regulation

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Abstract

The death of 17 children raised public fears over infant hepatitis B vaccination in China. Though the relation between hepatitis B and children's death was denied after prudent investigation, the negative impact remained. In order to prevent or minimize adverse events after vaccination, special strategy including regulation and reimbursement should be developed.

http://www.ncbi.nlm.nih.gov/pubmed/25483642

"The death of 17 children raised public fears over infant hepatitis B vaccination in China."

Current Medical Chemistry • 2014

Selective elevation of circulating CCL2/MCP1 levels in patients with longstanding post-vaccinal macrophagic myofasciitis and ASIA

Author information

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Abstract

Several medical conditions sharing similar signs and symptoms may be related to immune adjuvants. These conditions described as ASIA (Autoimmune/inflammatory Syndrome Induced by Adjuvants), include a condition characterized by macrophagic myofasciitis (MMF) assessing long-term persistence of vaccine derived-alum adjuvants into macrophages at sites of previous immunization. Despite increasing data describing clinical manifestations of ASIA have been reported, biological markers are particularly lacking for their characterization and follow up. We report an extensive cytokine screening performed in serum from 44 MMF patients compared both to sex and age matched healthy controls and to patients with various types of inflammatory neuromuscular diseases. Thirty cytokines were quantified using combination of Luminex® technology and ELISA. There was significant mean increase of serum levels of the monocytechemoattractant protein 1 (CCL2/MCP-1) in MMF patients compared to healthy subjects. MMF patients showed no elevation of other cytokines. This contrasted with inflammatory patients in whom CCL2/MCP-1 serum levels were unchanged, whereas several other inflammatory cytokines were elevated (IL1□, IL5 and CCL3/MIP1□). These results suggest that CCL2 may represent a biological marker relevant to the pathophysiology of MMF rather than a non specific inflammatory marker and that it should be checked in the other syndromes constitutive of ASIA.

http://www.ncbi.nlm.nih.gov/pubmed/?term=24083602

“These conditions described as ASIA, include a condition characterized by macrophagic myofasciitis (MMF) assessing long-term persistence of vaccine derived-alum adjuvants into macrophages at sites of previous immunization.”

Human Vaccines And Immunotherapeutics • 2014

Immunological persistence in 5 year olds previously vaccinated with hexavalent DTPa-HBV-IPV/Hib at 3, 5, and 11 months of age

Author information

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Abstract

The combined diphtheria-tetanus-acellular pertussis-hepatitis B-poliomyelitis/Haemophilus influenza vaccine (DTPa-HBV-IPV/Hib: Infanrix™ hexa, GlaxoSmithKline Vaccines) is used for primary vaccination of infants in a range of schedules world-wide. Antibody persistence after 4 DTPa-HBV-IPV/Hib doses in the first 2 y of life has been documented, but long-term persistence data following the 3, 5, 11-12 months (3-5-11) infant vaccination schedule, employed for example in Nordic countries, are limited. We assessed antibody persistence in 57 5-year-old children who had received either DTPa-HBV-IPV/Hib or DTPa-IPV/Hib (Infanrix™-IPV/Hib, GlaxoSmithKline Vaccines) in the 3-5-11 schedule. Among DTPa-HBV-IPV/Hib recipients, 7/12 retained seroprotective antibody concentrations for diphtheria, 10/12 for tetanus, 5/12 for hepatitis and 10/12 for Hib. Detectable antibodies were observed for 0/12 children for pertussis toxin (PT), 12/12 for filamentous haemagglutinin (FHA) and 8/12 for pertactin (PRN). Among DTPa-IPV/Hib recipients, 28/45 retained seroprotective anti-diphtheria concentrations, 34/44 for tetanus and 40/45 for Hib. Detectable antibodies were observed for 9/45 children for PT, 41/45 for FHA and 34/45 for PRN. Antibody persistence in DTPa-HBV-IPV/Hib and DTPa-IPV/Hib-vaccinees appeared similar in 5 y olds to that previously observed in children of a similar age who had received 4 prior doses of DTPa-HBV-IPV/Hib (or DTPa-IPV/Hib). As in subjects primed with 4 prior doses, we observed that antibodies markedly declined by 5 y of age, calling for the administration of a pre-school booster dose in order to ensure continued protection against pertussis.

http://www.ncbi.nlm.nih.gov/pubmed/?term=25483640

[regarding vaccine non-responders
and low-responders:

In this study 7 of 12 five year old children
retained seroprotective antibody concentrations
for diphtheria, 10 of 12 for tetanus, 5 of 12 for hepatitis
and 10 of 12 for Hib. The pro-vaccine lobby never
discusses non-responders and low responders and
the large variance in human response to vaccination.
Even vaccinated people can be fully non-responsive
or so low-responsive that they can communicate
diseases as easily as non-vaccinated people making
vaccination an entirely uncertain medical procedure
and adding substance and support to the position
that vaccination is not always effective]

Human Vaccines And Immunotherapeutics • 2014

Consumer reporting of adverse events following immunization

Author information

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Abstract

Surveillance of adverse events following immunisation (AEFI) is an essential component of vaccine safety monitoring. The most commonly utilized passive surveillance systems rely predominantly on reporting by health care providers (HCP). We reviewed adverse event reports received in Victoria, Australia since surveillance commencement in July 2007, to June 2013 (6 years) to ascertain the contribution of consumer (vaccinee or their parent/guardian) reporting to vaccine safety monitoring and to inform future surveillance system development directions. Categorical data included were: reporter type; serious and non-serious AEFI category; and, vaccinee age group. Chi-square test and 2-sample test of proportions were used to compare categories; trend changes were assessed using linear regression. Consumer reporting increased over the 6 years, reaching 21% of reports received in 2013 (P<0.001), most commonly for children aged less than 7 years. Consumer reports were 5% more likely to describe serious AEFI than HCP (P=0.018) and 10% more likely to result in specialist clinic attendance (P<0.001). Although online reporting increased to 32% of all report since its introduction in 2010, 85% of consumers continued to report by phone. Consumer reporting of AEFI is a valuable component of vaccine safety surveillance in addition to HCP reporting. Changes are required to AEFI reporting systems to implement efficient consumer AEFI reporting, but may be justified for their potential impact on signal detection sensitivity.

http://www.ncbi.nlm.nih.gov/pubmed/?term=25483686

“Consumer reporting increased over the 6 years, reaching 21% of reports received in 2013 (P<0.001), most commonly for children aged less than 7 years.”

Human Vaccines And Immunotherapeutics • 2014

Immunocompetent mouse models to evaluate intrahepatic T cell responses to HCV vaccines

Author information

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Abstract

Despite considerable progress in the development of immunocompetent mouse models using different high end technologies, most available small animal models for HCV study are unsuitable for challenge experiments, which are vital for vaccine development, as they fail to measure the T cell response in liver. A recently developed intra-hepatic challenge model results in HCV antigen expression in mouse hepatocytes and through the detection of the surrogate marker, SEAP, in serum, the effect of prior vaccination can be monitored longitudinally.

http://www.ncbi.nlm.nih.gov/pubmed/?term=25483684

[vaccination is inherently experimental.

There are so many unknowns

that this is indisputable]

Human Vaccines And Immunotherapeutics • 2014

The persistence of anti-HBs antibody and anamnestic response 20 years after primary vaccination with recombinant hepatitis B vaccine at infancy

Author information

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Abstract

Hepatitis B (HB) vaccine induces protective levels of antibody response (anti-HBs≥10 mIU/mL) in 90-99% of vaccinees. The levels of anti-HBs antibody decline after vaccination. The aim of this study was to evaluate the persistence of anti-HBs antibodies and immunologic memory in healthy adults at 20 years after primary vaccination with recombinant HB vaccine. Blood samples were collected from 300 adults at 20 years after primary HB vaccination and their sera were tested for anti-HBs antibody by ELISA technique. A single booster dose of HB vaccine was administered to a total of 138 subjects, whose anti-HBs antibody titer was <10 mIU/mL. The sera of subjects were re-tested for the anti-HBs antibody levels at 4 weeks after booster vaccination. At 20 years after primary vaccination 37.0% of participants had protective levels of antibody with geometric mean titer (GMT) of 55.44±77.01 mIU/mL. After booster vaccination, 97.1% of vaccinees developed protective levels of antibody and the GMT rose from 2.35±6.49 mIU/mL to 176.28±161.78 mIU/mL. 125/138 (90.6%) of re-vaccinated subjects also showed an anamnestic response to booster vaccination. At 20 years after primary vaccination with HB vaccine, low proportion of the subjects had protective levels of antibody. However, the majority of the re-vaccinated subjects developed protective levels of anti-HBs and showed an anamnestic response after booster vaccination. Additional follow-up studies are necessary to determine the duration of immunological memory.

http://www.ncbi.nlm.nih.gov/pubmed/?term=25483689

“At 20 years after primary vaccination 37.0% of participants had protective levels of antibody ...”

Human Vaccines And Immunotherapeutics • 2014

Serum and mucosal antibody responses to inactivated polio vaccine after sublingual immunization using a thermoresponsive gel delivery system

Author information

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Abstract

Administering vaccines directly to mucosal surfaces can induce both serum and mucosal immune responses. Mucosal responses may prevent establishment of initial infection at the port of entry and subsequent dissemination to other sites. The sublingual route is attractive for mucosal vaccination, but both a safe, potent adjuvant and a novel formulation are needed to achieve an adequate immune response. We report the use of a thermoresponsive gel (TRG) combined with a double mutant of a bacterial heat-labile toxin (dmLT) for sublingual immunization with a trivalent inactivated poliovirus vaccine (IPV) in mice. This TRG delivery system, which changes from aqueous solution to viscous gel upon contact with the mucosa at body temperature, helps to retain the formulation at the site of delivery and has functional adjuvant activity from the inclusion of dmLT. IPV was administered to mice either sublingually in the TRG delivery system or intramuscularly in phosphate-buffered saline. We measured poliovirus type-specific serum neutralizing antibodies as well as polio-specific serum Ig and IgA antibodies in serum, saliva, and fecal samples using enzyme-linked immunosorbent assays. Mice receiving sublingual vaccination via the TRG delivery system produced both mucosal and serum antibodies, including IgA. Intramuscularly immunized animals produced only serum neutralizing and binding Ig but no detectable IgA. This study provides proof of concept for sublingual immunization using the TRG delivery system, comprising a thermoresponsive gel and dmLT adjuvant.

http://www.ncbi.nlm.nih.gov/pubmed/?term=25483682

“This study provides proof of concept for sublingual immunization ...”

Vaccine • January 2014

Nanoparticle vaccines

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Abstract

Nanotechnology increasingly plays a significant role in vaccine development. As vaccine development orientates toward less immunogenic “minimalist” compositions, formulations that boost antigen effectiveness are increasingly needed. The use of nanoparticles in vaccine formulations allows not only improved antigen stability and immunogenicity, but also targeted delivery and slow release. A number of nanoparticle vaccines varying in composition, size, shape, and surface properties have been approved for human use and the number of candidates is increasing. However, challenges remain due to a lack of fundamental understanding regarding the in vivo behavior of nanoparticles, which can operate as either a delivery system to enhance antigen processing and/or as an immunostimulant adjuvant to activate or enhance immunity. This review provides a broad overview of recent advances in prophylactic nanovaccinology. Types of nanoparticles used are outlined and their interaction with immune cells and the biosystem are discussed. Increased knowledge and fundamental understanding of nanoparticle mechanism of action in both immunostimulatory and delivery modes, and better understanding of in vivo biodistribution and fate, are urgently required, and will accelerate the rational design of nanoparticle-containing vaccines.

http://www.sciencedirect.com/science/article/pii/S0264410X13016319

“As vaccine development orientates toward less immunogenic “minimalist” compositions, formulations that boost antigen effectiveness are increasingly needed. The use of nanoparticles in vaccine formulations allows not only improved antigen stability and immunogenicity, but also targeted delivery and slow release. A number of nanoparticle vaccines varying in composition, size, shape, and surface properties have been approved for human use and the number of candidates is increasing.”

Nucleic Acids Research • January 2014

Updates on the web-based VIOLIN vaccine database and analysis system

Author information

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Abstract

The integrative Vaccine Investigation and Online Information Network (VIOLIN) vaccine research database and analysis system (http://www.violinet.org) curates, stores, analyses and integrates various vaccine-associated research data. Since its first publication in NAR in 2008, significant updates have been made. Starting from 211 vaccines annotated at the end of 2007, VIOLIN now includes over 3240 vaccines for 192 infectious diseases and eight noninfectious diseases (e.g. cancers and allergies). Under the umbrella of VIOLIN, >10 relatively independent programs are developed. For example, Protegen stores over 800 protective antigens experimentally proven valid for vaccine development. VirmugenDB annotated over 200 ‘virmugens’, a term coined by us to represent those virulence factor genes that can be mutated to generate successful live attenuated vaccines. Specific patterns were identified from the genes collected in Protegen and VirmugenDB. VIOLIN also includes Vaxign, the first web-based vaccine candidate prediction program based on reverse vaccinology. VIOLIN collects and analyzes different vaccine components including vaccine adjuvants (Vaxjo) and DNA vaccine plasmids (DNAVaxDB). VIOLIN includes licensed human vaccines (Huvax) and veterinary vaccines (Vevax). The Vaccine Ontology is applied to standardize and integrate various data in VIOLIN. VIOLIN also hosts the Ontology of Vaccine Adverse Events (OVAE) that logically represents adverse events associated with licensed human vaccines.

Full Report

http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3964998/

“The integrative Vaccine Investigation and Online Information Network (VIOLIN) vaccine research database and analysis system curates, stores, analyses and integrates various vaccine-associated research data. Starting from 211 vaccines annotated at the end of 2007, VIOLIN now includes over 3,240 vaccines for 192 infectious diseases and eight noninfectious diseases ...”

Vaccine • January 2014

Co-administration of live measles and yellow fever vaccines and inactivated pentavalent vaccines is associated with increased mortality compared with measles and yellow fever vaccines only An observational study from Guinea-Bissau

Author information

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Abstract

BACKGROUND

Studies from low-income countries indicate that co-administration of inactivated diphtheria-tetanus-pertussis (DTP) vaccine and live attenuated measles vaccine (MV) is associated with increased mortality compared with receiving MV only. Pentavalent (DTP-H. Influenza type B-Hepatitis B) vaccine is replacing DTP in many low-income countries and yellow fever vaccine (YF) has been introduced to be given together with MV. Pentavalent and YF vaccines were introduced in Guinea-Bissau in 2008. We investigated whether co-administration of pentavalent vaccine with MV and yellow fever vaccine has similar negative effects.

METHODS

In 2007-2011, we conducted a randomised placebo-controlled trial of vitamin A at routine vaccination contacts among children aged 6-23 months in urban and rural Guinea-Bissau. In the present study, we included 2331 children randomised to placebo who received live vaccines only (MV or MV+YF) or a combination of live and inactivated vaccines (MV+DTP or MV+YF+pentavalent). Mortality was compared in Cox proportional hazards models stratified for urban/rural enrolment adjusted for age and unevenly distributed baseline factors.

RESULTS

While DTP was still used 685 children received MV only and 358 MV+DTP; following the change in programme, 940 received MV+YF only and 348 MV+YF+pentavalent. During 6 months of follow-up, the adjusted mortality rate ratio (MRR) for co-administered live and inactivated vaccines compared with live vaccines only was 3.24 (1.20-8.73). For MV+YF+pentavalent compared with MV+YF only, the adjusted MRR was 7.73 (1.79-33.4).

CONCLUSION

In line with previous studies of DTP, the present results indicate that pentavalent vaccine co-administered with MV and YF is associated with increased mortality.

http://www.ncbi.nlm.nih.gov/pubmed/24325827

“In line with previous studies of DTP, the present results indicate that pentavalent vaccine co-administered with MV and YF is associated with increased mortality.”

Autoimmunity Review • January 2014

A review on the association between inflammatory myopathies and vaccination

Author information

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Abstract

Several viruses and vaccines are among the environmental factors implicated as triggers of autoimmune inflammatory myopathies. Case histories report on the onset of dermatomyositis/polymyositis after immunization with various vaccines of patients with probable genetic predisposition. However, retrospective and epidemiological studies failed to ascertain an association between DM/PM and vaccines: no significant increase in the incidence of DM/PM was reported after large vaccination campaigns. The risk for vaccine-induced adverse events may be enhanced by adjuvants. Macrophagic myofasciitis is a novel inflammatory myopathy ascribed to an ongoing local immune reaction to a vaccine adjuvant. Isolated prospective studies showed that the administration of unadjuvanted, non-live vaccine to patients with DM/PM caused no short-term harmful effects to DM/PM immune processes. However, more research is warranted to clarify the incidence of vaccine-preventable infections, harmful effects of vaccination, and the influence of any immunomodulating agents on vaccination efficacy. Vaccination is an important disease prevention tool in modern medicine. This review does not address risk-benefit or cost-benefit analyses, and does not advocate the use of specific vaccines or vaccination programs. Despite a great deal of scientific uncertainty, the concept of a possible causal link between immunization and inflammatory myopathies should not be totally rejected.

http://www.ncbi.nlm.nih.gov/pubmed/24001753

“Macrophagic myofasciitis is a novel inflammatory myopathy ascribed to an ongoing local immune reaction to a vaccine adjuvant ... more research is warranted to clarify the incidence of vaccine-preventable infections, harmful effects of vaccination, and the influence of any immunomodulating agents on vaccination efficacy. Despite a great deal of scientific uncertainty, the concept of a possible causal link between immunization and inflammatory myopathies should not be totally rejected.”

Journal Of Autoimmunity • January 2014

Sjögren's syndrome: another facet of the autoimmune/inflammatory syndrome induced by adjuvants (ASIA)

Author information

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Abstract

Recently, a new syndrome, namely the "Autoimmune/inflammatory syndrome induced by adjuvants" (ASIA) has been defined. In this syndrome different conditions characterized by common signs and symptoms and induced by the presence of an adjuvant are included. The adjuvant is a substance capable of boosting the immune response and of acting as a trigger in the development of autoimmune diseases. Post-vaccination autoimmune phenomena represent a major issue of ASIA. Indeed, despite vaccines represent a mainstay in the improvement of human health, several of these have been implicated as a potential trigger for autoimmune diseases. Sjogren's Syndrome (SjS) is a systemic chronic autoimmune inflammatory disease characterized by the presence of an inflammatory involvement of exocrine glands accompanied by systemic manifestations. Own to the straight association between infectious agents exposure (mainly viruses) and sicca syndrome development, the possible link between vaccine and SjS is not surprising. Indeed, a few cases of SjS following vaccine delivery have been reported. At the same extent, the induction of SjS following silicone exposure has been described too. Thus, the aim of this review was to focus on SjS and its possible development following vaccine or silicone exposure in order to define another possible facet of the ASIA syndrome.

http://www.ncbi.nlm.nih.gov/pubmed/24774584

"despite vaccines represent a mainstay in the improvement of human health, several of these have been implicated as a potential trigger for autoimmune diseases. Sjogren's Syndrome (SjS) is a systemic chronic autoimmune inflammatory disease characterized by the presence of an inflammatory involvement of exocrine glands accompanied by systemic manifestations."

New England Journal Of Medicine • February 2014

Risk of intussusception after monovalent rotavirus vaccination

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Abstract

BACKGROUND

Although current rotavirus vaccines were not associated with an increased risk of intussusception in large trials before licensure, recent postlicensure data from international settings suggest the possibility of a small increase in risk of intussusception after monovalent rotavirus vaccination. We examined this risk in a population in the United States.

METHODS

Participants were infants between the ages of 4 and 34 weeks who were enrolled in six integrated health care organizations in the Vaccine Safety Datalink (VSD) project. We reviewed medical records and visits for intussusception within 7 days after monovalent rotavirus vaccination from April 2008 through March 2013. Using sequential analyses, we then compared the risk of intussusception among children receiving monovalent rotavirus vaccine with historical background rates. We further compared the risk after monovalent rotavirus vaccination with the risk in a concurrent cohort of infants who received the pentavalent rotavirus vaccine.

RESULTS

During the study period, 207,955 doses of monovalent rotavirus vaccine (including 115,908 first doses and 92,047 second doses) were administered in the VSD population. We identified 6 cases of intussusception within 7 days after the administration of either dose of vaccine. For the two doses combined, the expected number of intussusception cases was 0.72, resulting in a significant relative risk of 8.4. For the pentavalent rotavirus vaccine, 1,301,810 doses were administered during the study period, with 8 observed intussusception cases (7.11 expected), for a nonsignificant relative risk of 1.1. The relative risk of chart-confirmed intussusception within 7 days after monovalent rotavirus vaccination, as compared with the risk after pentavalent rotavirus vaccination, was 9.4 (95% confidence interval, 1.4 to 103.8). The attributable risk of intussusception after the administration of two doses of monovalent rotavirus vaccine was estimated to be 5.3 per 100,000 infants vaccinated.

CONCLUSIONS

In this prospective postlicensure study of more than 200,000 doses of monovalent rotavirus vaccine, we observed a significant increase in the rate of intussusception after vaccination, a risk that must be weighed against the benefits of preventing rotavirus-associated illness.

http://www.ncbi.nlm.nih.gov/pubmed/?term=24422678

“In this prospective postlicensure study of more than 200,000 doses of monovalent rotavirus vaccine, we observed a significant increase in the rate of intussusception after vaccination, a risk that must be weighed against the benefits of preventing rotavirus-associated illness.”

Trends In Microbiology • February 2014

Do we need a new vaccine to control the re-emergence of pertussis?

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Abstract

Bordetella pertussis causes whooping cough and is re-emerging in developed countries despite widespread immunization with acellular pertussis vaccines (Pa), which are less effective than the whole cell vaccines that they replaced. Efficacy of Pa could be improved by switching from alum to alternative adjuvants that generate more potent cell mediated immunity.

http://www.ncbi.nlm.nih.gov/pubmed/24485284

“Bordetella pertussis causes whooping cough and is re-emerging in developed countries despite widespread immunization with acellular pertussis vaccines ...”

Immunology Research • February 2014

Evolution of multiple sclerosis in France since the beginning of hepatitis B vaccination

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Abstract

Since the implementation of the mass vaccination campaign against hepatitis B in France, the appearance of multiple sclerosis, sometimes occurring in the aftermath of vaccinations, led to the publication of epidemiological international studies. This was also justified by the sharp increase in the annual incidence of multiple sclerosis reported to the French health insurance in the mid-1990s. Almost 20 years later, a retrospective reflection can be sketched from these official data and also from the national pharmacovigilance agency. Statistical data from these latter sources seem to show a significant correlation between the number of hepatitis B vaccinations performed and the declaration to the pharmacovigilance of multiple sclerosis occurring between 1 and 2 years later. The application of the Hill’s criteria to these data indicates that the correlation between hepatitis B vaccine and multiple sclerosis may be causal.

http://www.ncbi.nlm.nih.gov/pubmed/?term=25395338

“The application of the Hill’s criteria to these data indicates that the correlation between hepatitis B vaccine and multiple sclerosis may be causal.”

Human Vaccines & Immunotherapeutics content • February 2014

Toward a mechanism-based in vitro safety test for pertussis toxin

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Abstract

Pertussis vaccines are routinely administered to infants to protect them from whooping cough. Still, an adequate safety test for pertussis toxin (PT), one of the main antigens in these vaccines, is not available. The histamine sensitization test is currently the only assay accepted by regulatory authorities to test for the absence of active PT in vaccines. This is however, a lethal animal test with poor reproducibility. In addition, it is not clear whether the assumed underlying mechanism, i.e., ADP-ribosylation of G proteins, is the only effect that should be considered in safety evaluation of PT. The in vitro safety test for PT that we developed is based on the clinical effects of PT in humans. For this, human cell lines were chosen based on the cell types involved in the clinical effects of PT. These cell lines were exposed to PT and analyzed by microarray. In this review, we discuss the clinical effects of PT and the mechanisms that underlie them. The approach taken may provide as an example for other situations in which an in vitro assay based on clinical effects in humans is required.

Full Report

http://www.tandfonline.com/doi/pdf/10.4161/hv.28001

From the full report:

“Taken together, the main clinical effects in humans where Pertussis Toxin is involved are increased insulin secretion with resulting hypoglycemia, leukocytosis, lung edema and inflammatory responses, together resulting in pulmonary hypertension and pneumonia. Moreover, PT can induce systemic hypotension, and is possibly involved in inducing neurological problems.”

BMC Bioinformatics • March 2014

DNAVaxDB: the first web-based DNA vaccine database and its data analysis

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Xiang Z, He Y.

Abstract

Since the first DNA vaccine studies were done in the 1990s, thousands more studies have followed. Here we report the development and analysis of DNAVaxDB (http://www.violinet.org/dnavaxdb), the first publically available web-based DNA vaccine database that curates, stores, and analyzes experimentally verified DNA vaccines, DNA vaccine plasmid vectors, and protective antigens used in DNA vaccines. All data in DNAVaxDB are annotated from reliable resources, particularly peer-reviewed articles. Among over 140 DNA vaccine plasmids, some plasmids were more frequently used in one type of pathogen than others; for example, pCMVi-UB for G-bacterial DNA vaccines, and pCAGGS for viral DNA vaccines. Presently, over 400 DNA vaccines containing over 370 protective antigens from over 90 infectious and non-infectious diseases have been curated in DNAVaxDB. While extracellular and bacterial cell surface proteins and adhesin proteins were frequently used for DNA vaccine development, the majority of protective antigens used in Chlamydophila DNA vaccines are localized to the inner portion of the cell. The DNA vaccine priming, other vaccine boosting vaccination regimen has been widely used to induce protection against infection of different pathogens such as HIV. Parasitic and cancer DNA vaccines were also systematically analyzed. User-friendly web query and visualization interfaces are available in DNAVaxDB for interactive data search. To support data exchange, the information of DNA vaccines, plasmids, and protective antigens is stored in the Vaccine Ontology (VO). DNAVaxDB is targeted to become a timely and vital source of DNA vaccines and related data and facilitate advanced DNA vaccine research and development.

Full Report

http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4094999/

“... the first publically available
web-based DNA vaccine database
that curates, stores, and analyzes
experimentally verified DNA vaccines,
DNA vaccine plasmid vectors, and protective antigens
used in DNA vaccines. Presently, over 400 DNA vaccines
containing over 370 protective antigens from over
90 infectious and non-infectious diseases have
been curated in DNAVaxDB.”

Current Medicinal Chemistry • March 2014

Sudden infant death following hexavalent vaccination: a neuropathologic study

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Abstract

We examined a large number of sudden infant death syndrome victims in order to point out a possible causal relationship between a previous hexavalent vaccination and the sudden infant death. We selected 110 cases submitted to in-depth histological examination of the autonomic nervous system and provided with detailed clinical and environmental information. In 13 cases (11.8%) the death occurred in temporal association with administration of the hexavalent vaccine (from 1 to 7 days). In none of these victims congenital developmental alterations of the main nervous structures regulating the vital functions were observed. Only the hypoplasia of the arcuate nucleus was present in 5 cases. In one case in particular an acquired hyperacute encephalitis of the tractus solitarii nucleus was diagnosed in the brainstem. This study does not prove a causal relationship between the hexavalent vaccination and SIDS. However, we hypothesize that vaccine components could have a direct role in sparking off a lethal outcome in vulnerable babies. In conclusion, we sustain the need that deaths occurring in a short space of time after hexavalent vaccination are appropriately investigated and submitted to a post-mortem examination particularly of the autonomic nervous system by an expert pathologist to objectively evaluate the possible causative role of the vaccine in SIDS.

http://www.ncbi.nlm.nih.gov/pubmed/24083600

“we hypothesize that vaccine components could have a direct role in sparking off a lethal outcome in vulnerable babies.”

Journal Of Investigative Medicine • High Impact Case Reports • March 2014

Postural Orthostatic Tachycardia With Chronic Fatigue After HPV Vaccination as Part of the "Autoimmune/Auto-inflammatory Syndrome Induced by Adjuvants": Case Report and Literature Review

Author information

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Abstract

We report the case of a 14-year-old girl who developed postural orthostatic tachycardia syndrome (POTS) with chronic fatigue 2 months following Gardasil vaccination. The patient suffered from persistent headaches, dizziness, recurrent syncope, poor motor coordination, weakness, fatigue, myalgias, numbness, tachycardia, dyspnea, visual disturbances, phonophobia, cognitive impairment, insomnia, gastrointestinal disturbances, and a weight loss of 20 pounds. The psychiatric evaluation ruled out the possibility that her symptoms were psychogenic or related to anxiety disorders. Furthermore, the patient tested positive for ANA (1:1280), lupus anticoagulant, and antiphospholipid. On clinical examination she presented livedo reticularis and was diagnosed with Raynaud's syndrome. This case fulfills the criteria for the autoimmune/auto-inflammatory syndrome induced by adjuvants (ASIA). Because human papillomavirus vaccination is universally recommended to teenagers and because POTS frequently results in long-term disabilities (as was the case in our patient), a thorough follow-up of patients who present with relevant complaints after vaccination is strongly recommended.

http://www.ncbi.nlm.nih.gov/pubmed/26425598

"The patient suffered from persistent headaches, dizziness, recurrent syncope, poor motor coordination, weakness, fatigue, myalgias, numbness, tachycardia, dyspnea, visual disturbances, phonophobia, cognitive impairment, insomnia, gastrointestinal disturbances, and a weight loss of 20 pounds."

PLoS One • March 2014

Mitochondrial dysfunction in Gulf War illness revealed by 31Phosphorus Magnetic Resonance Spectroscopy: a case-control study

Author information

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Abstract

BACKGROUND

Approximately 1/3 of 1990-1 Gulf War veterans developed chronic multisymptom health problems. Implicated exposures bear mechanisms that adversely affect mitochondria. Symptoms emphasize fatigue, cognition and muscle (brain and muscle are aerobically demanding); with protean additional domains affected, compatible with mitochondrial impairment. Recent evidence supports treatments targeting cell bioenergetics (coenzyme10) to benefit Gulf War illness symptoms. However, no evidence has directly documented mitochondrial or bioenergetic impairment in Gulf War illness.

OBJECTIVE

We sought to objectively assess for mitochondrial dysfunction, examining post-exercise phosphocreatine-recovery time constant (PCr-R) using (31)Phosphorus Magnetic Resonance Spectroscopy ((31)P-MRS), in Gulf War veterans with Gulf War illness compared to matched healthy controls. PCr-R has been described as a "robust and practical" index of mitochondrial status.

DESIGN AND PARTICIPANTS

Case-control study from 2012-2013. Fourteen community-dwelling Gulf War veterans and matched controls from the San Diego area comprised 7 men meeting CDC and Kansas criteria for Gulf War illness, and 7 non-deployed healthy controls matched 1:1 to cases on age, sex, and ethnicity.

OUTCOME MEASURE

Calf muscle phosphocreatine was evaluated by (31)P-MRS at rest, through 5 minutes of foot pedal depression exercise, and in recovery, to assess PCr-R. Paired t-tests compared cases to matched controls.

RESULTS

PCr-R was significantly prolonged in Gulf War illness cases vs their matched controls: control values, mean ± SD, 29.0 ± 8.7 seconds; case values 46.1 ± 18.0 seconds; difference 17.1 ± 14.9 seconds; $p = 0.023$. PCr-R was longer for cases relative to their matched controls for all but one pair; moreover while values clustered under 31 seconds for all but one control, they exceeded 35 seconds (with a spread up to 70 seconds) for all but one case.

DISCUSSION

These data provide the first direct evidence supporting mitochondrial dysfunction in Gulf War illness. Findings merit replication in a larger study and/or corroboration with additional mitochondrial assessment tools.

http://www.ncbi.nlm.nih.gov/pubmed/24675771

"These data provide the first direct evidence supporting mitochondrial dysfunction in Gulf War illness."

Journal Of Investigative Medicine
High Impact Case Reports • March 2014

Postural Orthostatic Tachycardia With Chronic Fatigue After HPV Vaccination as Part of the "Autoimmune/Auto-inflammatory Syndrome Induced by Adjuvants"

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Abstract

We report the case of a 14-year-old girl who developed postural orthostatic tachycardia syndrome (POTS) with chronic fatigue 2 months following Gardasil vaccination. The patient suffered from persistent headaches, dizziness, recurrent syncope, poor motor coordination, weakness, fatigue, myalgias, numbness, tachycardia, dyspnea, visual disturbances, phonophobia, cognitive impairment, insomnia, gastrointestinal disturbances, and a weight loss of 20 pounds. The psychiatric evaluation ruled out the possibility that her symptoms were psychogenic or related to anxiety disorders. Furthermore, the patient tested positive for ANA (1:1280), lupus anticoagulant, and antiphospholipid. On clinical examination she presented livedo reticularis and was diagnosed with Raynaud's syndrome. This case fulfills the criteria for the autoimmune/auto-inflammatory syndrome induced by adjuvants (ASIA). Because human papillomavirus vaccination is universally recommended to teenagers and because POTS frequently results in long-term disabilities (as was the case in our patient), a thorough follow-up of patients who present with relevant complaints after vaccination is strongly recommended.

http://hic.sagepub.com/content/2/1/2324709614527812.abstract

"We report the case of a 14-year-old girl who developed postural orthostatic tachycardia syndrome (POTS) with chronic fatigue 2 months following Gardasil vaccination. The patient suffered from persistent headaches, dizziness, recurrent syncope, poor motor coordination, weakness, fatigue, myalgias, numbness, tachycardia, dyspnea, visual disturbances, phonophobia, cognitive impairment, insomnia, gastrointestinal disturbances, and a weight loss of 20 pounds. This case fulfills the criteria for the autoimmune/auto-inflammatory syndrome induced by adjuvants (ASIA)."

Clinical And Experimental Rheumatology • March 2014

Alum, an aluminum-based adjuvant, induces Sjögren's syndrome-like disorder in mice

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Abstract

OBJECTIVES

Adjuvant-induced innate immune responses have been suspected to play a role in the initiation of certain autoimmune disorders. This study investigates the role of alum, an aluminum-based adjuvant in the induction of Sjögren's syndrome-like disorder in mice.

METHODS

Inbred, female New Zealand Mixed (NZM) 2758 strain of mice were injected with alum. Control mice were treated similarly with PBS. The mice were monitored for salivary gland dysfunction by measuring pilocarpine-induced salivation. Presence of lymphocytic infiltrates within the submandibular glands was studied by histopathology. Autoantibodies to Ro and La proteins were analysed by ELISA and the presence of anti-nuclear antibodies (ANA) was analysed by indirect immunofluorescence.

RESULTS

By eight weeks after treatment, the saliva production in the alum-treated mice was significantly decreased in comparison to the PBS-treated mice. This functional loss persisted till the termination of experiments at 20 wks. The incidence and severity of sialoadenitis was significantly higher in the alum-treated mice. Although there were no differences in the levels of anti-Ro/La autoantibodies in sera of alum and PBS-treated groups, the alum group showed higher ANA reactivity.

CONCLUSIONS

In the NZM2758 mice, alum induces a Sjögren's syndrome-like disorder that is characterised by chronic salivary gland dysfunction and the presence of lymphocytic infiltrates within the salivary glands. Thus, the potential of aluminum-based adjuvants for induction of autoimmunity should be closely monitored in individuals genetically susceptible to developing autoimmune disorders.

http://www.ncbi.nlm.nih.gov/pubmed/24739520

"Adjuvant-induced innate immune responses have been suspected to play a role in the initiation of certain autoimmune disorders. This study investigates the role of alum, an aluminum-based adjuvant in the induction of Sjögren's syndrome-like disorder in mice."

Behavioral And Brain Functions • April 2014

A key role for an impaired detoxification mechanism in the etiology and severity of autism spectrum disorders

Author information

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Abstract

BACKGROUND

Autism Spectrum Disorders (ASD) is a syndrome with a number of etiologies and different mechanisms that lead to abnormal development. The identification of autism biomarkers in patients with different degrees of clinical presentation (i.e., mild, moderate and severe) will give greater insight into the pathogenesis of this disease and will enable effective early diagnostic strategies and treatments for this disorder.

METHODS

In this study, the concentration of two toxic heavy metals, lead (Pb) and mercury (Hg), were measured in red blood cells, while glutathione-s-transferase (GST) and vitamin E, as enzymatic and non-enzymatic antioxidants, respectively, were measured in the plasma of subgroups of autistic patients with different Social Responsiveness Scale (SRS) and Childhood Autism Rating Scale (CARS) scores. The results were compared to age- and gender-matched healthy controls.

RESULTS

The obtained data showed that the patients with autism spectrum disorder had significantly higher Pb and Hg levels and lower GST activity and vitamin E concentrations compared with the controls. The levels of heavy metals (Hg and Pb), GST and vitamin E were correlated with the severity of the social and cognitive impairment measures (SRS and CARS). Receiver Operating Characteristics (ROC) analysis and predictiveness curves indicated that the four parameters show satisfactory sensitivity, very high specificity and excellent predictiveness. Multiple regression analyses confirmed that higher levels of Hg and Pb, together with lower levels of GST and vitamin E, can be used to predict social and cognitive impairment in patients with autism spectrum disorders.

CONCLUSION

This study confirms earlier studies that implicate toxic metal accumulation as a consequence of impaired detoxification in autism and provides insight into the etiological mechanism of autism.

Full Report

http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4017810/

“This study confirms earlier studies that implicate toxic metal accumulation as a consequence of impaired detoxification in autism and provides insight into the etiological mechanism of autism.”

Epidemiology And Infection • April 2014

Pertussis resurgence: waning immunity and pathogen adaptation—two sides of the same coin

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Abstract

Pertussis or whooping cough has persisted and resurged in the face of vaccination and has become one of the most prevalent vaccine-preventable diseases in Western countries. The high circulation rate of Bordetella pertussis poses a threat to infants that have not been (completely) vaccinated and for whom pertussis is a severe, life-threatening, disease. The increase in pertussis is mainly found in age groups in which immunity has waned and this has resulted in the perception that waning immunity is the main or exclusive cause for the resurgence of pertussis. However, significant changes in B. pertussis populations have been observed after the introduction of vaccinations, suggesting a role for pathogen adaptation in the persistence and resurgence of pertussis. These changes include antigenic divergence with vaccine strains and increased production of pertussis toxin. Antigenic divergence will affect both memory recall and the efficacy of antibodies, while higher levels of pertussis toxin may increase suppression of the innate and acquired immune system. We propose these adaptations of B. pertussis have decreased the period in which pertussis vaccines are effective and thus enhanced the waning of immunity. We plead for a more integrated approach to the pertussis problem which includes the characteristics of the vaccines, the B. pertussis populations and the interaction between the two.

http://www.ncbi.nlm.nih.gov/pubmed/23406868

“We propose these adaptations of B. pertussis have decreased the period in which pertussis vaccines are effective and thus enhanced the waning of immunity.”

Environmental Pollution • April 2014

Perinatal multiple exposure to neurotoxic (lead, methylmercury, ethylmercury, and aluminum) substances and neurodevelopment at six and 24 months of age

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Abstract

We studied neurodevelopment in infants from two communities. Children living in the vicinity of tin-ore kilns and smelters - TOKS; n = 51) were compared to children from a fishing village (Itapuã; n = 45). Mean hair-Hg (HHg) concentrations were significantly higher in Itapuã children which received significantly ($p = 0.0000001$) less mean ethylmercury (88.6 µg) from Thimerosal-containing vaccines (TCV) than the TOKS children (120 µg). Breast-milk Pb concentrations were significantly higher in the TOKS mothers ($p = 0.000017$; 10.04 vs. 3.9 µg L(-1)). Bayley mental development index (MDI) and psychomotor development index (PDI) were statistically significant (respectively $p < 0.0000001$, $p = 0.000007$) lower for the TOKS children only at 24 months of age. Multivariate regression analysis showed that MDI was negatively affected by breast-milk Pb and by HHg. PDI was positively affected by breast-feeding and negatively affected by ethylmercury. Milestone achievements were negatively affected by breast-milk Pb (age of walking) and by HHg (age of talking).

http://www.ncbi.nlm.nih.gov/pubmed/24486466

“Milestone achievements were negatively affected by breast-milk lead (age of walking) and by Mean hair-mercury (age of talking).”

International Journal Of Epidemiology • May 2014

The non-specific effects of vaccines and other childhood interventions: the contribution of INDEPTH Health and Demographic Surveillance Systems

Author Information

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Abstract

Most childhood interventions (vaccines, micronutrients) in low-income countries are justified by their assumed effect on child survival. However, usually the interventions have only been studied with respect to their disease/deficiency-specific effects and not for their overall effects on morbidity and mortality. In many situations, the population-based effects have been very different from the anticipated effects; for example, the measles-preventive high-titre measles vaccine was associated with 2-fold increased female mortality; BCG reduces neonatal mortality although children do not die of tuberculosis in the neonatal period; vitamin A may be associated with increased or reduced child mortality in different situations; effects of interventions may differ for boys and girls. The reasons for these and other contrasts between expectations and observations are likely to be that the immune system learns more than specific prevention from an intervention; such training may enhance or reduce susceptibility to unrelated infections. INDEPTH member centres have been in an ideal position to document such additional non-specific effects of interventions because they follow the total population long term. It is proposed that more INDEPTH member centres extend their routine data collection platform to better measure the use and effects of childhood interventions. In a longer perspective, INDEPTH may come to play a stronger role in defining health research issues of relevance to low-income countries.

Conclusion

Existing studies suggest a general pattern, namely that the live vaccines (BCG, measles vaccine, OPV and vaccinia) are associated with beneficial non-specific effects, leading to reduced all-cause mortality, whereas the inactivated, alum-adjuvated DTP vaccine is associated with increased susceptibility to other unrelated infections, particularly in females.

Full Report: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4052142/

“... the inactivated, alum-adjuvated DTP vaccine is associated with increased susceptibility to other unrelated infections, particularly in females.”

Parasitology Research • May 2014

Cytotoxic effect of organic solvents and surfactant agents on Acanthamoeba castellanii cysts

Author information

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Abstract

Acanthamoeba castellanii is a protozoan parasite that may cause sight-threatening keratitis in some individuals. Its eradication is difficult because the trophozoites encyst making organisms highly resistant to anti-amoebic drugs. To test new anti-Acanthamoeba agents, usually having low water solubility, organic solvents and surfactant agents should be used. Therefore, the lethal effect of different concentrations of the solvents acetone, methanol, ethanol, and DMSO and surfactant agents Tween 20, Tween 80, and Triton X-100 was tested. The minimal inhibitory concentrations (MIC) were determined against Acanthamoeba cysts. Results of the present study showed that the MIC for ethanol, methanol, acetone and DMSO was 25, 12.5, 12.5, and 10%, respectively and for Tween 20, Tween 80, and Triton X-100 was 0.25, 0.06, and 0.03%, respectively. There was no significant inhibitory effect on the multiplication of Acanthamoeba cysts as compared to parasite control when using the concentrations 3.12% for ethanol, 1.6% for methanol and acetone, 1.25% for DMSO, and 0.016% for Tween 20. On the other hand, both Tween 80 and Triton X-100 showed highly significant difference in comparison to parasite control almost among all the range of concentrations used in this study, and both showed lethal effect of 19 and 27.2%, respectively at their least concentration.

http://www.ncbi.nlm.nih.gov/pubmed/24638907

“... both Tween 80 and Triton X-100 showed ... lethal effect of 19 and 27.2%, respectively at their least concentration.”

“Adjuvants are necessary components to warrant the efficacy of vaccines,

however the overstimulation of the immune system is also associated with adverse effects.”

International Immunopharmacology • May 2014

Systemic immunotoxicity reactions induced by adjuvanted vaccines

Author information

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Abstract

Vaccine safety is a topic of concern for the treated individual, the family, the health care personnel, and the others involved in vaccination programs as recipients or providers. Adjuvants are necessary components to warrant the efficacy of vaccines, however the overstimulation of the immune system is also associated with adverse effects. Local reactions are the most frequent manifestation of toxicity induced by adjuvanted vaccines and, with the exception of the acute phase response (APR), much less is known about the systemic reactions that follow vaccination. Their low frequency or subclinical expression meant that this matter has been neglected. In this review, various systemic reactions associated with immune stimulation will be addressed, including: APR, hypersensitivity, induction or worsening of autoimmune diseases, modification of hepatic metabolism and vascular leak syndrome (VLS), with an emphasis on the mechanism involved. Finally, the authors analyze the current focus of discussion about vaccine safety and opportunities to improve the design of new adjuvanted vaccines in the future.

http://www.ncbi.nlm.nih.gov/pubmed/?term=24607449

Autism • Causes & Prevalence • June 2014

Etiology of autism spectrum disorders: Genes, environment, or both?

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Abstract

Thus far, most of the research on both neurodevelopmental and neurodegenerative disorders has been focused on finding the presumed underlying genetic causes, while much less emphasis has been put on potential environmental factors. While some forms of autism are clearly genetic, the fact remains that heritability factors cannot adequately explain all reported cases nor their drastic increase over the last few decades. In particular, studies on twins have now shown that common environmental factors account for 55% of their risk for developing autism while genetic susceptibility explains only 37% of cases. Because the prenatal environment and early postnatal environment are shared between twins and because overt symptoms of autism emerge around the end of the first year of life, it is likely that at least some of the environmental factors contributing to the risk of autism exert their deleterious neurodevelopmental effect during this early period of life. Indeed, evidence has now emerged showing that autism may in part result from early-life immune insults induced by environmental xenobiotics. One of the most common xenobiotic with immuno-stimulating as well as neurotoxic properties to which infants under two years of age are routinely exposed worldwide is the aluminum (Al) vaccine adjuvant. In this review we discuss the mechanisms by which Al can induce adverse neurological and immunological effects and how these may provide important clues of Al's putative role in autism. Because of the tight connection between the development of the immune and the central nervous system, the possibility that immune-overstimulation in early infancy via vaccinations may play a role in neurobehavioural disorders needs to be carefully considered.

Conclusion

There is now sufficient evidence from both human and animal studies showing that cumulative exposure to aluminium adjuvants is not as benign as previously assumed. Given that vaccines are the only medical intervention that we attempt to deliver to every living human on earth and that by far the largest target population for vaccination are healthy children, a better appreciation and understanding of vaccine adjuvant risks appears warranted.

http://www.oapublishinglondon.com/article/1368

"Indeed, evidence has now emerged showing that autism may in part result from early-life immune insults induced by environmental xenobiotics. One of the most common xenobiotic with immuno-stimulating as well as neurotoxic properties to which infants under two years of age are routinely exposed worldwide is the aluminum (Al) vaccine adjuvant. In this review we discuss the mechanisms by which Al can induce adverse neurological and immunological effects and how these may provide important clues of Aluminum's putative role in autism."

"... the United States Centers for Disease Control and Prevention states that Thimerosal is safe and there is no relationship between [T]himerosal[-]containing vaccines and autism rates in children. This is puzzling because, in a study conducted directly by CDC epidemiologists, a 7.6-fold increased risk of autism from exposure to Thimerosal during infancy was found."

Biomedical Research International • June 2014

Methodological issues and evidence of malfeasance in research purporting to show thimerosal in vaccines is safe

Author information

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Abstract

There are over 165 studies that have focused on Thimerosal, an organic-mercury (Hg) based compound, used as a preservative in many childhood vaccines, and found it to be harmful. Of these, 16 were conducted to specifically examine the effects of Thimerosal on human infants or children with reported outcomes of death; acrodynia; poisoning; allergic reaction; malformations; auto-immune reaction; Well's syndrome; developmental delay; and neurodevelopmental disorders, including tics, speech delay, language delay, attention deficit disorder, and autism. In contrast, the United States Centers for Disease Control and Prevention states that Thimerosal is safe and there is "no relationship between [T]himerosal[-]containing vaccines and autism rates in children." This is puzzling because, in a study conducted directly by CDC epidemiologists, a 7.6-fold increased risk of autism from exposure to Thimerosal during infancy was found. The CDC's current stance that Thimerosal is safe and that there is no relationship between Thimerosal and autism is based on six specific published epidemiological studies coauthored and sponsored by the CDC. The purpose of this review is to examine these six publications and analyze possible reasons why their published outcomes are so different from the results of investigations by multiple independent research groups over the past 75+ years.

Full Report

http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4065774/

International Journal Of Epidemiology • June 2014

The non-specific effects of vaccines and other childhood interventions: the contribution of INDEPTH Health and Demographic Surveillance Systems

Author information

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Abstract

Most childhood interventions (vaccines, micronutrients) in low-income countries are justified by their assumed effect on child survival. However, usually the interventions have only been studied with respect to their disease/deficiency-specific effects and not for their overall effects on morbidity and mortality. In many situations, the population-based effects have been very different from the anticipated effects; for example, the measles-preventive high-titre measles vaccine was associated with 2-fold increased female mortality; BCG reduces neonatal mortality although children do not die of tuberculosis in the neonatal period; vitamin A may be associated with increased or reduced child mortality in different situations; effects of interventions may differ for boys and girls. The reasons for these and other contrasts between expectations and observations are likely to be that the immune system learns more than specific prevention from an intervention; such training may enhance or reduce susceptibility to unrelated infections. INDEPTH member centres have been in an ideal position to document such additional non-specific effects of interventions because they follow the total population long term. It is proposed that more INDEPTH member centres extend their routine data collection platform to better measure the use and effects of childhood interventions. In a longer perspective, INDEPTH may come to play a stronger role in defining health research issues of relevance to low-income countries.

Full Report

http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4052142/

“In many situations,

the population-based effects have been very different

from the anticipated effects; for example, the measles-preventive

high-titre measles vaccine was associated with

2-fold increased female mortality ...”

“Our results indicated that food emulsifier applied in relatively high concentrations in even the most frequently consumed foods can increase the absorption of DEHP, and its role may be related to the structure and function damages of mitochondria in enterocytes.”

Toxicology Science • June 2014

Food emulsifier polysorbate 80 increases intestinal absorption of di-(2-ethylhexyl) phthalate in rats

Author information

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Abstract

The aim of the present research was to explore whether food emulsifier polysorbate 80 can enhance the absorption of di-(2-ethylhexyl) phthalate (DEHP) and its possible mechanism. We established the high-performance liquid chromatography (HPLC) method for detecting DEHP and its major metabolite, mono-ethylhexyl phthalate (MEHP) in rat plasma, and then examined the toxicokinetic and bioavailability of DEHP with or without polysorbate 80 in rats. The study of its mechanism to increase the absorption of phthalates demonstrated that polysorbate 80 can induce mitochondrial dysfunction in time- and concentration-dependence manners in Caco-2 cells by reducing mitochondrial membrane potential, diminishing the production of the adenosine triphosphate, and decreasing the activity of electron transport chain. Our results indicated that food emulsifier applied in relatively high concentrations in even the most frequently consumed foods can increase the absorption of DEHP, and its role may be related to the structure and function damages of mitochondria in enterocytes.

Full Report

http://toxsci.oxfordjournals.org/content/139/2/317.long

Journal Of Infectious Disease • July 2014

Sex-based biology and the rational design of influenza vaccination strategies

Author information

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Abstract

Biological (ie, sex) differences as well as cultural (ie, gender) norms influence the acceptance and efficacy of vaccines for males and females. These differences are often overlooked in the design and implementation of vaccination strategies. Using seasonal and pandemic influenza vaccines, we document profound differences between the sexes in the acceptance, correlates of protection, and adverse reactions following vaccination in both young and older adults. Females develop higher antibody responses, experience more adverse reactions to influenza vaccines, and show greater vaccine efficacy than males. Despite greater vaccine efficacy in females, both young and older females are often less likely to accept influenza vaccines than their male counterparts. Identification of the biological mechanisms, including the hormones and genes, that underlie differential responses to vaccination is necessary. We propose that vaccines should be matched to an individual's biological sex, which could involve systematically tailoring diverse types of FDA-approved influenza vaccines separately for males and females. One goal for vaccines designed to protect against influenza and even other infectious diseases should be to increase the correlates of protection in males and reduce adverse reactions in females in an effort to increase acceptance and vaccine-induced protection in both sexes.

Full Report

http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4157517/

"Biological (ie, sex) differences as well as cultural (ie, gender) norms influence the acceptance and efficacy of vaccines for males and females. These differences are often [always] overlooked in the design and implementation of vaccination strategies."

“Seventy-nine infants received a total of 1,303 prescriptions comprising 77 formulations and 70 active drugs.

Eighty-six excipients were identified, of which, 9 were harmful excipients (HE) and 48 were potentially harmful excipients (PHE).”

European Journal Of Pediatrics • July 2014

Toxic excipients in medications for neonates in Brazil

Author information

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Abstract

The aim was to describe the exposure to excipients among neonates hospitalised in the neonatal intensive care unit (NICU) of a public hospital in Brasilia, Brazil. This was a retrospective study based on medicines that were prescribed electronically to neonates (≤28 days) who were admitted to the NICU of a hospital in Brasilia between January 1 and March 31, 2012. Excipients were identified from the medicine package leaflets and were classified according to toxicity. Seventy-nine infants received a total of 1,303 prescriptions comprising 77 formulations and 70 active drugs. Eighty-six excipients were identified, of which, 9 were harmful excipients (HE) and 48 were potentially harmful excipients (PHE). Almost all the neonates (98.7 %) were exposed to at least one HE and PHE. Preterm neonates (n = 64; 1,502 neonate days) presented high risk of exposure to polysorbate 80 (3.26/100 neonate days), sodium hydroxide (3.39), PG (3.19) and propylparaben (3.06). Full-term neonates (n = 15; 289 neonate days) presented risks in relation to phenol (4.84), ethanol (3.8) and sodium citrate (3.46).

CONCLUSION

Neonates in NICUs in Brazil are exposed to a wide variety of HE and PHE with unpredictable results.

http://www.ncbi.nlm.nih.gov/pubmed/24500397

Translational Neurodegeneration • August 2014

Measles-mumps-rubella vaccination timing and autism among young African American boys: a reanalysis of CDC data

Author information

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Abstract

BACKGROUND

A significant number of children diagnosed with autism spectrum disorder suffer a loss of previously-acquired skills, suggesting neurodegeneration or a type of progressive encephalopathy with an etiological basis occurring after birth. The purpose of this study is to investigate the effectof the age at which children got their first Measles-Mumps-Rubella (MMR) vaccine on autism incidence. This is a reanalysis of the data set, obtained from the U.S. Centers for Disease Control and Protection (CDC), used for the Destefano et al. 2004 publication on the timing of the first MMR vaccine and autism diagnoses.

METHODS

The author embarked on the present study to evaluate whether a relationship exists between child age when the first MMR vaccine was administered among cases diagnosed with autism and controls born between 1986 through 1993 among school children in metropolitan Atlanta. The Pearson's chi-squared method was used to assess relative risks of receiving an autism diagnosis within the total cohort as well as among different race and gender categories.

RESULTS

When comparing cases and controls receiving their first MMR vaccine before and after 36 months of age, there was a statistically significant increase in autism cases specifically among African American males who received the first MMR prior to 36 months of age. Relative risks for males in general and African American males were 1.69 (p=0.0138) and 3.36 (p=0.0019), respectively. Additionally, African American males showed an odds ratio of 1.73 (p=0.0200) for autism cases in children receiving their first MMR vaccine prior to 24 months of age versus 24 months of age and thereafter.

CONCLUSIONS

The present study provides new epidemiologic evidence showing that African American males receiving the MMR vaccine prior to 24 months of age or 36 months of age are more likely to receive an autism diagnosis.

http://www.ncbi.nlm.nih.gov/pubmed/25114790

"The present study provides new epidemiologic evidence showing that African American males receiving the MMR vaccine prior to 24 months of age or 36 months of age are more likely to receive an autism diagnosis."

Vaccine • September 2014

Interaction between neonatal vitamin A supplementation and timing of measles vaccination: a retrospective analysis of three randomized trials from Guinea-Bissau

Author information

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Abstract

BACKGROUND

In Guinea-Bissau we conducted three trials of neonatal vitamin A supplementation (NVAS) from 2002 to 2008. None of the trials found a beneficial effect on mortality. From 2003 to 2007, an early measles vaccine (MV) trial was ongoing, randomizing children 1:2 to early MV at 4.5 months or no early MV, in addition to the usual MV at 9 months. We have previously found interactions between vitamin A and vaccines.

OBJECTIVE

We investigated whether there were interactions between NVAS and early MV.

DESIGN

We compared the mortality of NVAS and placebo recipients: first, from 4.5 to 8 months for children randomized to early MV or no early MV; and second, from 9 to 17 months in children who had received two MV or one MV. Mortality rates (MR) were compared in Cox models producing mortality rate ratios (MRR).

RESULTS

A total of 5141 children were randomized to NVAS (N=3015) or placebo (N=2126) and were later randomized to early MV (N=1700) or no early MV (N=3441). Between 4.5 and 8 months, NVAS compared with placebo was associated with higher mortality in early MV recipients (MR=30 versus MR=0, p=0.01), but not in children who did not receive early MV (p for interaction between NVAS and early MV=0.03). From 9 to 17 months NVAS was not associated with mortality. Overall, from 4.5 to 17 months NVAS was associated with increased mortality in early MV recipients (Mortality rate ratio=5.39 (95% confidence interval: 1.62, 17.99)).

CONCLUSIONS

These observations indicate that NVAS may interact with vaccines given several months later. This may have implications for the planning of future child intervention programs.

http://www.ncbi.nlm.nih.gov/pubmed/25131735

“These observations indicate that neonatal vitamin A supplementation may interact with vaccines given several months later.”

BMC Pediatrics • August 2014

Neonatal vitamin A supplementation associated with a cluster of deaths and poor early growth in a randomised trial among low-birth-weight boys of vitamin A versus oral polio vaccine at birth

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Abstract

Background

The effect of oral polio vaccine administered already at birth (OPV0) on child survival was not examined before being recommended in 1985. Observational data suggested that OPV0 was harmful for boys, and trials have shown that neonatal vitamin A supplementation (NVAS) at birth may be beneficial for boys. We set out to test this research question in a randomised trial.

Methods

The trial was carried out at the Bandim Health Project, Guinea-Bissau. We planned to enrol 900 low-birth weight (LBW) boys in a randomised trial to investigate whether NVAS instead of OPV0 could lower infant mortality for LBW boys. At birth, the children were randomised to OPV (usual treatment) or VAS (intervention treatment) and followed for 6 months for growth and 12 months for survival. Hazard Ratios (HR) for mortality were calculated using Cox regression. We compared the individual anthropometry measurements to the 2006 WHO growth reference. We compared differences in z-scores by linear regression. Relative risks (RR) of being stunted or underweight were calculated in Poisson regression models with robust standard errors.

Results

In the rainy season we detected a cluster of deaths in the VAS group and the trial was halted immediately with 232 boys enrolled. The VAS group had significantly higher mortality than the OPV group in the rainy season (HR: 9.91 (1.23 – 80)). All deaths had had contact with the neonatal nursery; of seven VAS boys enrolled during one week in September, six died within two months of age, whereas only one died among the six boys receiving OPV ($p = 0.05$). Growth (weight and arm-circumference) in the VAS group was significantly worse until age 3 months.

Conclusion

VAS at birth instead of OPV was not beneficial for the LBW boys in this study. With the premature closure of the trial it was not possible to answer the research question. However, the results of this study call for extra caution when testing the effect of NVAS in the future.

http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4236664/

[example of the experimental nature of vaccination.

This test using Vitamin A Supplementation versus Oral Polio Vaccine resulted in the deaths of 6 African boys]

Human & Experimental Toxicology • August 2014

Vaccination to prevent varicella: Goldman and King's response to Myers' interpretation of Varicella Active Surveillance Project data

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Abstract

BACKGROUND

There is increasing evidence that herpes zoster (HZ) incidence rates among children and adults (aged <60 years) with a history of natural varicella are influenced primarily by the frequency of exogenous exposures, while asymptomatic endogenous reactivations help to cap the rate at approximately 550 cases/100,000 person-years when exogenous boosting becomes rare. The Antelope Valley Varicella Active Surveillance Project was funded by the Centers for Disease Control and Prevention in 1995 to monitor the effects of varicella vaccination in one of the three representative regions of the United States. The stability in the data collection and number of reporting sites under varicella surveillance from 1995-2002 and HZ surveillance during 2000-2001 and 2006-2007 contributed to the robustness of the discerned trends.

DISCUSSION

Varicella vaccination may be useful for leukemic children; however, the target population in the United States is all children. Since the varicella vaccine inoculates its recipients with live, attenuated varicella-zoster virus (VZV), clinical varicella cases have dramatically declined. Declining exogenous exposures (boosts) from children shedding natural VZV have caused waning cell-mediated immunity. Thus, the protection provided by varicella vaccination is neither lifelong nor complete. Moreover, dramatic increases in the incidence of adult shingles cases have been observed since HZ was added to the surveillance in 2000. In 2013, this topic is still debated and remains controversial in the United States.

SUMMARY

When the costs of the booster dose for varicella and the increased shingles recurrences are included, the universal varicella vaccination program is neither effective nor cost-effective.

http://www.ncbi.nlm.nih.gov/pubmed/24275643

"When the costs of the booster dose for varicella and the increased shingles recurrences are included, the universal varicella vaccination program is neither effective nor cost-effective."

Vaccine • September 2014

Interaction between neonatal vitamin A supplementation and timing of measles vaccination: a retrospective analysis of three randomized trials from Guinea-Bissau

Author information

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Abstract

BACKGROUND

In Guinea-Bissau we conducted three trials of neonatal vitamin A supplementation (NVAS) from 2002 to 2008. None of the trials found a beneficial effect on mortality. From 2003 to 2007, an early measles vaccine (MV) trial was ongoing, randomizing children 1:2 to early MV at 4.5 months or no early MV, in addition to the usual MV at 9 months. We have previously found interactions between vitamin A and vaccines.

OBJECTIVE

We investigated whether there were interactions between NVAS and early MV.

DESIGN

We compared the mortality of NVAS and placebo recipients: first, from 4.5 to 8 months for children randomized to early MV or no early MV; and second, from 9 to 17 months in children who had received two MV or one MV. Mortality rates (MR) were compared in Cox models producing mortality rate ratios (MRR).

RESULTS

A total of 5141 children were randomized to NVAS (N=3015) or placebo (N=2126) and were later randomized to early MV (N=1700) or no early MV (N=3441). Between 4.5 and 8 months, NVAS compared with placebo was associated with higher mortality in early MV recipients (MR=30 versus MR=0, p=0.01), but not in children who did not receive early MV (p for interaction between NVAS and early MV=0.03). From 9 to 17 months NVAS was not associated with mortality. Overall, from 4.5 to 17 months NVAS was associated with increased mortality in early MV recipients (Mortality rate ratio=5.39 (95% confidence interval: 1.62, 17.99)).

CONCLUSIONS

These observations indicate that NVAS may interact with vaccines given several months later.
This may have implications for the planning of future child intervention programs.

http://www.ncbi.nlm.nih.gov/pubmed/25131735

“These observations indicate that neonatal vitamin A supplementation may interact with vaccines given several months later.”

“This is the first report of measles transmission from a twice vaccinated individual.”

Oxford Journals Clinical Infectious Diseases • October 2014

Outbreak of Measles Among Persons With Prior Evidence of Immunity New York City, 2011

Author Information

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Abstract

Background

Measles was eliminated in the United States through high vaccination coverage and a public health system able to rapidly respond to measles. Measles may occur among vaccinated individuals, but secondary transmission from such individuals has not been documented.

Methods

Suspected cases and contacts exposed during a measles outbreak in New York City in 2011 were investigated. Medical histories and immunization records were obtained. Cases were confirmed by detection of measles-specific IgM and/or RNA. Tests for measles IgG, IgG avidity, measurement of measles neutralizing antibody titers, and genotyping were performed to characterize the cases.

Results

The index case had two doses of measles-containing vaccine. Of 88 contacts, four secondary cases were confirmed that had either two doses of measles-containing vaccine or a past positive measles IgG antibody. All cases had laboratory confirmation of measles infection, clinical symptoms consistent with measles, and high avidity IgG antibody characteristic of a secondary immune response. Neutralizing antibody titers of secondary cases reached >80,000 mIU/mL 3-4 days post-rash onset while that of the index was <500 mIU/mL 9 days post-rash onset. No additional cases occurred among 231 contacts of secondary cases.

Conclusions

This is the first report of measles transmission from a twice vaccinated individual. The clinical presentation and laboratory data of the index were typical of measles in a naïve individual. Secondary cases had robust anamnestic antibody responses. No tertiary cases occurred despite numerous contacts. This outbreak underscores the need for thorough epidemiologic and laboratory investigation of suspected measles cases regardless of vaccination status.

http://cid.oxfordjournals.org/content/early/2014/02/27/cid.ciu105

Indian Journal Of Medical Ethics • October 2014

Thimerosal as discrimination: vaccine disparity in the UN Minamata Convention on mercury

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Abstract

When addressing toxins, one unmistakable parallel exists between biology and politics: developing children and developing nations are those most vulnerable to toxic exposures. This disturbing parallel is the subject of this critical review, which examines the use and distribution of the mercury (Hg)-based compound, thimerosal, in vaccines. Developed in 1927, thimerosal is 49.55% Hg by weight and breaks down in the body into ethyl-Hg chloride, ethyl-Hg hydroxide and sodium thiosalicylate. Since the early 1930s, there has been evidence indicating that thimerosal poses a hazard to the health of human beings and is ineffective as an antimicrobial agent. While children in the developed and predominantly western nations receive doses of mostly no-thimerosal and reduced-thimerosal vaccines, children in the developing nations receive many doses of several unreduced thimerosal-containing vaccines (TCVs). Thus, thimerosal has continued to be a part of the global vaccine supply and its acceptability as a component of vaccine formulations remained unchallenged until 2010, when the United Nations (UN), through the UN Environment Programme, began negotiations to write the global, legally binding Minamata Convention on Hg. During the negotiations, TCVs were dropped from the list of Hg-containing products to be regulated. Consequently, a double standard in vaccine safety, which previously existed due to ignorance and economic reasons, has now been institutionalised as global policy. Ultimately, the Minamata Convention on Hg has sanctioned the inequitable distribution of thimerosal by specifically exempting TCVs from regulation, condoning a two-tier standard of vaccine safety: a predominantly no-thimerosal and reduced-thimerosal standard for developed nations and a predominantly thimerosal-containing one for developing nations. This disparity must now be evaluated urgently as a potential form of institutionalised discrimination.

http://www.ncbi.nlm.nih.gov/pubmed/?term=25101548

“the Minamata Convention on Mercury has sanctioned the inequitable distribution of thimerosal by specifically exempting TCVs from regulation, condoning a two-tier standard of vaccine safety; a predominantly no-thimerosal and reduced-thimerosal standard for developed nations and a predominantly thimerosal-containing one for developing nations. This disparity must now be evaluated urgently as a potential form of institutionalized discrimination.”

Annals Of Medical And Health Sciences Research • November 2014

Hepatitis B vaccination and associated oral manifestations: a non-systematic review of literature and case reports

Author information

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Abstract

Hepatitis B vaccine has been administered in children and adults routinely to reduce the incidence of the disease. Even though, hepatitis B vaccine is considered as highly safe, some adverse reactions have been reported. A literature search was carried out in PubMed, accessed via the National Library of Medicine PubMed interface, searching used the following keywords: Hepatitis B vaccine and complications from 1980 to 2014. A total of 1147 articles were obtained out of which articles, which discuss the complications occurring orally or occurring elsewhere in the body, which have the potential to manifest orally after hepatitis B vaccination were selected. A total of 82 articles were identified which included 58 case series or case reports, 15 review articles, 4 cross sectional studies, 3 prospective cohort studies, one retrospective cohort study and a case control study. After reviewing the literature, we observed that complications seen after Hepatitis B vaccination are sudden infant death syndrome, multiple sclerosis, chronic fatigue syndrome, idiopathic thrombocytopenic purpura, vasculititis optic neuritis, anaphylaxis, systemic lupus erytymatosus, lichen planus and neuro-muscular disorder. Of these complications, some are manifested orally or have the potential to manifest orally. Although, most of the complications are self-limiting, some are very serious conditions, which require hospitalization with immediate medical attention.

Full Report

http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4250977/

“A total of 82 articles were identified which included 58 case series or case reports, 15 review articles, 4 cross sectional studies, 3 prospective cohort studies, one retrospective cohort study and a case control study. After reviewing the literature, we observed that complications seen after Hepatitis B vaccination are sudden infant death syndrome, multiple sclerosis, chronic fatigue syndrome, idiopathic thrombocytopenic purpura, vasculititis optic neuritis, anaphylaxis, systemic lupus erytymatosus, lichen planus and neuro-muscular disorder. Of these complications, some are manifested orally or have the potential to manifest orally.”

Environmental Health • November 2014

Longitudinal analysis of the association between removal of dental amalgam, urine mercury and 14 self-reported health symptoms

Author information

Zwicker JD1, Dutton DJ, Emery JC.

Abstract

BACKGROUND

Mercury vapor poses a known health risk with no clearly established safe level of exposure. Consequently there is debate over whether the level of prolonged exposure to mercury vapor from dental amalgam fillings, combining approximately 50% mercury with other metals, is sufficiently high to represent a risk to health. The objective of our study is to determine if mercury exposure from amalgam fillings is associated with risk of adverse health effects.

METHODS

In a large longitudinal non-blind sample of participants from a preventative health program in Calgary, Canada we compared number of amalgam fillings, urine mercury measures and changes in 14 self-reported health symptoms, proposed to be mercury dependent sub-clinical measures of mental and physical health. The likelihood of change over one year in a sample of persons who had their fillings removed was compared to a sample of persons who had not had their fillings removed. We use non-parametric statistical tests to determine if differences in urine mercury were statistically significant between sample groups. Logistic regression models were used to estimate the likelihood of observing symptom improvement or worsening in the sample groups.

RESULTS

At baseline, individuals with dental amalgam fillings have double the measured urine mercury compared to a control group of persons who have never had amalgam fillings. Removal of amalgam fillings decreases measured urine mercury to levels in persons without amalgam fillings. Although urine mercury levels in our sample are considered by Health Canada to be too low to pose health risks, removal of amalgam fillings reduced the likelihood of self-reported symptom deterioration and increased the likelihood of symptom improvement in comparison to people who retained their amalgam fillings.

CONCLUSIONS

Our findings suggest that mercury exposure from amalgam fillings adversely impact health and therefore are a health risk. The use of safer alternative materials for dental fillings should be encouraged to avoid the increased risk of health deterioration associated with unnecessary exposure to mercury.

Full Report

http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4273453/

“Our findings suggest that mercury exposure from amalgam fillings adversely impact health and therefore are a health risk.”

Journal Of Autoimmunity • November 2014

Immunization with hepatitis B vaccine accelerates SLE-like disease in a murine model

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Abstract

Hepatitis-B vaccine (HBVv) can prevent HBV-infection and associated liver diseases. However, concerns regarding its safety, particularly among patients with autoimmune diseases (i.e. SLE) were raised. Moreover, the aluminum adjuvant in HBVv was related to immune mediated adverse events. Therefore, we examined the effects of immunization with HBVv or alum on SLE-like disease in a murine model. NZBWF1 mice were immunized with HBVv (Engerix), or aluminum hydroxide (alum) or phosphate buffered saline (PBS) at 8 and 12 weeks of age. Mice were followed for weight, autoantibodies titers, blood counts, proteinuria, kidney histology, neurocognitive functions (novel object recognition, staircase, Y-maze and the forced swimming tests) and brain histology. Immunization with HBVv induced acceleration of kidney disease manifested by high anti-dsDNA antibodies ($p < 0.01$), early onset of proteinuria ($p < 0.05$), histological damage and deposition of HBs antigen in the kidney. Mice immunized with HBVv and/or alum had decreased cells counts mainly of the red cell lineage ($p < 0.001$), memory deficits ($p < 0.01$), and increased activated microglia in different areas of the brain compare with mice immunized with PBS. Anxiety-like behavior was more pronounced among mice immunized with alum. In conclusion, herein we report that immunization with the HBVv aggravated kidney disease in an animal model of SLE. Immunization with either HBVv or alum affected blood counts, neurocognitive functions and brain gliosis. Our data support the concept that different component of vaccines may be linked with immune and autoimmune mediated adverse events.

http://www.ncbi.nlm.nih.gov/pubmed/25042822

“... concerns regarding its safety, [hepatitis B vaccine] particularly among patients with autoimmune diseases (i.e. SLE) were raised. Moreover, the aluminum adjuvant in HBVv was related to immune mediated adverse events. Our data support the concept that different component of vaccines may be linked with immune and autoimmune mediated adverse events.”

Frontiers In Neurology • November 2014

Clinical features in patients with long-lasting macrophagic myofasciitis

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Abstract

Macrophagic myofasciitis (MMF) is an emerging condition characterized by specific muscle lesions assessing abnormal long-term persistence of aluminum hydroxide within macrophages at the site of previous immunization. Affected patients usually are middle-aged adults, mainly presenting with diffuse arthromyalgias, chronic fatigue, and marked cognitive deficits, not related to pain, fatigue, or depression. Clinical features usually correspond to that observed in chronic fatigue syndrome/myalgic encephalomyelitis. Representative features of MMF-associated cognitive dysfunction include dysexecutive syndrome, visual memory impairment, and left ear extinction at dichotic listening test. Most patients fulfill criteria for non-amnestic/dysexecutive mild cognitive impairment, even if some cognitive deficits appear unusually severe. Cognitive dysfunction seems stable over time despite marked fluctuations. Evoked potentials may show abnormalities in keeping with central nervous system involvement, with a neurophysiological pattern suggestive of demyelination. Brain perfusion SPECT shows a pattern of diffuse cortical and subcortical abnormalities, with hypoperfusions correlating with cognitive deficiencies. The combination of musculoskeletal pain, chronic fatigue, and cognitive disturbance generates chronic disability with possible social exclusion. Classical therapeutic approaches are usually unsatisfactory making patient care difficult.

Full Report

http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4246686/

“The combination of musculoskeletal pain, chronic fatigue, and cognitive disturbance generates chronic disability with possible social exclusion. Classical therapeutic approaches are usually unsatisfactory making patient care difficult.”

Environmental Health • November 2014

Longitudinal analysis of the association between removal of dental amalgam, urine mercury and 14 self-reported health symptoms

Author information

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Abstract

BACKGROUND

Mercury vapor poses a known health risk with no clearly established safe level of exposure. Consequently there is debate over whether the level of prolonged exposure to mercury vapor from dental amalgam fillings, combining approximately 50% mercury with other metals, is sufficiently high to represent a risk to health. The objective of our study is to determine if mercury exposure from amalgam fillings is associated with risk of adverse health effects.

METHODS

In a large longitudinal non-blind sample of participants from a preventative health program in Calgary, Canada we compared number of amalgam fillings, urine mercury measures and changes in 14 self-reported health symptoms, proposed to be mercury dependent sub-clinical measures of mental and physical health. The likelihood of change over one year in a sample of persons who had their fillings removed was compared to a sample of persons who had not had their fillings removed. We use non-parametric statistical tests to determine if differences in urine mercury were statistically significant between sample groups. Logistic regression models were used to estimate the likelihood of observing symptom improvement or worsening in the sample groups.

RESULTS

At baseline, individuals with dental amalgam fillings have double the measured urine mercury compared to a control group of persons who have never had amalgam fillings. Removal of amalgam fillings decreases measured urine mercury to levels in persons without amalgam fillings. Although urine mercury levels in our sample are considered by Health Canada to be too low to pose health risks, removal of amalgam fillings reduced the likelihood of self-reported symptom deterioration and increased the likelihood of symptom improvement in comparison to people who retained their amalgam fillings.

CONCLUSIONS

Our findings suggest that mercury exposure from amalgam fillings adversely impact health and therefore are a health risk. The use of safer alternative materials for dental fillings should be encouraged to avoid the increased risk of health deterioration associated with unnecessary exposure to mercury.

Full Report

http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4273453/

“Our findings suggest that mercury exposure from amalgam fillings adversely impact health and therefore are a health risk.”

Clinical And Experimental Immunology • December 2014

Vaccine-associated varicella and rubella infections in severe combined immunodeficiency with isolated CD4 lymphocytopenia and mutations in IL7R detected by tandem whole exome sequencing and chromosomal microarray

Author information

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Abstract

In areas without newborn screening for severe combined immunodeficiency (SCID), disease-defining infections may lead to diagnosis, and in some cases, may not be identified prior to the first year of life. We describe a female infant who presented with disseminated vaccine-acquired varicella (VZV) and vaccine-acquired rubella infections at 13 months of age. Immunological evaluations demonstrated neutropenia, isolated CD4 lymphocytopenia, the presence of CD8(+) T cells, poor lymphocyte proliferation, hypergammaglobulinaemia and poor specific antibody production to VZV infection and routine immunizations. A combination of whole exome sequencing and custom-designed chromosomal microarray with exon coverage of primary immunodeficiency genes detected compound heterozygous mutations (one single nucleotide variant and one intragenic copy number variant involving one exon) within the IL7R gene. Mosaicism for wild-type allele (20-30%) was detected in pretransplant blood and buccal DNA and maternal engraftment (5-10%) demonstrated in pretransplant blood DNA. This may be responsible for the patient's unusual immunological phenotype compared to classical interleukin (IL)-7R□ deficiency. Disseminated VZV was controlled with anti-viral and immune-based therapy, and umbilical cord blood stem cell transplantation was successful. Retrospectively performed T cell receptor excision circle (TREC) analyses completed on neonatal Guthrie cards identified absent TREC. This case emphasizes the danger of live viral vaccination in severe combined immunodeficiency (SCID) patients and the importance of newborn screening to identify patients prior to high-risk exposures. It also illustrates the value of aggressive pathogen identification and treatment, the influence newborn screening can have on morbidity and mortality and the significant impact of newer genomic diagnostic tools in identifying the underlying genetic aetiology for SCID patients.

http://www.ncbi.nlm.nih.gov/pubmed/25046553

"This case emphasizes the danger of live viral vaccination in severe combined immunodeficiency (SCID) patients and the importance of newborn screening to identify patients prior to high-risk exposures."

Yale Journal Of Biology And Medicine • December 2014

‘Poisonous, Filthy, Loathsome, Damnable Stuff’: The Rhetorical Ecology of Vaccination Concern

Author Information

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Abstract

In this article, we analyze newspaper articles and advertisements mentioning vaccination from 1915 to 1922 and refer to historical studies of vaccination practices and attitudes in the early 20th century in order to assess historical continuities and discontinuities in vaccination concern. In the Progressive Era period, there were a number of themes or features that resonated with contemporary issues and circumstances: 1) fears of vaccine contamination; 2) distrust of medical professionals; 3) resistance to compulsory vaccination; and 4) the local nature of vaccination concern. Such observations help scholars and practitioners understand vaccine skepticism as longstanding, locally situated, and linked to the sociocultural contexts in which vaccination occurs and is mandated for particular segments of the population. A rhetorical approach offers a way to understand how discourses are engaged and mobilized for particular purposes in historical contexts. Historically situating vaccine hesitancy and addressing its articulation with a particular rhetorical ecology offers scholars and practitioners a robust understanding of vaccination concerns that can, and should, influence current approaches to vaccination skepticism.

Introduction

On June 26, 2014, Eric Kodish, MD, a medical ethicist at the Cleveland Clinic, wrote in the Washington Post that “The anti-vaccination movement is a relatively new one that has taken hold over the past decade. Started by a small community of parents, it is based on myths that have been perpetuated by the power of the Internet and endorsements from celebrities such as actress Jenny McCarthy, who has suggested that vaccinations may have caused her son’s autism” [1]. This statement encapsulates mainstream public health attitudes toward vaccine skepticism in the early 21st century — that it constitutes a unified national movement, that the movement is relatively new, and that it has gained authority due to the power of the Internet and celebrity endorsements.

Indeed, it does seem as if the medical and public health consensus concerning the value of vaccination is unraveling culturally in the United States. Medical researchers routinely study health messaging about vaccination, finding most recently that popular public health promotion programs do not convince committed non-vaccinators to change their minds [2]. A discourse of crisis pervades media reporting on outbreaks of infectious disease, and every flu season brings with it a series of escalating media exhortations to be vaccinated. Physicians report increasing frustrations with parents who refuse to vaccinate their children or who seek a different vaccination schedule [3,4]. The American Academy of Pediatrics (AAP) has had to state unequivocally that it is against firing patients as a result of their vaccination status [5]; and, as with Erik Kodish, medical ethicists accuse parents who do not vaccinate their children of negligence [1,6].

Yet national vaccination rates for most routine infectious diseases of childhood in the United States remain high, suggesting that ongoing concerns about vaccination occur in tandem with the general success of public health efforts to vaccinate children against what were once routine childhood diseases. National immunization rates suggest that there is no widespread refusal to vaccinate (see Table 1). Kodish repeats a common statistic indicating “1 in 10 parents in the United States now forgo or delay vaccinations for their kids,” yet without more information about what those parents eventually do, it is difficult to accept that statement as a threat to national public health [1]. After all, in those families are children whose parents simply delay vaccinations due to child illness at the time of the doctors’ visit or due to a specific decision to slow the pace of vaccination during infancy. In either case, Table 1 suggests that by 36 months, most children are caught up with individual vaccines and many of the national rates for those vaccines are at herd immunity levels.

Immunology Research • December 2014

Evolution of multiple sclerosis in France since the beginning of hepatitis B vaccination

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Abstract

Since the implementation of the mass vaccination campaign against hepatitis B in France, the appearance of multiple sclerosis, sometimes occurring in the aftermath of vaccinations, led to the publication of epidemiological international studies. This was also justified by the sharp increase in the annual incidence of multiple sclerosis reported to the French health insurance in the mid-1990s. Almost 20 years later, a retrospective reflection can be sketched from these official data and also from the national pharmacovigilance agency. Statistical data from these latter sources seem to show a significant correlation between the number of hepatitis B vaccinations performed and the declaration to the pharmacovigilance of multiple sclerosis occurring between 1 and 2 years later. The application of the Hill’s criteria to these data indicates that the correlation between hepatitis B vaccine and multiple sclerosis may be causal.

http://www.ncbi.nlm.nih.gov/pubmed/?term=25395338

“The application of the Hill’s criteria to these data indicates that the correlation between hepatitis B vaccine and multiple sclerosis may be causal.”

Immunology Research • December 2014

Chronic fatigue syndrome and fibromyalgia following immunization with the hepatitis B vaccine: another angle of the
'autoimmune (auto-inflammatory) syndrome induced by adjuvants'
(ASIA)

Author information

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Abstract

The objectives of this study were to gather information regarding demographic and clinical characteristics of patients diagnosed with either fibromyalgia (FM) or chronic fatigue (CFS) following hepatitis B vaccination (HBVv) and furthermore to apply the recently suggested criteria of autoimmune (auto-inflammatory) syndromes induced by adjuvants (ASIA), in the aim of identifying common characteristics that may suggest an association between fibromyalgia, chronic fatigue and HBV vaccination. Medical records of 19 patients with CFS and/or fibromyalgia following HBVv immunization were analyzed. All of which were immunized during 1990-2008 in different centers in the USA. All medical records were evaluated for demographics, medical history, the number of vaccine doses, as well as immediate and long term post-immunization adverse events and clinical manifestations. In addition, available blood tests, imaging results, treatments and outcomes were analyzed. ASIA criteria were applied to all patients. The mean age of patients was 28.6 ± 11 years, of which 68.4 % were females. 21.05 % had either personal or familial background of autoimmune disease. The mean latency period from the last dose of HBVv to onset of symptoms was 38.6 ± 79.4 days, ranging from days to a year. Eight (42.1 %) patients continued with the immunization program despite experiencing adverse events. Manifestations that were commonly reported included neurological manifestations (84.2 %), musculoskeletal (78.9 %), psychiatric (63.1 %), fatigue (63.1 %), gastrointestinal complains (58 %) and mucocutaneous manifestations (36.8 %). Autoantibodies were detected in 71 % of patients tested. All patients fulfilled the ASIA criteria. This study suggests that in some cases CFS and FM can be temporally related to immunization, as part of ASIA syndrome. The appearance of adverse event during immunization, the presence of autoimmune susceptibility and higher titers of autoantibodies all can be suggested as risk factors. ASIA criteria were fulfilled in all patients eluding the plausible link between ASIA and CFS/FM.

http://www.ncbi.nlm.nih.gov/pubmed/25427994

"This study suggests that

in some cases Chronic Fatigue Syndrome (CFS)

and fibromyalgia (FM) can be temporally related to

immunization, as part of ASIA syndrome."

"... a causal link with vaccine cannot be excluded in some individuals."

Immunology Research • December 2014

A sudden onset of a pseudo-neurological syndrome after HPV-16/18 AS04-adjuvated vaccine: might it be an autoimmune/inflammatory syndrome induced by adjuvants (ASIA) presenting as a somatoform disorder?

Author information

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Abstract

In last centuries, vaccines reduced the incidence of several infectious diseases. In last decades, some vaccines aimed at preventing also some cancers, where viruses play a causative role. However, several adverse events have been described after vaccines, but a causal relationship has been established only in a minority of cases. Here, we describe a pseudo-neurological syndrome occurred shortly after the administration of the bivalent HPV vaccine. Some autoimmune disorders, including neurological demyelinating diseases, have been reported after HPV vaccines, but the patient showed no organic lesions. The patient was diagnosed as having a functional somatoform syndrome, which was supposed to be autoimmune/inflammatory syndrome induced by adjuvants (ASIA), seen the temporal link with vaccination and the presence of anti-phospholipid autoantibodies. Immunological mechanisms of vaccines-and of adjuvants-have not been completely elucidated yet, and although there is no evidence of statistical association with many post-vaccination events, a causal link with vaccine cannot be excluded in some individuals.

http://www.ncbi.nlm.nih.gov/pubmed/25388965

Psychoneuroendocrinology • January 2015

Altered inflammatory activity associated with reduced hippocampal volume and more severe posttraumatic stress symptoms in Gulf War veterans

Author information

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Abstract

BACKGROUND

Inflammation may reduce hippocampal volume by blocking neurogenesis and promoting neurodegeneration. Posttraumatic stress disorder (PTSD) has been linked with both elevated inflammation and reduced hippocampal volume. However, few studies have examined associations between inflammatory markers and hippocampal volume, and none have examined these associations in the context of PTSD.

METHODS

We measured levels of the inflammatory markers interleukin-6 (IL-6) and soluble receptor II for tumor necrosis factor (sTNF-RII) as well as hippocampal volume in 246 Gulf War veterans with and without current and past PTSD as assessed with the Clinician Administered PTSD Scale (CAPS). Enzyme-linked immunosorbent assays were used to measure inflammatory markers, and 1.5Tesla magnetic resonance imaging (MRI) and Freesurfer version 4.5 were used to quantify hippocampal volume. Hierarchical linear regression and analysis of covariance models were used to examine if hippocampal volume and PTSD status would be associated with elevated levels of IL-6 and sTNF-RII.

RESULTS

Increased sTNF-RII, but not IL-6, was significantly associated with reduced hippocampal volume (□=-0.14, p=0.01). The relationship between sTNF-RII and hippocampal volume was independent of potential confounds and covariates, including PTSD status. Although we observed no PTSD diagnosis-related differences in either IL-6 or sTNF-RII, higher PTSD severity was associated with significantly increased sTNF-RII (□=0.24, p=0.04) and reduced IL-6 levels (□=-0.24, p=0.04).

CONCLUSIONS

Our results indicate that specific inflammatory proteins may be associated with brain structure and function as indexed by hippocampal volume and PTSD symptoms.

http://www.ncbi.nlm.nih.gov/pubmed/25465168

"Our results indicate that specific inflammatory proteins may be associated with brain structure and function as indexed by hippocampal volume and PTSD symptoms."

“Macrophagic myofasciitis (MMF) characterized by specific muscle lesions assessing long-term persistence of aluminum hydroxide within macrophages at the site of previous immunization has been reported with increasing frequency in the past 10 years.
The vaccines containing this adjuvant may trigger MMF in some patients.”

Rheumatology International • January 2015

Macrophagic myofasciitis and vaccination: consequence or coincidence?

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Abstract

Macrophagic myofasciitis (MMF) characterized by specific muscle lesions assessing long-term persistence of aluminum hydroxide within macrophages at the site of previous immunization has been reported with increasing frequency in the past 10 years. We describe clinical and laboratory findings in patients with MMF. We did a retrospective analysis of 16 cases observed in our Neuropathology Laboratory, between January 2000 and July 2013. The mean age of the 16 patients was 48.8 ± 18.0 years; 80.0 % were female. Chronic fatigue syndrome was found in 8 of 16 patients. Half of the patients had elevated creatinine kinase levels, and 25.0 % had a myopathic electromyogram. Thirteen patients received intramuscular administration of aluminum-containing vaccine prior to the onset of symptoms. MMF may mirror a distinctive pattern of an inflammatory myopathy. The vaccines containing this adjuvant may trigger MMF in some patients.

http://www.ncbi.nlm.nih.gov/pubmed/24923906

Harefuah • February 2015

The sick building syndrome as a part of 'ASIA'

(autoimmune/auto-inflammatory syndrome induced by adjuvants)

by Maoz-Segal R, Agmon-Levin N, Israeli E, Shoenfeld Y.

Abstract

The entity 'sick building syndrome' is poorly defined and comprises of a set of symptoms resulting from environmental exposure to a work or a living environment. The symptoms are mainly "allergic"-like and include nasal, eye, and mucous membrane irritation, dry skin as well as respiratory symptoms and general symptoms such as fatigue, lethargy, headaches and fever. The Autoimmune [Auto-inflammatory] Syndrome Induced by Adjuvants (ASIA) is a wider term which describes the role of various environmental factors in the pathogenesis of immune mediated diseases. Factors entailing an immune adjuvant activity such as infectious agents, silicone, aluminium salts and others were found in association with defined and non-defined immune mediated diseases. The sick building syndrome and ASIA share a similar complex of signs and symptoms and probably the same immunological mechanisms which further support a common denominator.

http://www.ncbi.nlm.nih.gov/pubmed/25856869

"Factors entailing an immune adjuvant activity such as infectious agents, silicone, aluminium salts and others were found in association with defined and non-defined immune mediated diseases."

"... 2,207 cases were considered probably or possibly related to vaccination.

These represent the largest ASIA cohort ever reported ..."

Immunology Research • February 2015

The epidemiological profile of ASIA syndrome after HPV vaccination: an evaluation based on the Vaccine Adverse Event Reporting Systems

Author information

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Abstract

The term "ASIA-Autoimmune/inflammatory Syndrome Induced by Adjuvants" describes an umbrella of clinical conditions sharing similar signs or symptoms, including post-vaccination phenomena. No information is available on the epidemiology of the ASIA syndrome, especially following HPV vaccination. We carried out an analysis of the VAERS database to retrieve all cases of suspected ASIA syndrome according to the Shoenfeld and Agmon-Levin's guideline for the diagnosis. After causality assessment and case validation, 2,207 cases were considered probably or possibly related to vaccination. These represent the largest ASIA cohort ever reported and allowed us to estimate epidemiological and clinical characteristic of this syndrome. The commonest clinical manifestation observed were pyrexia (58%), myalgia (27%) and arthralgia or arthritis (19%), and the estimated reporting rate was of 3.6 cases per 100,000 doses of HPV vaccine distributed (95% CI 3.4-3.7). This study presents the first systematic estimation of ASIA incidence and expands the knowledge on this pathology. Further analyses are needed to identify genetic and non-genetic risk factors for ASIA syndrome.

http://www.ncbi.nlm.nih.gov/pubmed/25381482

BMC Infectious Disease • February 2015

Pertussis outbreak in university students and evaluation of acellular pertussis vaccine effectiveness in Japan

Author information

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Abstract

BACKGROUND

Recent studies worldwide have reported increasing numbers of adults diagnosed with Bordetella pertussis despite receiving childhood vaccinations. This study describes a pertussis outbreak at a university medical faculty campus and examines the effectiveness of diphtheria, tetanus, and pertussis (DTaP) vaccination completed during infancy in Japan.

METHODS

After the outbreak, self-administered questionnaires and serum samples were collected from students on campus to determine the incidence of pertussis and underlying diseases. Pertussis was diagnosed on the basis of clinical criteria and serum anti-pertussis toxin antibody levels. Using data collected from 248 first and second grade students who had submitted copies of their vaccination records, we evaluated the effectiveness of DTaP vaccination in infancy against adult pertussis.

RESULTS

Questionnaire responses were obtained from 636 students (of 671 registered students; 95% response rate). Of 245 students who reported a continuous cough during the outbreak period, 84 (attack rate: 13.2%) were considered "probable" pertussis cases that met clinical criteria. The outbreak occurred mainly in first and second grade students in the Faculty of Medicine. Of 248 students who provided vaccination records, 225 had received 4 DTaP doses (coverage: 90.7%); the relative risk of the complete vaccination series compared to those with fewer than 4 doses or no doses for probable cases was 0.48 (95% confidence interval: 0.24-0.97).

CONCLUSIONS

Waning protection was suspected due to over time. Booster vaccination for teenagers and development of highly efficacious pertussis vaccines are needed.

http://www.ncbi.nlm.nih.gov/pubmed/?term=25656486

"Waning protection was suspected ..."

“The emerging epidemic of Hodgkin and non-Hodgkin lymphomas worldwide continues to defy our understanding ...”

Immunology Research • February 2015

Adjuvants and lymphoma risk as part of the ASIA spectrum

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Abstract

The emerging epidemic of Hodgkin and non-Hodgkin lymphomas worldwide continues to defy our understanding and forces the search for the causative factors. Adjuvants are known to act as triggers of immune and inflammatory responses. Animal experiments have demonstrated that long-term inflammation is related to aggravation of the immune network resulting in cellular and humoral responses leading to autoimmunity and lymphoma development. Chronic stimulation of the immune system is thought to be the key mechanism through which infectious diseases as well as autoimmune diseases can lead to lymphomagenesis. Many adjuvants can act similarly perturbing immune system’s function, inducing a state of prolonged immune activation related to chronic lymphatic drainage. Several mechanisms were proposed by which adjuvants induce inflammation, and they are discussed herein. Some of them are triggering inflammasome; others bind DNA, lipid moieties in cells, induce uric acid production or act as lipophilic and/or hydrophobic substances. The sustained inflammation increases the risk of genetic aberrations, where the initial polyclonal activation ends in monoclonality. The latter is the hallmark of malignant lymphoma. Thus, chronic adjuvant stimulation may lead to lymphoma.

http://www.ncbi.nlm.nih.gov/pubmed/?term=25582758

Archives Of Toxicology • February 2015

Ethylmercury and Hg2+ induce the formation of neutrophil extracellular traps (NETs) by human neutrophil granulocytes

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Abstract

Humans are exposed to different mercurial compounds from various sources, most frequently from dental fillings, preservatives in vaccines, or consumption of fish. Among other toxic effects, these substances interact with the immune system. In high doses, mercurials are immunosuppressive. However, lower doses of some mercurials stimulate the immune system, inducing different forms of autoimmunity, autoantibodies, and glomerulonephritis in rodents. Furthermore, some studies suggest a connection between mercury exposure and the occurrence of autoantibodies against nuclear components and granulocyte cytoplasmic proteins in humans. Still, the underlying mechanisms need to be clarified. The present study investigates the formation of neutrophil extracellular traps (NETs) in response to thimerosal and its metabolites ethyl mercury (EtHg), thiosalicylic acid, and mercuric ions (Hg2+). Only EtHg and Hg2+ triggered NETosis. It was independent of PKC, ERK1/2, p38, and zinc signals and not affected by the NADPH oxidase inhibitor DPI. Instead, EtHg and Hg2+ triggered NADPH oxidase-independent production of ROS, which are likely to be involved in mercurial-induced NET formation. This finding might help understanding the autoimmune potential of mercurial compounds. Some diseases, to which a connection with mercurials has been shown, such as Wegener's granulomatosis and systemic lupus erythematosus, are characterized by high prevalence of autoantibodies against neutrophil-specific auto-antigens. Externalization in the form of NETs may be a source for exposure to these self-antigens. In genetically susceptible individuals, this could be one step in the series of events leading to autoimmunity.

http://www.ncbi.nlm.nih.gov/pubmed/?term=25701957

"lower doses of some mercurials stimulate the immune system, inducing different forms of autoimmunity, autoantibodies, and glomerulonephritis in rodents. Furthermore, some studies suggest a connection between mercury exposure and the occurrence of autoantibodies ... This finding might help understanding the autoimmune potential of mercurial compounds."

Journal Of Applied Toxicology • March 2015

Tween-80 and impurity induce anaphylactoid reaction in zebrafish

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Abstract

A number of recent reports suspected that Tween-80 in injectable medicines, including traditional Chinese medicine injections could cause life-threatening anaphylactoid reaction, but no sound conclusion was drawn. A drug-induced anaphylactoid reaction is hard to be assayed in vitro and in conventional animal models. In this study, we developed a microplate-based quantitative in vivo zebrafish assay for assessing anaphylactoid reaction and live whole zebrafish mast cell tryptase activity was quantitatively measured at a wavelength of 405 nm using N-benzoyl-dl-arginine p-nitroanilide as a substrate. We assessed 10 batches of Tween-80 solutions from various national and international suppliers and three Tween-80 impurities (ethylene glycol, 2-chloroethanol and hydrogen peroxide) in this model and found that three batches of Tween-80 (nos 2, 20080709 and 20080616) and one Tween-80 impurity, hydrogen peroxide (H2 O2), induced anaphylactoid reactions in zebrafish. Furthermore, we found that H2 O2 residue and peroxide value were much higher in Tween-80 samples 2, 20080709 and 20080616. These findings suggest that H2 O2 residue in combination with oxidized fatty acid residues (measured as peroxide value) or more likely the oxidized fatty acid residues in Tween-80 samples, but not Tween-80 itself, may induce anaphylactoid reaction. High-throughput zebrafish tryptase assay developed in this report could be used for assessing safety of Tween-80-containing injectable medicines and potentially for screening novel mast cell-modulating drugs.

http://www.ncbi.nlm.nih.gov/pubmed/25345596

“A number of recent reports suspected that Tween-80 in injectable medicines, including traditional Chinese medicine injections could cause life-threatening anaphylactoid reaction, but no sound conclusion was drawn. These findings suggest that H2 O2 residue in combination with oxidized fatty acid residues (measured as peroxide value) or more likely the oxidized fatty acid residues in Tween-80 samples, but not Tween-80 itself, may induce anaphylactoid reaction.”

Journal Of Pediatrics • April 2015

Adverse events following Haemophilus influenzae type b vaccines in the Vaccine Adverse Event Reporting System 1990-2013

Author information

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Abstract

Objective

To characterize adverse events (AEs) after Haemophilus influenzae type b (Hib) vaccines reported to the US Vaccine Adverse Event Reporting System (VAERS), a spontaneous reporting surveillance system.

Study Design

We searched VAERS for US reports after Hib vaccines among reports received from January 1, 1990, to December 1, 2013. We reviewed a random sample of reports and accompanying medical records for reports classified as serious. All reports of death were reviewed. Physicians assigned a primary clinical category to each reviewed report. We used empirical Bayesian data mining to identify AEs that were disproportionally reported after Hib vaccines.

Results

VAERS received 29,747 reports after Hib vaccines; 5179 (17%) were serious, including 896 reports of deaths. Median age was 6 months (range 0-1022 months). Sudden infant death syndrome was the stated cause of death in 384 (51%) of 749 death reports with autopsy/death certificate records. The most common nondeath serious AE categories were neurologic (80; 37%), other noninfectious (46; 22%) (comprising mainly constitutional signs and symptoms); and gastrointestinal (39; 18%) conditions. No new safety concerns were identified after clinical review of reports of AEs that exceeded the data mining statistical threshold.

Conclusion

Review of VAERS reports did not identify any new or unexpected safety concerns for Hib vaccines.

http://www.ncbi.nlm.nih.gov/pubmed/25598306

“VAERS received 29,747 reports after Hib vaccines; 5179 (17%) were serious, including 896 reports of deaths.

Median age was 6 months (range 0-1022 months). Sudden infant death syndrome was the stated cause of death in 384 (51%) of 749 death reports with autopsy/death certificate records.

The most common nondeath serious AE categories were neurologic (80; 37%), other noninfectious (46; 22%) (comprising mainly constitutional signs and symptoms); and gastrointestinal (39; 18%) conditions.”

The Pediatric Infectious Disease Journal • April 2015

Seroprevalence of pertussis in the Gambia: evidence for continued circulation of bordetella pertussis despite high vaccination rates

Author information

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Abstract

BACKGROUND

Bordetella pertussis can cause severe respiratory disease and death in children. In recent years, large outbreaks have occurred in high-income countries; however, little is known about pertussis incidence in sub-Saharan Africa.

METHODS

We evaluated antibody responses to pertussis toxin (Ptx) from individuals aged between 2 and 90 years in rural Gambia. IgG-Ptx was measured using luminex xMAP technology. IgG-Ptx geometric mean concentrations (GMC) and their 95% confidence intervals were calculated. The proportion seropositive (>20 EU/mL or ≥62.5 EU/mL) and GMCs were compared by age, sex, ethnic group, vaccination status, birth order and number of siblings per household using logistic and linear regression.

RESULTS

76.3% had anti-Ptx levels <20 EU/mL, 17.5% had concentrations between 20 and 62.5 EU/mL, 4.4% had concentrations between 62.5 and 125 EU/mL and 1.8% had concentrations ≥125 EU/mL. The overall Ptx antibody GMC was 6.4 EU/mL (95% confidence interval: 5.8-6.9). Higher antibody concentrations were observed in older populations with evidence for an increase in infection risk with increasing age (1.9% yearly increase, 95% confidence interval: 1.3-2.5). No child under 6 years of age had GMC above 62.5 EU/mL but 29.5% had concentrations between 20 and 62.5 EU/mL.

CONCLUSIONS

These data provide evidence that B. pertussis is being transmitted within this population despite high vaccination coverage. Re-infection may occur implying that immunity from childhood vaccination may not be lifelong. In the absence of data on actual clinical cases of pertussis, seroprevalence studies remain valuable tools to assess the transmission dynamics of B. pertussis.

http://www.ncbi.nlm.nih.gov/pubmed/25764094

“These data provide evidence that B. pertussis is being transmitted within this population despite high vaccination coverage. Re-infection may occur implying that immunity from childhood vaccination may not be lifelong.”

Springerplus • April 2015

The mechanisms of action of vaccines containing aluminum adjuvants: an in vitro vs in vivo paradigm

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The theory of ‘inflammation’

The use of adjuvants in vaccination is usually associated with some degree of injection site inflammation, and this process is considered an essential part of adjuvant function (Qin et al. 2009). This is consistent with the ‘Danger Theory’ of immune activation as proposed by Polly Matzinger in 1994 (Matzinger 1994). According to this theory, initiation of the immune response is not dependent on microbial recognition, but rather on the ability of pathogens or other agents such as adjuvants to cause tissue damage. The danger signals released from damaged tissues then have the capacity to drive inflammation and initiate an adaptive immune response (Matzinger 1994). This provides an important mechanistic theory for alum adjuvants with many reports of inflammatory effects at the injection site and the induction of danger signals from cells following alum interaction. For example, nodule or granuloma formation in humans and animals following alum injection has been reported from the 1930s to present day (Glenny 1931; Harrison 1935; Farago 1940; Holt 1950; White et al. 1955; Munks et al. 2010; Lu and Hogenesch 2013; Vogelbruch et al. 2000; Bordet et al. 2001; Chong et al. 2006; Rock et al. 2010; Marsee et al. 2008). The development of alum granuloma is independent of the route of immunization and occurs from a few days to several years (e.g., up to >12 years) following immunization, supporting the hypothesis that vaccines containing alum lead to a short-term inflammatory effect in a normal environment as well as long-term inflammatory effects in a pathological environment, at the site of injection (Gherardi et al. 2001; Kool et al. 2008a). It has been shown that alum induces uric acid or monosodium urate (MSU) crystal as a danger signal (Kool et al. 2008a). Subsequently, other signals such as heat shock protein 70 (HSP70) (Wang et al. 2012), and deoxyribonucleic acid (DNA) (Marichal et al. 2011; McKee et al. 2013) have been illustrated as inducers of alum-mediated immune responses, indicating that the mechanisms by which alum particles induce inflammation is central to understanding its adjuvant properties.

A clear causal association of alum in triggering immune responses via cellular death and or enhancing the quality, duration, and magnitude of T- and B- cell responses will make a significant contribution to the rational design of effective and safe vaccines and development of new adjuvants for future use.

Full Report

http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4406982/

“The use of adjuvants in vaccination is usually associated with some degree of injection site inflammation, and this process is considered an essential part of adjuvant function. This is consistent with the ‘Danger Theory’ of immune activation as proposed by Polly Matzinger in 1994. According to this theory, initiation of the immune response is not dependent on microbial recognition, but rather on the ability of pathogens or other agents such as adjuvants to cause tissue damage.”

Ugeskrift For Laeger • April 2015

Aluminium allergy and granulomas induced by vaccinations for children

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Abstract

Vaccination with aluminium-adsorbed vaccines can induce aluminium allergy with persistent itching subcutaneous nodules at the injection site - vaccination granulomas. In this article we give an overview of childhood aluminium-adsorbed vaccines available in Denmark. Through literature studies we examine the incidence, the symptoms and the prognosis for the vaccination granulomas and the allergy. Finally we discuss the status in Denmark.

http://www.ncbi.nlm.nih.gov/pubmed/?term=25350883

“Vaccination with aluminium-adsorbed vaccines can induce aluminium allergy with persistent itching subcutaneous nodules at the injection site - vaccination granulomas.”

Prescrire International • May 2015

Efficacy of the HPV vaccine in late 2014

[No authors listed]

Abstract

Initial evaluation of the HPV 6, 11, 16, 18 vaccine showed about a 40% reduction in high-grade cervical dysplasia due to all virus genotypes among young women aged 16 to 23 years who were not yet sexually active. These results were obtained after 4 years of follow-up and were confirmed after an additional 3 years. Clinical assessment of the HPV 16, 18 vaccine yielded similar results. The interval between initial HPV infection and diagnosis of cervical cancer seems to be at least 20 years. Comparisons of vaccinated and unvaccinated cohorts are consistent with the results of clinical trials, but follow-up is still too short because most of the women studied have not reached the age at which the incidence of high-grade dysplasia peaks. The available evidence shows no replacement of HPV vaccine genotypes by other highly oncogenic genotypes but, once again, follow-up is relatively short. In late 2014, follow-up is still too short to show whether HPV vaccination prevents cervical cancer in young women before they become sexually active. Earlier clinical trials showing efficacy in preventing high-grade dysplasia have not been challenged by epidemiological data. Overall, it will be several more years before conclusive evidence is obtained. In 2015, screening remains the cornerstone for reducing the incidence of invasive cervical cancer.

http://www.ncbi.nlm.nih.gov/pubmed/26034805

“ In late 2014, follow-up is still too short to show whether HPV vaccination prevents cervical cancer in young women before they become sexually active. Earlier clinical trials showing efficacy in preventing high-grade dysplasia have not been challenged by epidemiological data. Overall, it will be several more years before conclusive evidence is obtained. In 2015, screening remains the cornerstone for reducing the incidence of invasive cervical cancer.”

Clinics In Dermatology • May 2015

Cutaneous reactions to vaccinations

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Abstract

Vaccinations are important for infectious disease prevention; however, there are adverse effects of vaccines, many of which are cutaneous. Some of these reactions are due to nonspecific inflammation and irritation at the injection site, whereas other reactions are directly related to the live attenuated virus. Rarely, vaccinations have been associated with generalized hypersensitivity reactions, such as erythema multiforme, Stevens-Johnson syndrome, urticaria, acute generalized exanthematous pustulosis, and drug hypersensitivity syndrome. The onset of certain inflammatory dermatologic conditions, such as lichen planus, granuloma annulare, and pemphigoid, were reported to occur shortly after vaccine administration. Allergic contact dermatitis can develop at the injection site, typically due to adjuvant ingredients in the vaccine, such as thimerosal and aluminum. Vaccinations are important to promote development of both individual and herd immunity. Although most vaccinations are considered relatively safe, there may be adverse effects associated with any vaccine. Cutaneous manifestations make up a large portion of the types of reactions associated with vaccines. There are many different reasons for the development of a cutaneous reaction to a vaccination. Some are directly related to the injection of a live attenuated virus, such as varicella or vaccinia (for immunity to smallpox), whereas others cause more nonspecific erythema and swelling at the injection site, as a result of local inflammation or irritation. Vaccinations have also been associated in rare reports with generalized hypersensitivity reactions, such as erythema multiforme, Stevens-Johnson syndrome, urticaria, acute generalized exanthematous pustulosis, and drug hypersensitivity syndrome. There have been case reports associating the administration of a vaccine with the new onset of a dermatologic condition, such as lichen planus, granuloma annulare, and Sweet syndrome. Finally, allergic contact dermatitis can develop at the injection site, typically due to adjuvant ingredients in the vaccine, such as thimerosal and aluminum.

http://www.ncbi.nlm.nih.gov/pubmed/25889134

“there are adverse effects of vaccines,

many of which are cutaneous ...

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dermatologic conditions, such as

lichen planus,

granuloma annulare,

and pemphigoid,

were reported to occur shortly

after vaccine administration.”

Expert Review Of Vaccines • June 2015

The avian influenza vaccine Emerflu Why did it fail?

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Abstract

Emerflu is an inactivated, split-virion pandemic preparedness vaccine, containing 30 µg of hemagglutinin (HA) and 600 µg of aluminum hydroxide adjuvant. It is administered in two doses, 3 weeks apart. Only moderate immunogenicity was evident from clinical studies with the vaccine in adults, and HA antibody responses were below the criteria established by the EMA and US FDA for licensure. With the exception of Australia, the vaccine remains unlicensed. Further clinical development appears to have been suspended, and newer adjuvants such as MF59 and AS03 have since demonstrated safety and superior immunogenicity with lower HA doses. Emerflu is symbolic of the failure of aluminum salts as an adjuvant for influenza vaccines. Reasons for this failure are unclear, and may reflect problems with the adjuvant-antigen complex or interference in the immune response by heterosubtypic immunity.

http://www.ncbi.nlm.nih.gov/pubmed/26098721

“Emerflu is symbolic of the failure of aluminum salts as an adjuvant for influenza vaccines.”

"These results provide a neurobiological substrate for brain dysfunction in aluminum hydroxide adjuvant-induced MMF patients."

PLoS One • June 2015

Neuropsychological Correlates of Brain Perfusion SPECT in Patients with Macrophagic Myofasciitis

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Abstract

BACKGROUND

Patients with aluminum hydroxide adjuvant-induced macrophagic myofasciitis (MMF) complain of arthromyalgias, chronic fatigue and cognitive deficits. This study aimed to characterize brain perfusion in these patients.

METHODS

Brain perfusion SPECT was performed in 76 consecutive patients (aged 49±10 y) followed in the Garches-Necker-Mondor-Hendaye reference center for rare neuromuscular diseases. Images were acquired 30 min after intravenous injection of 925 MBq 99mTc-ethylcysteinate dimer (ECD) at rest. All patients also underwent a comprehensive battery of neuropsychological tests, within 1.3±5.5 mo from SPECT. Statistical parametric maps (SPM12) were obtained for each test using linear regressions between each performance score and brain perfusion, with adjustment for age, sex, socio-cultural level and time delay between brain SPECT and neuropsychological testing.

RESULTS

SPM analysis revealed positive correlation between neuropsychological scores (mostly exploring executive functions) and brain perfusion in the posterior associative cortex, including cuneus/precuneus/occipital lingual areas, the periventricular white matter/corpus callosum, and the cerebellum, while negative correlation was found with amygdalo-hippocampal/entorhinal complexes. A positive correlation was also observed between brain perfusion and the posterior associative cortex when the time elapsed since last vaccine injection was investigated.

CONCLUSIONS

Brain perfusion SPECT showed a pattern of cortical and subcortical changes in accordance with the MMF-associated cognitive disorder previously described. These results provide a neurobiological substrate for brain dysfunction in aluminum hydroxide adjuvant-induced MMF patients.

Full Report

http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4451975/

“The fluorescent nanodiamond technology is able to overcome the limitations of previously used organic fluorophores, thus appearing as a choice methodology for studying distribution, persistence and long-term neurotoxicity of alum adjuvants and beyond ...”

BMC Medicine • June 2015

Fluorescent nanodiamonds as a relevant tag for the assessment of alum adjuvant particle biodisposition

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Abstract

BACKGROUND

Aluminum oxyhydroxide (alum) is a crystalline compound widely used as an immunologic adjuvant of vaccines. Concerns linked to alum particles have emerged following recognition of their causative role in the so-called macrophagic myofasciitis (MMF) lesion in patients with myalgic encephalomyelitis, revealing an unexpectedly long-lasting biopersistence of alum within immune cells and a fundamental misconception of its biodisposition. Evidence that aluminum-coated particles phagocytozed in the injected muscle and its draining lymph nodes can disseminate within phagocytes throughout the body and slowly accumulate in the brain further suggested that alum safety should be evaluated in the long term. However, lack of specific staining makes difficult the assessment of low quantities of bona fide alum adjuvant particles in tissues.

METHODS

We explored the feasibility of using fluorescent functionalized nanodiamonds (mfNDs) as a permanent label of alum (Alhydrogel(®)). mfNDs have a specific and perfectly photostable fluorescence based on the presence within the diamond lattice of nitrogen-vacancy centers (NV centers). As the NV center does not bleach, it allows the microspectrometric detection of mfNDs at very low levels and in the long-term. We thus developed fluorescent nanodiamonds functionalized by hyperbranched polyglycerol (mfNDs) allowing good coupling and stability of alum:mfNDs (AluDia) complexes. Specificities of AluDia complexes were comparable to the whole reference vaccine (anti-hepatitis B vaccine) in terms of particle size and zeta potential.

RESULTS

In vivo, AluDia injection was followed by prompt phagocytosis and AluDia particles remained easily detectable by the specific signal of the fND particles in the injected muscle, draining lymph nodes, spleen, liver and brain. In vitro, mfNDs had low toxicity on THP-1 cells and AluDia showed cell toxicity similar to alum alone. Expectedly, AluDia elicited autophagy, and allowed highly specific detection of small amounts of alum in autophagosomes.

CONCLUSIONS

The fluorescent nanodiamond technology is able to overcome the limitations of previously used organic fluorophores, thus appearing as a choice methodology for studying distribution, persistence and long-term neurotoxicity of alum adjuvants and beyond of other types of nanoparticles.

http://www.ncbi.nlm.nih.gov/pubmed/26082187

International Journal Of Epidemiology • June 2015

An enigma: why vitamin A supplementation does not always reduce mortality even though vitamin A deficiency is associated with increased mortality

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Abstract

BACKGROUND

Vitamin A deficiency (VAD) is associated with increased mortality. To prevent VAD, WHO recommends high-dose vitamin A supplementation (VAS) every 4-6 months for children aged between 6 months and 5 years of age in countries at risk of VAD. The policy is based on randomized clinical trials (RCTs) conducted in the late 1980s and early 1990s. Recent RCTs indicate that the policy may have ceased to be beneficial. In addition, RCTs attempting to extend the benefits to younger children have yielded conflicting results. Stratified analyses suggest that whereas some subgroups benefit more than expected from VAS, other subgroups may experience negative effects.

METHODS AND RESULTS

We reviewed the potential modifiers of the effect of VAS. The variable effect of VAS was not explained by underlying differences in VAD. Rather, the effect may depend on the sex of the child, the vaccine status and previous supplementation with vitamin A. Vitamin A is known to affect the Th1/Th2 balance and, in addition, recent evidence suggests that vitamin A may also induce epigenetic changes leading to down-regulation of the innate immune response. Thus VAS protects against VAD but has also important and long-lasting immunological effects, and the effect of providing VAS may vary depending on the state of the immune system.

CONCLUSIONS

To design optimal VAS programmes which target those who benefit and avoid those harmed, more studies are needed. Work is ongoing to define whether neonatal VAS should be considered in subgroups. In the most recent RCT in older children, VAS doubled the mortality for males but halved mortality for females. Hence, we urgently need to re-assess the effect of VAS on older children in large-scale RCTs powered to study effect modification by sex and other potential effect modifiers, and with nested immunological studies.

Full Report

http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4521135/

“To prevent Vitamin A deficiency, WHO recommends high-dose vitamin A supplementation every 4-6 months for children aged between 6 months and 5 years of age in countries at risk of Vitamin A deficiency. The policy is based on randomized clinical trials conducted in the late 1980s and early 1990s. Recent RCTs indicate that the policy may have ceased to be beneficial.”

Clinical Rheumatology • July 2015

Hypothesis: Human papillomavirus vaccination syndrome-small fiber neuropathy and dysautonomia could be its underlying pathogenesis

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Abstract

Vaccination has been one of the most effective public health measures in the history of medicine. However, seemingly inexplicit adverse reactions have been described after the injection of the newer vaccines vs. human papillomavirus (HPV). The symptoms more often reported are chronic pain with paresthesias, headaches, fatigue, and orthostatic intolerance. Adverse reactions appear to be more frequent after HPV vaccination when compared to other type of immunizations. Different isolated cases and small series have described the development of complex regional pain syndrome (CRPS), postural orthostatic tachycardia syndrome (POTS), and fibromyalgia after HPV vaccination. These are illnesses often difficult to diagnose that have overlapping clinical features. Sympathetic nervous system dysfunction seems to play a major role in the pathogenesis of these syndromes. Also, small fiber neuropathy has been recently recognized in CRPS, POTS, and fibromyalgia. This article forwards the hypothesis that small fiber neuropathy and dysautonomia could be the common underlying pathogenesis to the group of rare, but severe reactions that follow HPV vaccination. Clinicians should be aware of the possible association between HPV vaccination and the development of these difficult to diagnose painful dysautonomic syndromes.

http://www.ncbi.nlm.nih.gov/pubmed/25990003

“Different isolated cases and small series have described the development of complex regional pain syndrome (CRPS), postural orthostatic tachycardia syndrome (POTS), and fibromyalgia after HPV vaccination. These are illnesses often difficult to diagnose that have overlapping clinical features. Sympathetic nervous system dysfunction seems to play a major role in the pathogenesis of these syndromes. Also, small fiber neuropathy has been recently recognized in CRPS, POTS, and fibromyalgia.”

Archives Of Diseases In Childhood • July 2015

Potentially harmful excipients in neonatal medicines: a pan-European observational study

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Abstract

OBJECTIVES

We aimed to describe administration of eight potentially harmful excipients of interest (EOI)-parabens, polysorbate 80, propylene glycol, benzoates, saccharin sodium, sorbitol, ethanol and benzalkonium chloride-to hospitalised neonates in Europe and to identify risk factors for exposure.

METHODS

All medicines administered to neonates during 1 day with individual prescription and demographic data were registered in a web-based point prevalence study. Excipients were identified from the Summaries of Product Characteristics. Determinants of EOI administration (geographical region, gestational age (GA), active pharmaceutical ingredient, unit level and hospital teaching status) were identified using multivariable logistical regression analysis.

RESULTS

Overall 89 neonatal units from 21 countries participated. Altogether 2095 prescriptions for 530 products administered to 726 neonates were recorded. EOI were found in 638 (31%) prescriptions and were administered to 456 (63%) neonates through a relatively small number of products (n=142; 27%). Parabens, found in 71 (13%) products administered to 313 (43%) neonates, were used most frequently. EOI administration varied by geographical region, GA and route of administration. Geographical region remained a significant determinant of the use of parabens, polysorbate 80, propylene glycol and saccharin sodium after adjustment for the potential covariates including anatomical therapeutic chemical class of the active ingredient.

CONCLUSIONS

European neonates receive a number of potentially harmful pharmaceutical excipients. Regional differences in EOI administration suggest that EOI-free products are available and provide the potential for substitution to avoid side effects of some excipients.

http://www.ncbi.nlm.nih.gov/pubmed/?term=25854872

"We aimed to describe administration of eight potentially harmful excipients of interest— (EOI)-parabens, polysorbate 80, propylene glycol, benzoates, saccharin sodium, sorbitol, ethanol and benzalkonium chloride—to hospitalised neonates in Europe and to identify risk factors for exposure."

Expert Review Of Vaccines • July 2015

Are we entering a new age for human vaccine adjuvants?

Author information

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Abstract

Major advances in adjuvant development for human vaccines have been reported recently for a range of indications, including malaria, influenza and varicella zoster virus. Furthermore, there is an increased understanding of adjuvant mechanisms of action and a greater emphasis on the importance of formulation and characterization. This progress may signify a new golden age of vaccine adjuvant discovery and development.

http://www.ncbi.nlm.nih.gov/pubmed/25947042

Brain & Cognition • August 2015

Word-finding impairment in veterans of the 1991 Persian Gulf War

Author information

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Abstract

Approximately one quarter of 1991 Persian Gulf War Veterans experience cognitive and physiological sequelae that continue to be unexplained by known medical or psychological conditions. Difficulty coming up with words and names, familiar before the war, is a hallmark of the illness. Three Gulf War Syndrome subtypes have been identified and linked to specific war-time chemical exposures. The most functionally impaired veterans belong to the Gulf War Syndrome 2 (Syndrome 2) group, for which subcortical damage due to toxic nerve gas exposure is the suspected cause. Subcortical damage is often associated with specific complex language impairments, and Syndrome 2 veterans have demonstrated poorer vocabulary relative to controls. 11 Syndrome 1, 16 Syndrome 2, 9 Syndrome 3, and 14 age-matched veteran controls from the Seabees Naval Construction Battalion were compared across three measures of complex language. Additionally, functional magnetic resonance imaging (fMRI) was collected during a covert category generation task, and whole-brain functional activity was compared between groups. Results demonstrated that Syndrome 2 veterans performed significantly worse on letter and category fluency relative to Syndrome 1 veterans and controls. They also exhibited reduced activity in the thalamus, putamen, and amygdala, and increased activity in the right hippocampus relative to controls. Syndrome 1 and Syndrome 3 groups tended to show similar, although smaller, differences than the Syndrome 2 group. Hence, these results further demonstrate specific impairments in complex language as well as subcortical and hippocampal involvement in Syndrome 2 veterans. Further research is required to determine the extent of language impairments in this population and the significance of altered neurologic activity in the aforementioned brain regions with the purpose of better characterizing the Gulf War Syndromes.

http://www.ncbi.nlm.nih.gov/pubmed/26114921

“Results demonstrated that Syndrome 2 veterans performed significantly worse on letter and category fluency relative to Syndrome 1 veterans and controls. They also exhibited reduced activity in the thalamus, putamen, and amygdala, and increased activity in the right hippocampus relative to controls. Hence, these results further demonstrate specific impairments in complex language as well as subcortical and hippocampal involvement in Syndrome 2 veterans.”

Brain Connectivity • August 2015

Shared Brain Connectivity Issues, Symptoms, and Comorbidities in Autism Spectrum Disorder, Attention Deficit/Hyperactivity Disorder, and Tourette Syndrome

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Abstract

The prevalence of neurodevelopmental disorders, including autism spectrum disorder (ASD), attention deficit/hyperactivity disorder (ADHD), and Tourette syndrome (TS), has increased over the past two decades. Currently, about one in six children in the United States is diagnosed as having a neurodevelopmental disorder. Evidence suggests that ASD, ADHD, and TS have similar neuropathology, which includes long-range underconnectivity and short-range overconnectivity. They also share similar symptomatology with considerable overlap in their core and associated symptoms and a frequent overlap in their comorbid conditions. Consequently, it is apparent that ASD, ADHD, and TS diagnoses belong to a broader spectrum of neurodevelopmental illness. Biologically, long-range underconnectivity and short-range overconnectivity are plausibly related to neuronal insult (e.g., neurotoxicity, neuroinflammation, excitotoxicity, sustained microglial activation, proinflammatory cytokines, toxic exposure, and oxidative stress). Therefore, these disorders may a share a similar etiology. The main purpose of this review is to critically examine the evidence that ASD, ADHD, and TS belong to a broader spectrum of neurodevelopmental illness, an abnormal connectivity spectrum disorder, which results from neural long-range underconnectivity and short-range overconnectivity. The review also discusses the possible reasons for these neuropathological connectivity findings. In addition, this review examines the role and issue of axonal injury and regeneration in order to better understand the neuropathophysiological interplay between short- and long-range axons in connectivity issues.

http://www.ncbi.nlm.nih.gov/pubmed/25602622

"The prevalence of neurodevelopmental disorders, including autism spectrum disorder (ASD), attention deficit/hyperactivity disorder (ADHD), and Tourette syndrome (TS), has increased over the past two decades. Currently, about one in six children in the United States is diagnosed as having a neurodevelopmental disorder."

[this defines a pandemic of neurological disorders]

Clinical And Experimental Rheumatology • August 2015

Autoimmune/auto-inflammatory syndrome induced by adjuvants (ASIA) after quadrivalent human papillomavirus vaccination in Colombians: a call for personalised medicine

Author information

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Abstract

This was a case study in which 3 patients with autoimmune/auto-inflammatory syndrome induced by adjuvants (ASIA) after quadrivalent human papillomavirus vaccination (HPV) were evaluated and described. All the patients were women. Diagnosis consisted of HLA-B27 enthesitis related arthritis, rheumatoid arthritis and systemic lupus erythematous, respectively. Our results highlight the risk of developing ASIA after HPV vaccination and may serve to increase the awareness of such a complication. Factors that are predictive of developing autoimmune diseases should be examined at the population level in order to establish preventive measures in at-risk individuals for whom healthcare should be personalized and participatory.

http://www.ncbi.nlm.nih.gov/pubmed/25962455

“This was a case study in which 3 patients with autoimmune/auto-inflammatory syndrome induced by adjuvants (ASIA) after quadrivalent human papillomavirus vaccination (HPV) were evaluated and described. All the patients were women.”

Vaccine • September 2015

Spontaneous reports of vasculitis as an adverse event following immunization: A descriptive analysis across three international databases

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Abstract

BACKGROUND

Vasculitides have been reported as adverse events following immunization (AEFI) following various vaccines. We describe reports of vasculitis to three international spontaneous reporting systems.

RESULTS

We retrieved 1797 reports of vasculitis in EV, 1171 in VAERS, and 2606 in VigiBase®. Vasculitis was predominantly reported in children aged 1-17 years, and less frequently in the elderly (>65 years). The generic term "vasculitis" was the most frequently reported AEFI in this category across the three databases (range 21.9% to 27.5% of all reported vasculitis for vaccines). For the more specific terms, Henoch-Schoenlein Purpura (HSP) was most frequently reported, (19.1% on average), followed by Kawasaki disease (KD) (16.1% on average) and polymyalgia rheumatica (PMR) (9.2% on average). Less frequently reported subtypes were cutaneous vasculitis (CuV), vasculitis of the central nervous system (CNS-V), and Behcet's syndrome (BS). HSP, PMR and CuV were more frequently reported with influenza vaccines: on average in 29.3% for HSP reports, 61.5% for PMR reports and in 39.2% for CuV reports. KD was reported with pneumococcal vaccines in 32.0% of KD reports and with rotavirus vaccines in more than 20% of KD reports. BS was most frequently reported after hepatitis and HPV vaccines and CNS-V after HPV vaccines.

CONCLUSION

Similar reporting patterns of vasculitides were observed in different databases. Implementation of standardized case definitions for specific vasculitides could improve overall data quality and comparability of reports.

http://www.ncbi.nlm.nih.gov/pubmed/26392009

"We retrieved 1797 reports of vasculitis in EV, 1171 in VAERS, and 2606 in VigiBase®. Vasculitis was predominantly reported in children aged 1-17 years, and less frequently in the elderly (>65 years). The generic term "vasculitis" was the most frequently reported AEFI in this category across the three databases (range 21.9% to 27.5% of all reported vasculitis for vaccines). For the more specific terms, Henoch-Schoenlein Purpura (HSP) was most frequently reported, (19.1% on average), followed by Kawasaki disease (KD) (16.1% on average) and polymyalgia rheumatica (PMR) (9.2% on average). Less frequently reported subtypes were cutaneous vasculitis (CuV), vasculitis of the central nervous system (CNS-V), and Behcet's syndrome (BS). HSP, PMR and CuV were more frequently reported with influenza vaccines: on average in 29.3% for HSP reports, 61.5% for PMR reports and in 39.2% for CuV reports. KD was reported with pneumococcal vaccines in 32.0% of KD reports and with rotavirus vaccines in more than 20% of KD reports. BS was most frequently reported after hepatitis and HPV vaccines and CNS-V after HPV vaccines."

Epidemiologie Mikrobiologie Imunology • September 2015

Antigenic variability of Bordetella pertussis strains isolated in 1967-2010 in the Czech Republic—possible explanation for the rise in cases of pertussis?

by Zavadilová J, Lzicarová D, Musílek M, Krízová P, Fabiánová K.

Abstract

OBJECTIVE

Comparison of antigenic structures of Bordetella pertussis (B. pertussis) strains isolated from 1967 to 2010 in the Czech Republic.

MATERIAL AND METHODS

Seventy strains of B. pertussis were referred to the National Reference Laboratory (NRL) for Pertussis and Diphtheria within the surveillance of pertussis from all over the Czech Republic (CR) between 1967 and 2010. To study the strains, the analysis was performed of the genome sequences encoding the surface immunogenic structures--the pertussis toxin S1 subunit gene (ptxA), pertactin gene region 1 (prnA), type 3 fimbriae gene (fim3)--and pertussis toxin promoter (ptxP) responsible for the regulation of the production of pertussis toxin.

RESULTS

For the study set of B. pertussis strains, the sequencing analysis revealed changes in all genomic regions studied. The isolates from three periods differ in the allelic profile. In period I (19671978) with the use of whole cell pertussis vaccine (wP), the following two profiles were the most common: ptxP(1), ptxA(2), prnA(1), fim3(1) and ptxP(1), ptxA(1), prnA(3), fim3(1). In period 2 (19902007) with the switch to acellular pertussis vaccine (aP), the most common profile was: ptxP(3), ptxA(1), prnA(2), fim3(2). Period 3 (20082010) with the use of aP was characterized by the predominance of the following two profiles which had never been found in period 1: ptxP(3), ptxA(1), prnA(2), fim3(2) and ptxP(3) ptxA(1), prnA(2), fim3(1).

CONCLUSIONS

Sequencing of the genomic regions ptxP, ptxA, prnA, and fim3 of B. pertussis strains isolated in the CR between 1967 and 2010 confirmed changes in the allelic variants of these regions. The incidence of strains carrying the new allelic variants was increasing after 1995 at the expense of those carrying the original variants. The study results can be interpreted as a partial genetic escape of pathogenic strains of B. pertussis beyond the reach of the pertussis vaccines.

http://www.ncbi.nlm.nih.gov/pubmed/26448300

“The study results can be interpreted as a partial genetic escape of pathogenic strains of B. pertussis beyond the reach of the pertussis vaccines.”

“Since then [1964], the literature has been **flooded** with case reports and case series of granulomatous and systemic autoimmune disorders related to vaccines ...”

Lupus • September 2015

Human adjuvant-related syndrome or autoimmune/inflammatory syndrome induced by adjuvants. Where have we come from? Where are we going? A proposal for new diagnostic criteria

Author information

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Abstract

In 1964, Miyoshi reported a series of patients with diverse symptoms after receiving treatment with silicone or paraffin fillers. Miyoshi named this condition ‘human adjuvant disease’. Since then, the literature has been flooded with case reports and case series of granulomatous and systemic autoimmune disorders related to vaccines, infection or other adjuvants such as silicone and other biomaterials. A new term -autoimmune/inflammatory syndrome induced by adjuvants--has recently been coined for a process that includes several clinical features previously described by Miyoshi plus other clinical and laboratory parameters related to exposure to diverse external stimuli. Disorders such as siliconosis, Gulf War syndrome, macrophagic myofasciitis syndrome, sick building syndrome and post-vaccination syndrome have been included in autoimmune/inflammatory syndrome induced by adjuvants. Disorders such as Spanish toxic oil syndrome and Ardystil syndrome could also be included. Furthermore, biomaterials other than silicone should also be considered as triggering factors for these adjuvant-related syndromes. New diagnostic criteria in this field have been proposed. Nevertheless, many of these criteria are too subjective, leading to some patients being diagnosed with chronic fatigue syndrome or other ‘central sensitization syndromes’. Diagnostic criteria based only on objective clinical and laboratory data to be further discussed and validated are proposed herein.

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Journal Of Vaccines & Vaccination • September 2015

Vaccines and Drug-induced Lung Injury

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Abstract

The corresponding author has no conflict of interest to declare. The author is invited to submit this manuscript in the Short Communication section. Drug-induced lung injuries (DLIs) are adverse drug reactions that specifically occur in the pulmonary system. The main causative agents include cytotoxic drugs, antibiotics, interferon, and anti-rheumatic drugs. More recently, biological reaction modifiers and molecular targeted drugs have emerged as causes of DLIs. Interstitial lung diseases are the most common form of DLIs [1].

Vaccines have rarely been associated with DLIs. One possible reason is that the causal relationship is difficult to prove. This problem is true for vaccines against human papilloma virus (HPV). The author has recently reported a case of interstitial pneumonia that occurred after the vaccination with HPV-16/18 adjuvant system 04 (AS04) vaccines (Cervarix) [2]. Detailed information of this case is available on the respiratory medicine case reports website (http://www.dx.doi.org/ 10.1016/j.rmcr.2015.06.003).

A middle-aged woman, who had no pre-existing pulmonary diseases, completed three doses of Cervarix. Non-specific interstitial pneumonia developed three months after the last vaccination. A lung biopsy specimen showed lymphocytic alveolitis, providing evidence that cell-mediated immunity likely contributed to the occurrence. The patient had increased levels of serum biomarkers specific to interstitial pneumonias such as Krebs von der Lungen (KL)-6 and surfactant protein (SP)-D. Other causes except the vaccination were eliminated. Of note was that the interstitial pneumonia spontaneously resolved with complete remission of chest radiographic findings and serum biomarkers. The self-limiting course suggested that the interstitial pneumonia occurred with a temporal association with the vaccination. A re-challenge test to Cervarix was not conducted for safety reasons. The interstitial pneumonia was finally diagnosed as a DLI according to the clinical course, chest images, pathological findings, and specific use of Cervarix. Assuming that all drugs are capable of causing a lung injury is the first step for diagnosing DLIs [1]. Vaccines are not exceptions in that DLIs can develop even after the treatment has been completed [1]. Most cases of vaccine-associated DLIs have been diagnosed by clinical judgments [3-5]. Gold standard tests have not been established for the diagnosis of DLIs; however the likelihood of an adverse reaction can be semi-quantified using the Naranjo algoris. Such algorisms can reduce inter- and intra-individual variations with regard to the assessment [6]. Chest imaging findings are non-specific but useful for early diagnosis.[1] Measurements of KL-6 and SP-D may play a supplementary role in the diagnosis of DLIs [1,7]. An ex-vivo drug stimulation test using peripheral lymphocytes has a quite limited diagnostic value [7]. Further studies are required to develop diagnostic procedures, which are more sensitive and specific to a drug adverse reaction.

Influenza vaccines can cause several types of DLIs, including acute respiratory distress syndrome [3-5]. Watanabe et al. reviewed 7 cases (4 males and 3 females) of DLIs secondary to the influenza vaccination [5]. The median age of onset was relatively high (59 years). Previous pulmonary diseases were present in four cases. All patients had acute symptoms. The time to onset was 1 to 10 days. They all had severe clinical manifestations, but recovered after receiving corticosteroid therapy. Of note, 6 of the 7 cases were Asians [5]. Genetic and environmental factors may affect difference in the susceptibility to DLIs [7].

Unlike influenza vaccines, Cervarix caused a mild and subclinical form of DLI. How did Cervarix affect the pulmonary system? In the disease process of DLIs, drugs can act as a hapten, interact with immune receptors, and trigger danger signals [7]. These actions probably underlie the onset of immune-mediated DLIs [1,7]. These processes were probably attributed to the Cervarix-associated DLI. As a reason, the pathologically proven lymphocytic alveolitis was suggestive of cell-mediated immune responses [2]. Of the constituents of Cervarix, the AS04 adjuvant appeared to be most responsible owing to its strong immunogenicity [8].

Large-scale analyses have not shown that AS04-adjuvanted vaccines increase risks for developing autoimmune disorders [9,10]. This trend still remains significant when the subjects are stratified by age [10]. However, the immune-mediated diseases assessed are confined to gastrointestinal, metabolic, musculoskeletal, neuroinflammatory, and skin disorders [10]. Any lung disorders including interstitial pneumonia are not listed. Further studies are needed to clarify the prevalence, outcomes, and risk factors for the Cervarix-associated DLI.

Full Report With References

http://www.omicsonline.org/open-access/vaccines-and-druginduced-lung-injury-2157-7560-1000291.pdf

Journal Of Biological Chemistry • October 2015

Formaldehyde Crosslinking: A Tool for the Study of Chromatin Complexes

Author information

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Abstract

Formaldehyde has been used for decades to probe macromolecular structure and function and to trap complexes, cells, and tissues for further analysis. Formaldehyde crosslinking is routinely employed for detection and quantification of protein-DNA interactions, interactions between chromatin proteins, and interactions between distal segments of the chromatin fiber. Despite widespread use and a rich biochemical literature, important aspects of formaldehyde behavior in cells have not been well described. Here, we highlight features of formaldehyde chemistry relevant to its use in analyses of chromatin complexes, focusing on how its properties may influence studies of chromatin structure and function.

http://www.ncbi.nlm.nih.gov/pubmed/?term=26354429

“ Formaldehyde [a vaccine ingredient] has been used for decades to probe macromolecular structure and function and to trap complexes, cells, and tissues for further analysis. Despite widespread use and a rich biochemical literature, important aspects of formaldehyde behavior in cells have not been well described.”

International Journal Of General Medicine • October 2015

A case of polymyalgia rheumatica following influenza B infection

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Abstract

Polymyalgia rheumatica (PMR) is relatively common among the elderly, and is characterized by multiple body aches with an elevated erythrocyte sedimentation rate. Even though the etiology of PMR remains unknown, a number of infectious agents have been suggested to cause PMR. Also, there are reports of PMR after influenza vaccination. The exact role of influenza vaccination on the development of PMR remains unknown, but may be associated with specific human leukocyte antigens (HLAs), such as HLA-DRB1 and HLA-DQB1. Whether postvaccination PMR is caused by influenza virus antigen or adjuvants in the vaccine is another unanswered question. We herein report a case of an 85-year-old woman who developed PMR shortly after contracting influenza virus B. Even though infections are hypothesized to be one of the causes of PMR, this is the first-ever case of PMR following influenza virus infection. Further studies may elucidate the exact role of influenza virus infection on the etiology and pathogenesis of PMR.

http://www.ncbi.nlm.nih.gov/pubmed/26527896

“this is the first-ever case of Polymyalgia rheumatica following influenza virus infection. Further studies may elucidate the exact role of influenza virus infection on the etiology and pathogenesis of Polymyalgia rheumatica.”

Frontiers In Pediatrics • October 2015

A Prospective Longitudinal Assessment of Medical Records for Diagnostic Substitution among Subjects Diagnosed with a Pervasive Developmental Disorder in the United States

Author information

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Abstract

BACKGROUND

Previously, investigators suggested that diagnostic substitution from other diagnoses, e.g., mental retardation (MR) and/or cerebral palsy (CP) to pervasive developmental disorder (PDD) is a driving factor behind increases in autism. This study evaluated potential diagnostic substitution among subjects diagnosed with PDD vs. MR or CP by examining birth characteristic overlap.

METHODS

SAS(®) and StatsDirect software examined medical records for subjects within the Vaccine Safety Datalink database who were Health Maintenance Organization-enrolled from birth until diagnosed with an International Classification of Disease, 9th revision (ICD-9) outcome of PDD (299.xx, n=84), CP (343.xx, n=300), or MR (317.xx, 318.xx, or 319.xx, n=51).

RESULTS

Subjects with PDD had significantly ($p<0.01$) increased: male/female ratio (PDD=5.5 vs. CP=1.5 or MR=1.3), mean age of initial diagnosis in years (PDD=3.13 vs. CP=1.09 or MR=1.62), mean gestational age in weeks at birth (PDD=38.73 vs. CP=36.20 or MR=34.84), mean birth weight in grams (PDD=3,368 vs. CP=2,767 or MR=2,406), and mean Appearance-Pulse-Grimace-Activity-Respiration scores at 1 min (PDD=7.82 vs. CP=6.37 or MR=6.76) and 5 min (PDD=8.77 vs. CP=7.92 or MR=8.04), as compared to subjects diagnosed with CP or MR.

CONCLUSION

This study suggests diagnostic substitution cannot fully explain increased PDD prevalence during the 1990s within the United States.

http://www.ncbi.nlm.nih.gov/pubmed/26528457

“This study suggests diagnostic substitution cannot fully explain increased pervasive developmental disorder (PDD) prevalence during the 1990s within the United States.”

Autoimmunity Review • October 2015

On vaccine's adjuvants and autoimmunity: Current evidence and future perspectives

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Abstract

Adjuvants are compounds incorporated into vaccines to enhance immunogenicity and the development of these molecules has become an expanding field of research in the last decades. Adding an adjuvant to a vaccine antigen leads to several advantages, including dose sparing and the induction of a more rapid, broader and strong immune response. Several of these molecules have been approved, including aluminium salts, oil-in-water emulsions (MF59, AS03 and AF03), virosomes and AS04. Adjuvants have recently been implicated in the new syndrome named "ASIA-Autoimmune/inflammatory Syndrome Induced by Adjuvants", which describes an umbrella of clinical conditions including post-vaccination adverse reactions. Recent studies implicate a web of mechanisms in the development of vaccine adjuvant-induced autoimmune diseases, in particular, in those associated with aluminium-based compounds. Fewer and unsystematised data are instead available about other adjuvants, despite recent evidence indicating that vaccines with different adjuvants may also cause specific autoimmune adverse reactions possible towards different pathogenic mechanisms. This topic is of importance as the specific mechanism of action of each single adjuvant may have different effects on the course of different diseases. Herein, we review the current evidence about the mechanism of action of currently employed adjuvants and discuss the mechanisms by which such components may trigger autoimmunity.

http://www.ncbi.nlm.nih.gov/pubmed/26031899

"Adding an adjuvant to a vaccine antigen leads to several advantages, including dose sparing and the induction of a more rapid, broader and strong immune response. Adjuvants have recently been implicated in the new syndrome named "ASIA-Autoimmune/inflammatory Syndrome Induced by Adjuvants", which describes an umbrella of clinical conditions including post-vaccination adverse reactions. Recent studies implicate a web of mechanisms in the development of vaccine adjuvant-induced autoimmune diseases, in particular, in those associated with aluminium-based compounds."

Future Microbiology • October 2015

Investigating pertussis toxin and its impact on vaccination

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Abstract

Whooping cough, caused by Bordetella pertussis, remains a major global health problem. Each year around 40 million of pertussis cases resulting in 200,000-400,000 annual deaths occur worldwide. Pertussis toxin is a major virulence factor of B. pertussis. Murine studies have shown its importance in bacterial colonization and in immunomodulation to evade innate or adaptive immunity. The toxin is composed of an A protomer expressing ADP-ribosyltransferase activity and a B oligomer, responsible for toxin binding to target cells. The toxin is also a major protective antigen in all currently available vaccines. However, vaccine escape mutants with altered toxin expression have recently been isolated in countries with high vaccination coverage illustrating the need for improved pertussis vaccines.

http://www.ncbi.nlm.nih.gov/pubmed/25689536

“[pertussis toxin] is also a major protective antigen in all currently available vaccines. However, vaccine escape mutants with altered toxin expression have recently been isolated in countries with high vaccination coverage illustrating the need for improved pertussis vaccines.”

Journal Of Biological Chemistry • October 2015

Pertussis Toxin Exploits Specific Host Cell Signaling Pathways for Promoting Invasion and Translocation of Escherichia coli K1 RS218 in Human Brain-derived Microvascular Endothelial Cells

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Abstract

Pertussis toxin (PTx), an AB5 toxin and major virulence factor of the whooping cough-causing pathogen Bordetella pertussis, has been shown to affect the blood-brain barrier. Dysfunction of the blood-brain barrier may facilitate penetration of bacterial pathogens into the brain, such as Escherichia coli K1 (RS218). In this study, we investigated the influence of PTx on blood-brain barrier permissiveness to E. coli infection using human brain-derived endothelial HBMEC and TY10 cells as in vitro models. Our results indicate that PTx acts at several key points of host cell intracellular signaling pathways, which are also affected by E. coli K1 RS218 infection. Application of PTx increased the expression of the pathogen binding receptor gp96. Further, we found an activation of STAT3 and of the small GTPase Rac1, which have been described as being essential for bacterial invasion involving host cell actin cytoskeleton rearrangements at the bacterial entry site. In addition, we showed that PTx induces a remarkable relocation of VE-cadherin and □-catenin from intercellular junctions. The observed changes in host cell signaling molecules were accompanied by differences in intracellular calcium levels, which might act as a second messenger system for PTx. In summary, PTx not only facilitates invasion of E. coli K1 RS218 by activating essential signaling cascades; it also affects intercellular barriers to increase paracellular translocation.

http://www.ncbi.nlm.nih.gov/pubmed/?term=26324705

“Pertussis toxin (PTx), [an ingredient in several vaccines] an AB5 toxin and major virulence factor of the whooping cough-causing pathogen Bordetella pertussis, has been shown to affect the blood-brain barrier. Dysfunction of the blood-brain barrier may facilitate penetration of bacterial pathogens into the brain, such as Escherichia coli K1 (RS218).”

Vaccine • November 2015

Genetic diversity and population dynamics of Bordetella pertussis in China between 1950-2007

Author information

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Abstract

Pertussis is an acute respiratory infectious disease caused by the bacterium Bordetella pertussis. Although pertussis vaccination was introduced in the 1960s, pertussis is still an endemic disease in China. To better understand the genetic diversity of the Chinese B. pertussis population, we characterized 115 clinical isolates obtained in China during 1950-2007 using multilocus variable-number tandem repeat analysis (MLVA). Forty-six different B. pertussis MLVA profiles (MTs) were identified, of which 13 were new MTs. Analysis using a minimum-spanning tree showed that distinct MTs were prevalent during different periods, suggesting that a dynamic change in B. pertussis MTs occurred over time in China. The predominant MTs in recent isolates from China were different from those of many developed countries. A decreasing trend in genetic diversity of the B. pertussis population was observed following the introduction of pertussis vaccines. Similar to the pertactin 2 (prn2) allele, the novel pertussis toxin promoter (ptxP3) allele first emerged in 2000, but unlike trends elsewhere, ptxP1 remained predominant among the isolates, further reflecting the unique temporal trends in the B. pertussis population in China. Our results suggest that temporal changes in the B. pertussis population may be closely associated with vaccination coverage and the vaccine types used. These data may lead to an improved understanding of the virulence mechanism of B. pertussis and facilitate new strategies for controlling this infectious disease.

http://www.ncbi.nlm.nih.gov/pubmed/26409140

“Although pertussis vaccination was introduced in the 1960s, pertussis is still an endemic disease in China. Our results suggest that temporal changes in the B. pertussis population may be closely associated with vaccination coverage ...”

[viral mutation or ‘drift’]

Drug Safety • November 2015

Comparative Safety of Vaccine Adjuvants: A Summary of Current Evidence and Future Needs

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Abstract

Use of highly pure antigens to improve vaccine safety has led to reduced vaccine immunogenicity and efficacy. This has led to the need to use adjuvants to improve vaccine immunogenicity. The ideal adjuvant should maximize vaccine immunogenicity without compromising tolerability or safety. Unfortunately, adjuvant research has lagged behind other vaccine areas such as antigen discovery, with the consequence that only a very limited number of adjuvants based on aluminium salts, monophosphoryl lipid A and oil emulsions are currently approved for human use. Recent strategic initiatives to support adjuvant development by the National Institutes of Health should translate into greater adjuvant choices in the future. Mechanistic studies have been valuable for better understanding of adjuvant action, but mechanisms of adjuvant toxicity are less well understood. The inflammatory or danger-signal model of adjuvant action implies that increased vaccine reactogenicity is the inevitable price for improved immunogenicity. Hence, adjuvant reactogenicity may be avoidable only if it is possible to separate inflammation from adjuvant action. The biggest remaining challenge in the adjuvant field is to decipher the potential relationship between adjuvants and rare vaccine adverse reactions, such as narcolepsy, macrophagic myofasciitis or Alzheimer's disease. While existing adjuvants based on aluminium salts have a strong safety record, there are ongoing needs for new adjuvants and more intensive research into adjuvants and their effects.

http://www.ncbi.nlm.nih.gov/pubmed/26446142

"Use of highly pure antigens to improve vaccine safety has led to reduced vaccine immunogenicity and efficacy. The biggest remaining challenge in the adjuvant field is to decipher the potential relationship between adjuvants and rare vaccine adverse reactions, such as narcolepsy, macrophagic myofasciitis or Alzheimer's disease."

Vaccine • November 2015

A measles outbreak in a middle school with high vaccination coverage and evidence of prior immunity among cases, Beijing, P.R. China

Author information

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Abstract

BACKGROUND

Age-appropriate receipt of ≥2 measles-containing vaccine (MCV) doses has been considered evidence of immunity against measles. Transmission of measles is rarely reported among such persons.

METHODS

We report a measles outbreak in a middle school in Beijing that has high coverage with≥2 documented MCV doses. History of previous measles and documentation of MCV receipt were collected for all individuals. Cases were identified by active surveillance and confirmed by laboratory tests. Measles immunoglobulin G (IgG) titers and clinical presentations were obtained for each case.

RESULTS

Of 1331 individuals without a prior history of measles, 1172 (88.1% [95%CI:86.4-91.5%]) and 1078 (81.0% [95%CI:78.9-83.1%]) had age-appropriate receipt of ≥2 MCV doses by domestic and U.S. CDC/ACIP criteria, respectively. Thirteen measles cases occurred in the outbreak. The index case and 3 secondary cases were students. The 9 tertiary cases included 2 teachers and 7 students. All 11 student cases received ≥2 age-appropriate MCV doses by Chinese domestic criteria; 8 were age-appropriately vaccinated by U.S. CDC/ACIP criteria. Measles IgG was detected during the acute phase of measles for all but 2 cases -the first case and 1 tertiary case. Among students with age-appropriate receipt of ≥2 MCV doses, the length of time since the last MCV was significantly associated with risk of measles: for the 1172 students, the risk was 4.6 [OR5.6;95%CI:1.4-22.9] and 5.5 [OR6.5;95%CI:1.4-29.8] times higher when the last MCV dose was 5-9 years and ≥10 years prior, respectively, compared with <5 years prior; for the 1078 students, the risk was 4.1 [OR5.1;95%CI:1.3-20.7] times higher when the last MCV dose was 5-9 years prior compared with <5 years prior.

CONCLUSIONS

This is the first report from China showing measles transmission among persons with prior evidence of immunity. Secondary vaccine failure may have played an important role in measles transmission. Further laboratory surveillance is needed to assess the persistence of vaccine-induced immunity of domestically-produced MCV in China.

http://www.ncbi.nlm.nih.gov/pubmed/26589518

“This is the first report from China showing measles transmission among persons with prior evidence of immunity. Secondary vaccine failure may have played an important role in measles transmission.”

Vaccine • November 2015

Risk of spontaneous abortion and other pregnancy outcomes in 15-25 year old women exposed to human papillomavirus-16/18 AS04-adjuvanted vaccine in the United Kingdom

Author information

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Abstract

BACKGROUND
We assessed the risk of spontaneous abortion (SA) after inadvertent exposure to HPV-16/18-vaccine during pregnancy using an observational cohort design.

METHODS
The study population included women aged 15-25 years registered with the Clinical Practice Research Datalink General Practice OnLine Database in the United Kingdom (UK), who received at least one HPV-16/18-vaccine dose between 1st September 2008 and 30th June 2011. Exposed women had the first day of gestation between 30 days before and 45 days (90 days for the extended exposure period) after any HPV-16/18-vaccine dose. Non-exposed women had the first day of gestation 120 days-18 months after the last dose. SA defined as foetal loss between weeks 1 and 23 of gestation (UK definition).

RESULTS
The frequency of SA was 11.6% (among 207 exposed) and 9.0% (632 non-exposed), women: hazard ratio (HR) adjusted for age at first day of gestation 1.30 (95% confidence interval: 0.79-2.12). Sensitivity analysis per number of doses administered (-30 to +45-day risk period) showed a HR for SA of 1.11 (0.64-1.91) for 18/178 women with one dose during the risk period versus 2.55 (1.09-5.93) in 6/29 women with two doses within a 4-5 weeks period. The proportion of pre-term/full-term/postterm deliveries, small/large for gestational age infants, and birth defects was not significantly different between exposed and non-exposed women. Results were consistent using a (United States) SA definition of foetal loss between weeks 1-19 and/or the extended risk period.

CONCLUSION
There was no evidence of an increased risk of SA and other adverse pregnancy outcomes in young women inadvertently HPV-16/18-vaccinated around gestation. Nevertheless, women who are pregnant or trying to become pregnant are advised to postpone vaccination until completion of pregnancy.

http://www.ncbi.nlm.nih.gov/pubmed/26206268

Full Report: http://www.sciencedirect.com/science/article/pii/S0264410X15009688

“The frequency of SA was 11.6% (among 207 exposed) and 9.0% (632 non-exposed) ... Results were consistent using a (United States) SA definition of foetal loss between weeks 1-19 and/or the extended risk period ... women who are pregnant or trying to become pregnant are advised to postpone vaccination until completion of pregnancy.”

Journal Of Maternal, Fetal & Neonatal Medicine • November 2015

The prevalence and pattern of pharmaceutical and excipient exposure in a neonatal unit in Slovenia

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Abstract

OBJECTIVE

Because of the restraints on conducting studies on pharmaceutical use in sick newborns, many drugs are used off-label in this population. Moreover, industrially manufactured pharmaceuticals may contain different excipients, which may be either untested or not licensed for use in neonates. The aim of our study was to determine the prevalence and pattern of pharmaceutical and excipient exposure in newborns hospitalized at the Department of Neonatology, Ljubljana, Slovenia.

METHODS

A longitudinal prospective cross-sectional study was performed during a one-month period and included all hospitalized neonates. Route of administration, site of action, type of manufacture, licensing status, type and concentrations of excipients for all pharmaceuticals given to the neonates were determined.

RESULTS

Twenty seven different pharmaceutical preparations were prescribed to a total of 48 hospitalized newborns. In most cases, newborns were prescribed various pharmaceuticals that were not approved for use in this population. Newborns were exposed to 60 different excipients in industrially manufactured pharmaceutical preparations. More than half of the received pharmaceuticals contained potentially harmful and harmful excipients.

CONCLUSIONS

Two-thirds of pharmaceutical preparations for neonates were used off-label. Newborns receive more auxiliary substances, which may be unsuitable for this age group and may even be toxic to them, via industrially manufactured pharmaceuticals.

http://www.ncbi.nlm.nih.gov/pubmed/?term=25316561

“Newborns receive more auxiliary substances, which may be unsuitable for this age group and may even be toxic to them, via industrially manufactured pharmaceuticals.”

Vaccine • December 2015

A sera-epidemiological study on pertussis immunity levels among community populations and an analysis of the underlying factors in Tianjin China

Author information

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Abstract

BACKGROUND

The aim of this study is to characterize the sera-epidemiology of pertussis immunity levels among community populations and to identify the underlying factors. Moreover, our study will help resolve new issues encountered during the control and prevention of pertussis reemergence.

METHODS

The anti-pertussis antibody levels among community populations were examined using enzyme linked immunosorbent assays (ELISA) over three years. Comparative studies were carried out to assess the efficacy of different types of vaccines. Meanwhile, the duration of protection provided by DTaP within the under-7 age group was subjected to further analysis.

RESULTS

The average positive rate for anti-pertussis antibody was 49.15% across all community populations, among which the 4-12 age group showed a rate substantially lower than those of other groups (P<0.001). There was no statistically significant difference in anti-pertussis antibody levels (P=0.977) between people receiving three and four doses of the vaccine. The surveillance results showed that the positive antibody response rate elicited by component pertussis combo (DTcP) vaccines (84.44%) was strikingly higher than that elicited by acellular pertussis combo (DTaP) vaccines (37.22%, P<0.001). More specifically, when given 4 doses of DTcP vaccines, 66.67% of the people showed positive anti-pertussis toxin (PT) antibody levels, which was higher than the ratio of 9.87% (P<0.001) in the case of DTaP vaccines. The positive anti-pertussis antibody levels peaked at 73% within the first five months following vaccination and then gradually decreased to below 20% in four years. The positive rate was inversely correlated with the length of time after vaccination (r=-0.929, P=0.003).

CONCLUSIONS

The anti-pertussis antibody levels were not only relatively low among community populations, but also dropped excessively rapidly among vaccinated populations. Natural infection is an important contributor to the high pertussis immunity levels seen in adolescents and adults. The efficacy of DTaP remains to be improved.

http://www.ncbi.nlm.nih.gov/pubmed/26562317

“The anti-pertussis antibody levels were not only relatively low among community populations, but also dropped excessively rapidly among vaccinated populations. Natural infection is an important contributor to the high pertussis immunity levels seen in adolescents and adults. The efficacy of DTaP remains to be improved.”

Journal Of Infectious Disease • December 2015

The Decline of Pertussis-Specific Antibodies After Tetanus, Diphtheria, and Acellular Pertussis Immunization in Late Pregnancy

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Abstract

We prospectively measured pertussis-specific antibodies 9-15 months after delivery in women immunized with tetanus, diphtheria, and acellular pertussis (Tdap) after the 20th week of their recent pregnancy. The Tdap-immunized women (n = 38) exhibited a decline in geometric mean concentrations between their peripartum and follow-up levels for immunoglobulin G to pertussis toxin (21.48 [95% confidence interval, 12.51-36.89] vs 11.72 [7.09-19.37] IU/mL];); filamentous hemagglutinin (185.95 [157.93-218.94] vs 140.33 IU/mL [113.46-173.57] IU/mL); and pertactin (171.52 [120.73-243.67] vs 83.74 [60.58-115.75] IU/mL) (all P < .001). For women immunized with Tdap during late pregnancy, pertussis-specific immunoglobulin G levels decreased significantly 9-15 months after delivery.

http://www.ncbi.nlm.nih.gov/pubmed/26160743

“For women immunized with Tdap during late pregnancy, pertussis-specific immunoglobulin G levels decreased significantly 9-15 months after delivery.”

Current Pharmaceutical Design • 2015

Why are Excipients Important to Neonates?

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Abstract

Neonates are given many medicines. A significant proportion of these medicines contain excipients. Excipients are used to facilitate the manufacture and use of medicines. Without excipients, it would not be feasible to formulate some drugs into appropriate medicinal products. For others the removal of excipients would reduce the shelf life and make them uneconomic to produce or too expensive for users to purchase. Excipients are also important because some of them can cause harm. Accordingly, it is important to minimize excipient exposure when possible and to only use them when there is a clear pharmaceutical requirement. On balance it is generally safe to use medicines containing excipients. This review introduces physicians and nurses to the functions of excipients in medicines and describes some potential adverse effects of excipients in neonates. The review also provides pharmaceutical scientists with an insight to issues that arise when excipients are administered to neonates. The review answers some key questions about excipients, addresses some case studies of excipient use, proposes approaches for clinicians who prescribe and administer medicines containing excipients and identifies areas for research that seeks to establish the safety profiles of excipients in neonates."

http://www.ncbi.nlm.nih.gov/pubmed/?term=26323411

"Accordingly, it is important to minimize excipient exposure when possible and to only use them when there is a clear pharmaceutical requirement."

Current Pharmaceutical Design • 2015

Neonatal Formulations: The Need for a Tailored, Knowledge Driven Approach

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Abstract

To attain effective and safe pharmacotherapy in neonates, caregivers have to consider both the clinical characteristics of the newborn and the pharmacokinetic estimates of a given compound during prescription and administration. Overall, clearance in neonates is low when compared to other pediatric subpopulations. Despite this overall low clearance, there is already extensive between individual variability in clearance in early life. As a consequence, neonates are in urgent need of tailored drug product development that considers the need for both low and flexible dosing to maintain dose accuracy. During the development of such formulations tailored for neonates, there is also a need for guidance on excipient exposure. The available knowledge on the safety or toxicity of excipients is limited and difficult to retrieve, but there are initiatives (e.g. Safety and Toxicity of Excipients for Pediatrics [STEP] database initiative) to improve the present situation. In addition, population focussed studies on aspects of clinical pharmacology of excipients in neonates should be conducted. The propylene glycol research project and the European Study for Neonatal Excipient Exposure (ESNEE) initiative illustrate its feasibility. Finally, until tailored formulations make it to the market, compounding practices for drug formulations in neonates should be evaluated to guarantee correct dosing, product stability, safety and to support pharmacists in their daily practice.

http://www.ncbi.nlm.nih.gov/pubmed/?term=26323412

“Overall, clearance in neonates is low when compared to other pediatric subpopulations.”

Current Pharmaceutical Design • 2015

Development of a Physiologically-Based Pharmacokinetic Model for Preterm Neonates: Evaluation with In Vivo Data

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Abstract

Among pediatric patients, preterm neonates and newborns are the most vulnerable subpopulation. Rapid developmental changes of physiological factors affecting the pharmacokinetics of drug substances in newborns require extreme care in dose and dose regimen decisions. These decisions could be supported by in silico methods such as physiologically-based pharmacokinetic (PBPK) modeling. In a comprehensive literature search, the physiological information of preterm neonates that is required to establish a PBPK model has been summarized and implemented into the database of a generic PBPK software. Physiological parameters include the organ weights and blood flow rates, tissue composition, as well as ontogeny information about metabolic and elimination processes in the liver and kidney. The aim of this work is to evaluate the model's accuracy in predicting the pharmacokinetics following intravenous administration of two model drugs with distinct physicochemical properties and elimination pathways based on earlier reported in vivo data. To this end, PBPK models of amikacin and paracetamol have been set up to predict their plasma levels in preterm neonates. Predicted plasma concentration-time profiles were compared to experimentally obtained in vivo data. For both drugs, plasma concentrationtime profiles following single and multiple dosing were appropriately predicted for a large range gestational and postnatal ages. In summary, PBPK simulations in preterm neonates appear feasible and might become a useful tool in the future to support dosing decisions in this special patient population.

http://www.ncbi.nlm.nih.gov/pubmed/?term=26323410

"Among pediatric patients, preterm neonates and newborns are the most vulnerable subpopulation. Rapid developmental changes of physiological factors affecting the pharmacokinetics of drug substances in newborns require extreme care in dose and dose regimen decisions."

Vaccine • December 2015

Needle-free and adjuvant-free epicutaneous boosting of pertussis immunity: Preclinical proof of concept

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Abstract

The limited durability of pertussis vaccine-induced protection requires novel approaches to reactivate immunity and limit pertussis resurgence in older children and adults. We propose that periodic boosters could be delivered using a novel epicutaneous delivery system (Viaskin) to deliver optimized pertussis antigens such as genetically-detoxified pertussis toxin (rPT). To best mimic the human situation in which vaccine-induced memory cells persist, whereas antibodies wane, we developed a novel adoptive transfer murine model of pertussis immunity. This allowed demonstrating that a single application of Viaskin delivering rPT and/or pertactin and filamentous hemagglutinin effectively reactivates vaccine-induced pertussis immunity and protects against Bordetella pertussis challenge. Recalling pertussis immunity without needles nor adjuvant may considerably facilitate the acceptance and application of periodic boosters.

http://www.ncbi.nlm.nih.gov/pubmed/?term=26067183

“Recalling pertussis immunity without needles nor adjuvant may considerably facilitate the acceptance and application of periodic boosters.”

Example Of A Current Research Study In Progress • January 2016

NIHJ Research Portfolio Online Reporting Tools
RePORT

Project Number:
1R15ES012209-01
Contact PI / Project Leader:
Kiningham, Kinsley K.

Title:

Mechanism Of Thimerosal Induced Neurotoxicity

Awardee Organization:
Marshall University

Abstract Text:

DESCRIPTION (provided by applicant):

Mercurials are potent neurotoxins, which localize to both neurons and glia within the central nervous system and elicit a range of deleterious actions. Sodium ethylmercurithiosalicylate (thimerosal) is a widely used ethyl mercury containing preservative used in over-the-counter medications, cleaners and cosmetics. Recent concern has been raised on the use of thimerosal in over 30 vaccines licensed in the United States. With the addition of several important vaccines over the last few years, exposure to mercury has increased among infants, leading some investigators to suggest an association between thimerosal exposure and autism. There is limited toxicological information regarding ethyl mercury; therefore, estimates of health risks from thimerosal exposure have been based on mechanistic studies of methyl mercury, a close chemical relative about which much is known. These estimates may actually underestimate the toxicity of ethyl mercury containing agents. The wide use of thimerosal makes understanding the mechanism(s) of its toxicity a significant human health issue. The overall goal of this project is to investigate the mechanism by which thimerosal causes neuronal cell death. The hypothesis to be tested is that thimerosal results in dose-dependent activation of specific signaling molecules and redox-sensitive transcription factors known to activate pro-death genes in neurons. If this hypothesis is correct then pharmacological intervention should attenuate toxicity as a result of thimerosal exposure. Using a human neuroblastoma cell line, SK-N-SH, this project will test the hypothesis in four specific aims. Aim 1 will identify in a dose-dependent manner the predominant cell death pathway (apoptotic versus necrotic) associated with thimerosal exposure and to determine if it is associated with an increase in reactive oxygen species and caspase-3 dependent. Aim 2 will determine if cell death is mediated through an AP-1-dependent pathway. In addition, this specific aim will establish the role of c-Jun-N-terminal kinase; an enzyme, which phosphorylates and activates AP-1, in thimerosal-mediated neuronal death. Aim 3 will determine if the cell death pathway is mediated through an NFkappaB-dependent mechanism. Aim 4 will determine if thimerosal toxicity can be attenuated by the administration of S-adenosylmethionine, an enzyme which increases endogenous levels of glutathione. This project will generate mechanistic data on thimerosal neurotoxicity and potentially identify specific targets for pharmacological intervention.

https://projectreporter.nih.gov/project_info_description.cfm?projectnumber=1R15ES012209-01

“This project will generate mechanistic data on thimerosal neurotoxicity and potentially identify specific targets for pharmacological intervention.”

Chapter Six
Autism
1987 - 2015

In 1976, children received 10 vaccines before attending school. Today they will receive over 36 injections. The American Academy of Pediatrics and the Center for Disease Control assured parents that it was safe to not only give these vaccines, but that they could be given at one time with complete safety. Is this true? Or are we being lied to on a grand scale?

The medical establishment has created a set of terms, which they use constantly to boost their egos and firm up their authority as the unique holders of medical wisdom–the mantra is “evidence-based medicine”, as if everything outside their anointing touch is bogus and suspect. A careful examination of many of the accepted treatments reveals that most have little or no scientific “evidence-based” data to support it. One often repeated study found that almost 80% of medical practice had no scientific backing.

Most men of medicine recognize that some things are obvious without a placebo controlled, double-blind, randomized study. For example, there has never been such a study to see if smashing your finger with a hammer will be painful, but we accept it without such pristine evidence. The same is true with removing brain tumors or sewing up severe lacerations.

I find it interesting that there exist an incredible double standard when it comes to our evidence versus theirs. The proponents of vaccination safety can just say they are safe, without any supporting evidence what-so-ever, and it is to be accepted without question. They can announce that mercury is not only safe, but that it seems to actually increase the IQ, and we are to accept it. They can proclaim thimerosal safe to use in vaccines without their having ever been a single study on its safety in over 60 years of use, and we are to accept it.

Yet, let me, or anyone else, suggest that excessive vaccination can increase the risk of not only autism, but also schizophrenia and neurodegenerative diseases, and they will scream like banshees –Where is the evidence? Where is the evidence? When we produce study after study, they always proclaim them to be insufficient evidence or unacceptable studies. More often than not, they just completely ignore the evidence. This is despite the fact that we produce dozens or even hundreds of studies that not only demonstrate the link clinically and scientifically, but also clearly show the mechanism by which the damage is being done —even on a molecular level. These include cell culture studies, mixed cell cultures, organotypic tissue studies, in vivo animal studies using multiple species and even human studies. To the defenders of vaccine safety—our evidence is never sufficient and, if we face reality—never will be.

~ Dr. Russell Blaylock

The Vaccine Court

The United States federal court has presided over landmark cases for the autism community, filing official court decisions that have linked vaccinations as an environmental trigger of autism. The court in which all of these decisions are rendered is the Office of Special Masters of the United States Courts of Federal Claims, otherwise known as “Vaccine Court.”

The U.S. government created this specific court in 1986 to protect pharmaceutical companies from the direct lawsuits that were arising due to the preponderance of illnesses and injuries that were stemming from the company’s vaccination products. By establishing the Vaccine Court, the government now protects the pharmaceutical industry by trying the cases and awarding damages from a federal excise tax added to the cost of each dosage of a vaccine.

In the “Vaccine Court,” the burden of proof lays squarely on the claimant. In other words, a family must show a clear causal connection between a vaccination and its adverse effects. For the autism community, this standard is made more challenging because the “Vaccine Court” does not accept “autism” as a legal determination. This is because autism is a clinical diagnosis, labeled on the basis of a collection of clinical features and created by causes that are still unknown. But the autism community has still persevered, and compelled the court to acknowledge the link between their children’s autism diagnoses and vaccinations’ environmental triggers.

Vaccine Injury Court

The Bailey Banks Case

The judge rules that the Banks family successfully demonstrates that “the MMR vaccine at issue actually caused the conditions from which Bailey suffered and continues to suffer.” This includes Bailey’s diagnosis of Pervasive Developmental Disorder-Not Otherwise Specified, which has long been recognized as an autism spectrum disorder by the CDC and other federal health agencies.

BOX LINK

Vaccine Injury Court

The Richelle Oxley Case

The Oxley family presents their case that Richelle’s disabilities, including encephalopathy and autistic behaviors, are a result of the pertussis vaccine. The judge rules in their favor, stating that their “claim is strongly supported” by the presented evidence, and that there is “not a preponderance of the evidence that Richelle’s condition is due to factors unrelated to the administration of the vaccine.”

BOX LINK

Vaccine Injury Court

The Eric Lassiter Case

The Lassiter family presents Eric’s diptheria-pertusis-tetanus vaccination as the cause of his injuries, a diagnosis described as “static encepalopathy with autistic tendencies in addition to delayed development.” The judge rules that the Department of Health & Human Services’ “respondent’s evidence and proffered explanations are weak, unconvincing and insufficient” and that the Lassiter family “has presented a better case in support of. . . injury. The Court concludes that a preponderance of the evidence requires a finding for the petitioner.”

BOX LINK

Vaccine Injury Court

The Hannah Poling Case

The Division of Vaccine Injury Compensation, Department of Health and Human Services concedes that Hannah’s vaccinations aggravated her mitochondrial disorder, resulting in “features of autism spectrum disorder.”

BOX LINK

Journal Of The American Academy Of Child And Adolescent Psychiatry • May 1987

Reduced natural killer cell activity in autism

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Abstract

Natural killer (NK) cells arc believed to afford protection against malignancy and viral infections. In addition, these cells may be involved in regulating the immune response because altered NK activity is often associated with autoimmune disorders. An investigation of the natural cytotoxic potential of peripheral blood mononuclear cells from 31 patients with autism has been carried out using K562 tumor cells as target cells. Cells of 12 of the patients induced significantly reduced levels of cytotoxicity; this was not correlated with a quantitative alteration in patient NK cells as determined by use of the Leu-11 monoclonal antibody. This observation of altered NK cell activity, and previously reported findings of other immune abnormalities in autism, suggest that immune changes may be directly related to underlying biological processes of autism or that these changes may be an indirect reflection of the actual pathological mechanism.

http://www.jaacap.com/article/S0890-8567(09)65685-9/abstract

"This observation of altered NK cell activity, and previously reported findings of other immune abnormalities in autism, suggest that immune changes may be directly related to underlying biological processes of autism or that these changes may be an indirect reflection of the actual pathological mechanism."

Alternative Medicine Review • October 2001

Trace element analysis in hair: factors determining accuracy, precision, and reliability

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Abstract

Trace element analysis in biological samples has improved significantly over the last 40 years. Improvements in instrumentation such as inductively coupled plasma-mass spectrometry and microwave digestion have resulted in improved precision, accuracy, reliability, and detection limits. The analysis of human scalp hair has benefited significantly from these improvements. A recent article in the Journal of the American Medical Association found significant inter-laboratory variation amongst several laboratories performing trace metal hair testing. It concluded that standardization was necessary to improve inter-laboratory comparability, and an accompanying commentary described the characteristics of a laboratory that should be used in performing hair analysis. The objective of this study is to demonstrate that good laboratory practices will generate precise, accurate, and reliable results. A method for establishing reference ranges and specific data on an analytical method will also be presented. The use of prescribed clinical quality control, including method validation, proficiency testing, split sampling, and good laboratory practices clearly demonstrates that measuring trace elements in hair can be analytically valid.

http://www.ncbi.nlm.nih.gov/pubmed/?term=11703167

“The use of prescribed clinical quality control, including method validation, proficiency testing, split sampling, and good laboratory practices clearly demonstrates that measuring trace elements in hair can be analytically valid.”

Laboratory Medicine • September 2002

Vaccines and Autism

Author Information

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Abstract

Autism research is characterized by diverse findings.

There is no consensus about the biological determinants of autism.

This paper examines the autistic immune profile
and the possible role of vaccines in autism.

Vaccinations may be one of the triggers for autism. Substantial data demonstrate immune abnormality in many autistic children consistent with impaired resistance to infection, activation of inflammatory response, and autoimmunity. Impaired resistance may predispose to vaccine injury in autism.

A mercurial preservative in childhood vaccines, thimerosal, may cause direct neurotoxic, immunodepressive, and au- toimmune injury and contribute to early-onset and regressed autism. Live viruses in measles, mumps, and rubella (MMR) may result in chronic infection of the gut and trigger regressed autism. Thimerosal injection may potentiate MMR injury.

Consideration of vaccine etiology must include recognition of compromised gut and nutrition in most autistic children. An integrated view of the underlying biological problems in autistic children serves our understanding of the possible role of vaccines. Development of screening methods for deferral of vaccines in at-risk children is a worthy goal.

http://labmed.oxfordjournals.org/content/labmed/33/9/708.full.pdf

“Vaccinations may be one of the triggers for autism. Development of screening methods for deferral of vaccines in at-risk children is a worthy goal.”

“In this study, we postulated that infectious agent antigens such as streptokinase, dietary peptides (gliadin and casein) and ethyl mercury (xenobiotic) bind to different lymphocyte receptors and tissue enzyme ...”

International Journal Of Immunopathology And Pharmacology • September 2003

Infections, toxic chemicals and dietary peptides binding to lymphocyte receptors and tissue enzymes are major instigators of autoimmunity in autism

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Abstract

Similar to many complex autoimmune diseases, genetic and environmental factors including diet, infection and xenobiotics play a critical role in the development of autism. In this study, we postulated that infectious agent antigens such as streptokinase, dietary peptides (gliadin and casein) and ethyl mercury (xenobiotic) bind to different lymphocyte receptors and tissue enzyme (DPP IV or CD26). We assessed this hypothesis first by measuring IgG, IgM and IgA antibodies against CD26, CD69, streptokinase (SK), gliadin and casein peptides and against ethyl mercury bound to human serum albumin in patients with autism. A significant percentage of children with autism developed anti-SK, anti-gliadin and casein peptides and anti-ethyl mercury antibodies, concomitant with the appearance of anti-CD26 and anti-CD69 autoantibodies. These antibodies are synthesized as a result of SK, gliadin, casein and ethyl mercury binding to CD26 and CD69, indicating that they are specific. Immune absorption demonstrated that only specific antigens, like CD26, were capable of significantly reducing serum anti-CD26 levels. However, for direct demonstration of SK, gliadin, casein and ethyl mercury to CD26 or CD69, microtiter wells were coated with CD26 or CD69 alone or in combination with SK, gliadin, casein or ethyl mercury and then reacted with enzyme labeled rabbit anti-CD26 or anti-CD69. Adding these molecules to CD26 or CD69 resulted in 28-86% inhibition of CD26 or CD69 binding to anti-CD26 or anti-CD69 antibodies. The highest % binding of these antigens or peptides to CD26 or CD69 was attributed to SK and the lowest to casein peptides. We, therefore, propose that bacterial antigens (SK), dietary peptides (gliadin, casein) and Thimerosal (ethyl mercury) in individuals with pre-disposing HLA molecules, bind to CD26 or CD69 and induce antibodies against these molecules. In conclusion, this study is apparently the first to demonstrate that dietary peptides, bacterial toxins and xenobiotics bind to lymphocyte receptors and/or tissue enzymes, resulting in autoimmune reaction in children with autism.

http://www.ncbi.nlm.nih.gov/pubmed/14611720

Annals Of Neurology • January 2005

Neuroglial activation and neuroinflammation in the brain of patients with autism

Author information

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Abstract

Autism is a neurodevelopmental disorder characterized by impaired communication and social interaction and may be accompanied by mental retardation and epilepsy. Its cause remains unknown, despite evidence that genetic, environmental, and immunological factors may play a role in its pathogenesis. To investigate whether immune-mediated mechanisms are involved in the pathogenesis of autism, we used immunocytochemistry, cytokine protein arrays, and enzyme-linked immunosorbent assays to study brain tissues and cerebrospinal fluid (CSF) from autistic patients and determined the magnitude of neuroglial and inflammatory reactions and their cytokine expression profiles. Brain tissues from cerebellum, midfrontal, and cingulate gyrus obtained at autopsy from 11 patients with autism were used for morphological studies. Fresh-frozen tissues available from seven patients and CSF from six living autistic patients were used for cytokine protein profiling. We demonstrate an active neuroinflammatory process in the cerebral cortex, white matter, and notably in cerebellum of autistic patients. Immunocytochemical studies showed marked activation of microglia and astroglia, and cytokine profiling indicated that macrophage chemoattractant protein (MCP)-1 and tumor growth factor-beta1, derived from neuroglia, were the most prevalent cytokines in brain tissues. CSF showed a unique proinflammatory profile of cytokines, including a marked increase in MCP-1. Our findings indicate that innate neuroimmune reactions play a pathogenic role in an undefined proportion of autistic patients, suggesting that future therapies might involve modifying neuroglial responses in the brain.

http://www.ncbi.nlm.nih.gov/pubmed/15546155

International Review Of Neurobiology • March 2005

Immunological findings in autism

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Abstract

The immunopathogenesis of autism is presented schematically in Fig. 1. Two main immune dysfunctions in autism are immune regulation involving pro-inflammatory cytokines and autoimmunity. Mercury and an infectious agent like the measles virus are currently two main candidate environmental triggers for immune dysfunction in autism. Genetically immune dysfunction in autism involves the MHC region, as this is an immunologic gene cluster whose gene products are Class I, II, and III molecules. Class I and II molecules are associated with antigen presentation. The antigen in virus infection initiated by the virus particle itself while the cytokine production and inflammatory mediators are due to the response to the putative antigen in question. The cell-mediated immunity is impaired as evidenced by low numbers of CD4 cells and a concomitant T-cell polarity with an imbalance of Th1/Th2 subsets toward Th2. Impaired humoral immunity on the other hand is evidenced by decreased IgA causing poor gut protection. Studies showing elevated brain specific antibodies in autism support an autoimmune mechanism. Viruses may initiate the process but the subsequent activation of cytokines is the damaging factor associated with autism. Virus specific antibodies associated with measles virus have been demonstrated in autistic subjects. Environmental exposure to mercury is believed to harm human health possibly through modulation of immune homeostasis. A mercury link with the immune system has been postulated due to the involvement of postnatal exposure to thimerosal, a preservative added in the MMR vaccines. The occupational hazard exposure to mercury causes edema in astrocytes and, at the molecular level, the CD95/Fas apoptotic signaling pathway is disrupted by Hg2+. Inflammatory mediators in autism usually involve activation of astrocytes and microglial cells. Proinflammatory chemokines (MCP-1 and TARC), and an anti-inflammatory and modulatory cytokine, TGF-beta1, are consistently elevated in autistic brains. In measles virus infection, it has been postulated that there is immune suppression by inhibiting T-cell proliferation and maturation and downregulation MHC class II expression. Cytokine alteration of TNF-alpha is increased in autistic populations. Toll-like-receptors are also involved in autistic development. High NO levels are associated with autism. Maternal antibodies may trigger autism as a mechanism of autoimmunity. MMR vaccination may increase risk for autism via an autoimmune mechanism in autism. MMR antibodies are significantly higher in autistic children as compared to normal children, supporting a role of MMR in autism. Autoantibodies (IgG isotype) to neuron-axon filament protein (NAFP) and glial fibrillary acidic protein (GFAP) are significantly increased in autistic patients (Singh et al., 1997). Increase in Th2 may explain the increased autoimmunity, such as the findings of antibodies to MBP and neuronal axonal filaments in the brain. There is further evidence that there are other participants in the autoimmune phenomenon. (Kozlovskaia et al., 2000). The possibility of its involvement in autism cannot be ruled out. Further investigations at immunological, cellular, molecular, and genetic levels will allow researchers to continue to unravel the immunopathogenic mechanisms' associated with autistic processes in the developing brain. This may open up new avenues for prevention and/or cure of this devastating neurodevelopmental disorder.

http://www.ncbi.nlm.nih.gov/pubmed/16512356

"Mercury and an infectious agent like the measles virus are currently two main candidate environmental triggers for immune dysfunction in autism. Studies showing elevated brain specific antibodies in autism support an autoimmune mechanism. Viruses may initiate the process but the subsequent activation of cytokines is the damaging factor associated with autism. Virus specific antibodies associated with measles virus have been demonstrated in autistic subjects."

The Neuroscientist • October 2005

Large brains in autism: the challenge of pervasive abnormality

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Abstract

The most replicated finding in autism neuroanatomy-a tendency to unusually large brains-has seemed paradoxical in relation to the specificity of the abnormalities in three behavioral domains that define autism. We now know a range of things about this phenomenon, including that brains in autism have a growth spurt shortly after birth and then slow in growth a few short years afterward, that only younger but not older brains are larger in autism than in controls, that white matter contributes disproportionately to this volume increase and in a nonuniform pattern suggesting postnatal pathology, that functional connectivity among regions of autistic brains is diminished, and that neuroinflammation (including microgliosis and astrogliosis) appears to be present in autistic brain tissue from childhood through adulthood. Alongside these pervasive brain tissue and functional abnormalities, there have arisen theories of pervasive or widespread neural information processing or signal coordination abnormalities (such as weak central coherence, impaired complex processing, and underconnectivity), which are argued to underlie the specific observable behavioral features of autism. This convergence of findings and models suggests that a systems- and chronic disease-based reformulation of function and pathophysiology in autism needs to be considered, and it opens the possibility for new treatment targets.

http://www.ncbi.nlm.nih.gov/pubmed/16151044

“This convergence of findings and models suggests that a systems- and chronic disease-based reformulation of function and pathophysiology in autism needs to be considered ...”

“Although the etiology of autism is unknown,

data suggest that autism results from multiple etiologies with both genetic and environmental contributions,

which may explain the spectrum of behaviors seen in this disorder.”

Journal of NeuroVirology • November 2005

Autistic disorder and viral infections

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Autistic disorder (autism) is a behaviorally defined developmental disorder with a wide range of behaviors. Although the etiology of autism is unknown, data suggest that autism results from multiple etiologies with both genetic and environmental contributions, which may explain the spectrum of behaviors seen in this disorder. One proposed etiology for autism is viral infection very early in development. The mechanism, by which viral infection may lead to autism, be it through direct infection of the central nervous system (CNS), through infection elsewhere in the body acting as a trigger for disease in the CNS, through alteration of the immune response of the mother or offspring, or through a combination of these, is not yet known. Animal models in which early viral infection results in behavioral changes later in life include the influenza virus model in pregnant mice and the Borna disease virus model in newborn Lewis rats. Many studies over the years have presented evidence both for and against the association of autism with various viral infections. The best association to date has been made between congenital rubella and autism; however, members of the herpes virus family may also have a role in autism. Recently, controversy has arisen as to the involvement of measles virus and/or the measles, mumps, rubella (MMR) vaccine in the development of autism. Biological assays lend support to the association between measles virus or MMR and autism whereas epidemiologic studies show no association between MMR and autism. Further research is needed to clarify both the mechanisms whereby viral infection early in development may lead to autism and the possible involvement of the MMR vaccine in the development of autism.

http://www.jneurovirol.com/o_pdf/11(1)/001-010.pdf

Journal Of Child Neurology • February 2006

Developmental Regression and Mitochondrial Dysfunction in a Child With Autism

Author Information

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Case Report

A 19-month-old girl was born after a normal full-term pregnancy. There was no family history of autism or affective, neuromuscular, or hearing disorders. Her development was progressing well, with normal receptive and expressive language and use of prelinguistic gestures, such as pointing for joint attention. Imaginary play and social reciprocity were typical for age. She used at least 20 words and could point to five body parts on command. Several immunizations were delayed owing to frequent bouts of otitis media with fever.

Within 48 hours after immunizations to diphtheria, tetanus, and pertussis; Haemophilus influenzae B; measles, mumps, and rubella; polio; and varicella (Varivax), the patient developed a fever to 38.9°C, inconsolable crying, irritability, and lethargy and refused to walk. Four days later, the patient was waking up multiple times in the night, having episodes of opistho-tonus, and could no longer normally climb stairs. Instead, she crawled up and down the stairs. Low-grade intermittent fever was noted for the next 12 days. Ten days following immunization, the patient developed a generalized erythematous macular rash beginning in the abdomen. The patient's pediatrician diagnosed this as due to varicella vaccination. For 3 months, the patient was irritable and increasingly less responsive verbally, after which the patient's family noted clear autistic behaviors, such as spinning, gaze avoidance, disrupted sleep/wake cycle, and perseveration on specific television programs. All expressive language was lost by 22 months. The patient continued to have chronic yellow watery diarrhea intermittently for 6 months, which was evaluated with negative testing for Clostridium difficile, ova/parasites, and culture. Four months later, an evaluation with the Infant and Toddlers Early Intervention program for possible autism was initiated. Along with the regression, her appetite remained poor for 6 months and her body weight did not increase. This resulted in a decline on a standard growth chart for weight from the 97th to the 75th percentile.

Evaluation at 23 months showed atopic dermatitis, slow hair growth, generalized mild hypotonia, toe walking, and normal tendon reflexes. The Childhood Autism Rating Scale (CARS) score was 33 (mild autism range), and she also met Diagnostic and Statistical Manual for Mental Disorders-IV criteria for autism. Laboratory findings included repeated measurements of aspartate aminotransferase 40 IU/L (normal < 31 IU/L), serum bicarbonate 20 mmol/L (normal 21–31 mmol/L), serum creatine kinase level 203 IU/L (normal < 170 IU/L), and fasting lactic acid 3.3 mmol/L (normal 0.5–2.2 mmol/L). Quantitative urinary organic acid analyses showed trace amounts of dicarboxylic acids (adipic, suberic, octenedioic acids) and small amounts of ethylmalonic and methylsuccinic acids, consistent with a fatty acid oxidation dysfunction. Quantitative plasma amino acids were all within the normal range; however, the alanine to lysine ratio (a surrogate marker for pyruvate; Dr Richard Kelley, personal communication, 2001) was elevated at 3.2 (normal 1.5–2.5). Cranial magnetic resonance imaging, otoacoustic emission testing, overnight electroencephalography with slow-wave sleep, serum lead, chromosomes, and fragile X by DNA testing were all normal.

The patient was referred for muscle biopsy (J.S.) because of persistent mild lactic acidosis, elevated serum creatine kinase level, and increased aspartate aminotransferase. A fresh vastus lateralis biopsy was performed and examined as described previously.7,8 The biopsy showed abnormal histology with type I myofiber atrophy, increased myofiber lipid content, and reduced cytochrome c oxidase activity. Oxidative phosphorylation enzymology showed markedly reduced complex I, I + III, and III activity. Complex IV activity was near the 5% confidence limit of the control group (Table 1). Mitochondrial DNA sequencing of the skeletal muscle was normal.

Now 6 years old, our patient has been treated with vitamin supplements since 2½ years of age. Even before starting supplementation, the patient began speaking again at 23 months old and had a four-word vocabulary of "bubbles," "ball," "drink," and "cracker." Levocarnitine 250 mg and thiamine 50 mg three times per day were initiated when the patient was 29 months old. Coenzyme Q10 was added at age 33 months. Although she still exhibits mild autistic behaviors, our patient has continued to improve in language functions and sociability such that she now attends a regular kindergarten with an aide. There have been slow yet steady improvements in muscle tone, motor coordination, and gastrointestinal symptoms with occupational therapy, applied behavioral analysis interventions, and mitochondrial enzyme cofactor supplements. After the age of 2 years, growth trajectory has continued along the 75th percentile for both height and weight. Laboratory tests were repeated at ages 2 years and 10 months (aspartate aminotransferase 47 IU/L, normal < 38 IU/L; alanine transferase 20 IU/L, normal < 40 IU/L; serum creatine kinase level 105 IU/L, normal < 194 IU/L), 4 years old (aspartate aminotransferase 36 IU/L; alanine transferase 19 IU/L; serum creatine kinase level 169 IU/L), and 6 years old (aspartate aminotransferase 36 IU/L; alanine transferase 21 IU/L; alanine to lysine ratio 1.58, normal < 1.5 to 2.5). During an acute illness owing to C difficile, the aspartate aminotransferase was on one occasion elevated to 50 IU/L; however, the serum creatine kinase level remained normal at 169 IU/L. Urine organic acids and serum amino acids have been normal at ages 3 and 6 years. Childhood Autism Rating Scale scores since beginning kindergarten have been under 30.

Full Report

http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2536523/

Toxicology And Applied Pharmacology • July 2006

Porphyrinuria in childhood autistic disorder: implications for environmental toxicity

Author information

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Abstract

To address a possible environmental contribution to autism, we carried out a retrospective study on urinary porphyrin levels, a biomarker of environmental toxicity, in 269 children with neurodevelopmental and related disorders referred to a Paris clinic (2002-2004), including 106 with autistic disorder. Urinary porphyrin levels determined by high-performance liquid chromatography were compared between diagnostic groups including internal and external control groups. Coproporphyrin levels were elevated in children with autistic disorder relative to control groups. Elevation was maintained on normalization for age or to a control heme pathway metabolite (uroporphyrin) in the same samples. The elevation was significant ($P < 0.001$). Porphyrin levels were unchanged in Asperger's disorder, distinguishing it from autistic disorder. The atypical molecule precoproporphyrin, a specific indicator of heavy metal toxicity, was also elevated in autistic disorder ($P < 0.001$) but not significantly in Asperger's. A subgroup with autistic disorder was treated with oral dimercaptosuccinic acid (DMSA) with a view to heavy metal removal. Following DMSA there was a significant ($P = 0.002$) drop in urinary porphyrin excretion. These data implicate environmental toxicity in childhood autistic disorder.

http://www.ncbi.nlm.nih.gov/pubmed/?term=16782144

"These data implicate environmental toxicity in childhood autistic disorder."

[note: in the medical literature vaccination is considered an environmental toxicant]

Lancet • July 2006

Prevalence of disorders of the autism spectrum in a population cohort of children in South Thames: the Special Needs and Autism Project (SNAP)

Author information

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Abstract

BACKGROUND

Recent reports have suggested that the prevalence of autism and related spectrum disorders (ASDs) is substantially higher than previously recognised. We sought to quantify prevalence of ASDs in children in South Thames, UK.

METHODS

Within a total population cohort of 56 946 children aged 9-10 years, we screened all those with a current clinical diagnosis of ASD (n=255) or those judged to be at risk for being an undetected case (n=1515). A stratified subsample (n=255) received a comprehensive diagnostic assessment, including standardised clinical observation, and parent interview assessments of autistic symptoms, language, and intelligence quotient (IQ). Clinical consensus diagnoses of childhood autism and other ASDs were derived. We used a sample weighting procedure to estimate prevalence.

FINDINGS

The prevalence of childhood autism was 38.9 per 10,000 (95% CI 29.9-47.8) and that of other ASDs was 77.2 per 10,000 (52.1-102.3), making the total prevalence of all ASDs 116.1 per 10,000 (90.4-141.8). A narrower definition of childhood autism, which combined clinical consensus with instrument criteria for past and current presentation, provided a prevalence of 24.8 per 10,000 (17.6-32.0). The rate of previous local identification was lowest for children of less educated parents.

INTERPRETATION

Prevalence of autism and related ASDs is substantially greater than previously recognised. Whether the increase is due to better ascertainment, broadening diagnostic criteria, or increased incidence is unclear. Services in health, education, and social care will need to recognise the needs of children with some form of ASD, who constitute 1% of the child population.

http://www.ncbi.nlm.nih.gov/pubmed/?term=16844490

"Prevalence of autism and related ASDs is substantially greater than previously recognised."

Journal Of Leukocyte Biology • July 2006

The immune response in autism: a new frontier for autism research

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Abstract

Autism spectrum disorders (ASD) are part of a broad spectrum of neurodevelopmental disorders known as pervasive developmental disorders, which occur in childhood. They are characterized by impairments in social interaction, verbal and nonverbal communication and the presence of restricted and repetitive stereotyped behaviors. At the present time, the etiology of ASD is largely unknown, but genetic, environmental, immunological, and neurological factors are thought to play a role in the development of ASD. Recently, increasing research has focused on the connections between the immune system and the nervous system, including its possible role in the development of ASD. These neuroimmune interactions begin early during embryogenesis and persist throughout an individual's lifetime, with successful neurodevelopment contingent upon a normal balanced immune response. Immune aberrations consistent with a dysregulated immune response, which so far, have been reported in autistic children, include abnormal or skewed T helper cell type 1 (T(H)1)/T(H)2 cytokine profiles, decreased lymphocyte numbers, decreased T cell mitogen response, and the imbalance of serum immunoglobulin levels. In addition, autism has been linked with autoimmunity and an association with immune-based genes including human leukocyte antigen (HLA)-DRB1 and complement C4 alleles described. There is potential that such aberrant immune activity during vulnerable and critical periods of neurodevelopment could participate in the generation of neurological dysfunction characteristic of ASD. This review will examine the status of the research linking the immune response with ASD.

Abstract: http://www.ncbi.nlm.nih.gov/pubmed/?term=16698940

Full Report: http://www.jleukbio.org/content/80/1/1.long

"There is potential that such aberrant immune activity during vulnerable and critical periods of neurodevelopment could participate in the generation of neurological dysfunction characteristic of ASD. This review will examine the status of the research linking the immune response with ASD."

Pathophysiology • August 2006

Oxidative stress in autism

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Abstract

Autism is a severe developmental disorder with poorly understood etiology. Oxidative stress in autism has been studied at the membrane level and also by measuring products of lipid peroxidation, detoxifying agents (such as glutathione), and antioxidants involved in the defense system against reactive oxygen species (ROS). Lipid peroxidation markers are elevated in autism, indicating that oxidative stress is increased in this disease. Levels of major antioxidant serum proteins, namely transferrin (iron-binding protein) and ceruloplasmin (copper-binding protein), are decreased in children with autism. There is a positive correlation between reduced levels of these proteins and loss of previously acquired language skills in children with autism. The alterations in ceruloplasmin and transferrin levels may lead to abnormal iron and copper metabolism in autism. The membrane phospholipids, the prime target of ROS, are also altered in autism. The levels of phosphatidylethanolamine (PE) are decreased, and phosphatidylserine (PS) levels are increased in the erythrocyte membrane of children with autism as compared to their unaffected siblings. Several studies have suggested alterations in the activities of antioxidant enzymes such as superoxide dismutase, glutathione peroxidase, and catalase in autism. Additionally, altered glutathione levels and homocysteine/methionine metabolism, increased inflammation, excitotoxicity, as well as mitochondrial and immune dysfunction have been suggested in autism. Furthermore, environmental and genetic factors may increase vulnerability to oxidative stress in autism. Taken together, these studies suggest increased oxidative stress in autism that may contribute to the development of this disease. A mechanism linking oxidative stress with membrane lipid abnormalities, inflammation, aberrant immune response, impaired energy metabolism and excitotoxicity, leading to clinical symptoms and pathogenesis of autism is proposed.

http://www.ncbi.nlm.nih.gov/pubmed/16766163

“According to the Autism Society of America, autism is now considered to be an epidemic.”

Journal Of Toxicology And Environmental Health Part B, Critical Review • November 2006

Evidence of toxicity, oxidative stress, and neuronal insult in autism

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Abstract

According to the Autism Society of America, autism is now considered to be an epidemic. The increase in the rate of autism revealed by epidemiological studies and government reports implicates the importance of external or environmental factors that may be changing. This article discusses the evidence for the case that some children with autism may become autistic from neuronal cell death or brain damage sometime after birth as result of insult; and addresses the hypotheses that toxicity and oxidative stress may be a cause of neuronal insult in autism. The article first describes the Purkinje cell loss found in autism, Purkinje cell physiology and vulnerability, and the evidence for postnatal cell loss. Second, the article describes the increased brain volume in autism and how it may be related to the Purkinje cell loss. Third, the evidence for toxicity and oxidative stress is covered and the possible involvement of glutathione is discussed. Finally, the article discusses what may be happening over the course of development and the multiple factors that may interplay and make these children more vulnerable to toxicity, oxidative stress, and neuronal insult.

http://www.ncbi.nlm.nih.gov/pubmed/17090484

Neurotoxicology • May 2008

Immunologic and neurodevelopmental susceptibilities of autism

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Abstract

Symposium 5 focused on research approaches that are aimed at understanding common patterns of immunological and neurological dysfunction contributing to neurodevelopmental disorders such as autism and ADHD. The session focused on genetic, epigenetic, and environmental factors that might act in concert to influence autism risk, severity and co-morbidities, and immunological and neurobiological targets as etiologic contributors. The immune system of children at risk of autism may be therefore especially susceptible to psychological stressors, exposure to chemical triggers, and infectious agents. Identifying early biomarkers of risk provides tangible approaches toward designing studies in animals and humans that yield a better understanding of environmental risk factors, and can help identify rational intervention strategies to mitigate these risks.

Full Report

http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2475601/

Alternative Therapies In Health And Medicine • November 2008

The history of vaccinations in the light of the autism epidemic

Author information

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Abstract

Autism has been characterized as a behavioral disorder since it was first described by Leo Kanner in 1943. The number of autistic children has increased over the last decade. The incidence of autism was 1 in 10000 before the 1970s and has steadily increased to 1 in 150 in 2008 with a male:female predominance of 4:1. The cause of this epidemic has remained unknown, but several hypotheses have been studied. Many of these suggest an environmental trigger, such as the ethyl mercury contained in the preservative thimerosal, which has been used in vaccines since 1931. Other possible triggers associated with vaccinations are chemical toxins and live viruses. James has published studies suggesting a genetic predisposition in the families of autistic children, exposing them to a deficiency in glutathione and an inability to detoxify heavy metals. Vargas has shown autism to encompass ongoing inflammation in the brains of autistic children. The Hannah Poling vaccine decision was a landmark case. Poling's family was awarded funds for ongoing medical care of an autistic child who was found to have mitochondrial dysfunction exacerbated by vaccines that left her with autistic behavior and seizures. Several studies have emerged supporting the fact that a significant number of autistic children do have mitochondrial dysfunction. The impact that the Poling case will have on the ability of parents of autistic children to gain access to funds to enable them to properly care for their children remains to be seen.

http://www.ncbi.nlm.nih.gov/pubmed/19043939

"The Hannah Poling vaccine decision was a landmark case. Poling's family was awarded funds for ongoing medical care of an autistic child who was found to have mitochondrial dysfunction exacerbated by vaccines that left her with autistic behavior and seizures. Several studies have emerged supporting the fact that a significant number of autistic children do have mitochondrial dysfunction. The impact that the Poling case will have on the ability of parents of autistic children to gain access to funds to enable them to properly care for their children remains to be seen."

Alternative Therapies In Health And Medicine • November 2008

A possible central mechanism in autism spectrum disorders Part 1

Author information

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Abstract

The autism spectrum disorders (ASD) are a group of related neurodevelopmental disorders that have been increasing in incidence since the 1980s. Despite a considerable amount of data being collected from cases, a central mechanism has not been offered. A careful review of ASD cases discloses a number of events that adhere to an immunoexcitotoxic mechanism. This mechanism explains the link between excessive vaccination, use of aluminum and ethylmercury as vaccine adjuvants, food allergies, gut dysbiosis, and abnormal formation of the developing brain. It has now been shown that chronic microglial activation is present in autistic brains from age 5 years to age 44 years. A considerable amount of evidence, both experimental and clinical, indicates that repeated microglial activation can initiate priming of the microglia and that subsequent stimulation can produce an exaggerated microglial response that can be prolonged. It is also known that one phenotypic form of microglia activation can result in an outpouring of neurotoxic levels of the excitotoxins, glutamate and quinolinic acid. Studies have shown that careful control of brain glutamate levels is essential to brain pathway development and that excesses can result in arrest of neural migration, as well as dendritic and synaptic loss. It has also been shown that certain cytokines, such as TNF-alpha, can, via its receptor, interact with glutamate receptors to enhance the neurotoxic reaction. To describe this interaction I have coined the term immunoexcitotoxicity, which is described in this article.

http://www.ncbi.nlm.nih.gov/pubmed/?term=19043938

“This mechanism explains the link between excessive vaccination, use of aluminum and ethylmercury as vaccine adjuvants, food allergies, gut dysbiosis, and abnormal formation of the developing brain.”

Alternative Therapies In Health And Medicine • January 2009

A possible central mechanism in autism spectrum disorders, Part 2 immunoexcitotoxicity

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Abstract

In this section, I explore the effects of mercury and inflammation on transsulfuration reactions, which can lead to elevations in androgens, and how this might relate to the male preponderance of autism spectrum disorders (ASD). It is known that mercury interferes with these biochemical reactions and that chronically elevated androgen levels also enhance the neurodevelopmental effects of excitotoxins. Both androgens and glutamate alter neuronal and glial calcium oscillations, which are known to regulate cell migration, maturation, and final brain cytoarchitectural structure. Studies have also shown high levels of DHEA and low levels of DHEA-S in ASD, which can result from both mercury toxicity and chronic inflammation. Chronic microglial activation appears to be a hallmark of ASD. Peripheral immune stimulation, mercury, and elevated levels of androgens can all stimulate microglial activation. Linked to both transsulfuration problems and chronic mercury toxicity are elevations in homocysteine levels in ASD patients. Homocysteine and especially its metabolic products are powerful excitotoxins. Intimately linked to elevations in DHEA, excitotoxicity and mercury toxicity are abnormalities in mitochondrial function. A number of studies have shown that reduced energy production by mitochondria greatly enhances excitotoxicity. Finally, I discuss the effects of chronic inflammation and elevated mercury levels on glutathione and metallothionein.

http://www.ncbi.nlm.nih.gov/pubmed/19161050

“In this section, I explore the effects of mercury and inflammation on transsulfuration reactions, which can lead to elevations in androgens, and how this might relate to the male preponderance of autism spectrum disorders (ASD).”

Alternative Therapies In Health And Medicine • March 2009

A possible central mechanism in autism spectrum disorders Part 3 the role of excitotoxin food additives and the synergistic effects of other environmental toxins

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Abstract

There is compelling evidence from a multitude of studies of various design indicating that foodborne excitotoxin additives can elevate blood and brain glutamate to levels known to cause neurodegeneration and in the developing brain, abnormal connectivity. Excitotoxins are also secreted by microglial activation when they are in an activated state. Recent studies, discussed in part 1 of this article, indicate that chronic microglial activation is common in the autistic brain. The interaction between excitotoxins, free radicals, lipid peroxidation products, inflammatory cytokines, and disruption of neuronal calcium homeostasis can result in brain changes suggestive of the pathological findings in cases of autism spectrum disorders. In addition, a number of environmental neurotoxins, such as fluoride, lead, cadmium, and aluminum, can result in these pathological and biochemical changes.

http://www.ncbi.nlm.nih.gov/pubmed/19284184

“There is compelling evidence from a multitude of studies of various design indicating that foodborne excitotoxin additives can elevate blood and brain glutamate to levels known to cause neurodegeneration and in the developing brain, abnormal connectivity.”

Dr. Paul Offit and Dr. Jon Poling: New England Journal of Medicine

By Anne Dachel

On August 7, the New England Journal of Medicine published the opposing opinions of Dr. Jon Poling, father of Hannah Poling, and Dr. Paul Offit, Infectious Disease Specialist from Children's Hospital of Philadelphia, on the Vaccine Court case in which the federal government conceded that vaccines were a factor in the development of autism in Hannah. Titled, Vaccines and Autism Revisited, the letters run in the "Correspondance" section of NEJM.

In the May 15 NEJM Perspective section, Offit split every hair he could to try and lessen the impact of the Poling case. He tried to convince the public that there was no scientific basis for the concession. Offit's remarks led to the August 7 response by Dr. Poling.

In his August 7 piece, Poling went after Offit's opinion about his daughter's case using phrases like "*Offit misrepresents my position*," "*Offit confuses issues*," and "*His opinion is unsupported by clinical trials*."

Poling also said that he agreed with the remarks made by former head of the National Institutes of Health, Dr. Bernadine Healy, on CBS News, who said, "*I don't think you should ever turn your back on any scientific hypothesis because you're afraid of what it might show. . . . If you know that susceptible group, you can save those children. If you turn your back on the notion there is a susceptible group . . . what can I say*?"

The fair and balanced NEJM then allowed Offit to respond to Poling at the bottom of the article. Offit defended his remarks by claiming that the science is on his side and the facts support his view. He made one stunning comment. He brought up Healy's remarks about the need for further study of a subgroup of children who might be damaged by vaccines. Offit wrote, "*Now, Poling and Healy are standard-bearers for the poorly conceived hypothesis that children receive too many vaccines too early. As a consequence, some parents are choosing to delay, withhold, or separate vaccines.*"

That was really a low blow. To claim that one of the top doctors in the U.S. was promoting a "*poorly conceived hypothesis*" and that "*the public airing of that hypothesis caused thousands of parents to avoid the MMR; many children were hospitalized and several died from measles as a result,*" was really pitting doctor against doctor in the vaccine war. (Amanda Peet just told us on Good Morning America, "*Please don't listen to me. . . . Go to the experts.*" Well, here they are and they don't agree!)

I had to go back to the remarks made by Healy on CBS Evening News (Click HERE) on May 12 to figure out what exactly she said that could be described as a "*poorly conceived hypothesis.*" Soft-spoken and reasonable in her conversation with CBS reporter Sharyl Attkisson, Healy called for more studies on vaccines and autism. She said that we need to do the studies to find out if there is a subgroup of children who are susceptible to a particular vaccine, to vaccines plural, or to components in vaccines. She urged scientists "*to take another look at that hypothesis, not deny it.*"

Healy said nothing to undermine that vaccine program. She told the public, "*A susceptible group does not mean that vaccines aren't good.*" She firmly stated that she didn't believe "*the public would lose faith in vaccines*."

We have the most heated controversy in medicine today over vaccines and Healy addressed it by saying, "*It is the job of the public health community and of physicians to be out there and to say yes, we can make it safer because we are able to say, this is a subset. We're going to deliver it in a way we think is safer.*"

Sharyl Attkisson then brought up the fact that health officials will deny there is a link between vaccines and autism. They say there's no evidence.

Healy, shaking her head, firmly stated twice, "*You can't say that*."

Why? Because they haven't studied "*the population that got sick.*"

Healy said that she hasn't seen "*major studies that focus on 300 kids who got autistic symptoms within a period of a few weeks of getting a vaccine.*"

Healy noted the primate and mouse studies that have been too quickly dismissed. She challenged the conclusions of the IOM Report of 2004 where we were told not to "*pursue susceptibility groups.*" Healy said, "*I really take issue with that conclusion. The reason they didn't want to look for those susceptibility groups was because if they found them, . . . that would scare the public away.*"

Offit might think that the endless epidemiological studies have settled the question, but Healy made it clear, "*Populations do not test causality, they test associations. You have to go into the laboratory*."

Healy chided the medical community by saying, "*The fact that there is concern that you don't want to know that susceptible group is a real disappointment to me*."

She ended a chilling comment about vaccines and the link to autism: "*The question has not been answered.*"

From his remarks, it's pretty obvious that Offit is opposed to any open scientific inquiry. Healy didn't say that all children were receiving too many too soon, as Offit claimed. She said we need to find that subgroup of children.

The CDC studies that are always being promoted in the press haven't settled a thing. The public is growing increasingly skeptical of health officials and their claims. They don't want to risk the health of their children by giving them vaccines with possibly damaging side effects. Healy's was the refreshing voice of reason in this debate. Too bad Offit refused to listen.

Perhaps the ending of the Poling/Offit pieces said it all. After Poling's remarks, he listed his conflicts from the lecturing and consulting fees he had received from different pharmaceutical companies. At the end of Offit's, all we see is "Children's Hospital of Philadelphia." Here's the body copy from NEJM:

Vaccines and Autism Revisited
Related Article
by Offit, P. A.

To the Editor: In his Perspective article on a possible connection between vaccines and autism, Offit (May 15 issue)1 speculates about my daughter, Hannah, and repeats inaccuracies from a March New York Times opinion piece that was officially corrected by the Times and our April 5 letter.

By omitting critical information from my March 6, 2008, statement, Offit misrepresents my position. I said, "*Many in the autism community and their champions believe that the result in this case may well signify a land-*

mark decision as it pertains to children developing autism following vaccinations. This still remains to be seen, but currently there are almost 5,000 other cases pending."

Offit's remarks about Hannah's case are not evidence-based. He has no access to my daughter's personal medical records, legal documents, or affidavits. In contrast, physicians from the Department of Health and Human Services (DHHS) who studied this information recommended that the government concede Hannah's case. The clinical history Offit presents contains significant inaccuracies, and the resulting conclusions are consequently flawed.

Offit confuses issues by comparing Hannah's case with unrelated decisions in "vaccine court." The Office of the Secretary of DHHS, through the Department of Justice, conceded Hannah's case. There was no courtroom hearing and no decision from the "unusual vaccine court."

Offit is frequently cited regarding the "biologically plausible" theory that simultaneous administration of multiple vaccines is safe. His opinion is unsupported by clinical trials, much less investigations in potentially susceptible subpopulations.

Despite the high frequency of mitochondrial dysfunction in autistic children,2 studies have not established primary or secondary roles. To explore this question, we need an immunization database for children with metabolic disorders to establish safety guidelines3 and improve vaccine safety for minority subgroups of children.

I agree with the statement of Bernadine Healy, former director of the National Institutes of Health, who said, "*I don't think you should ever turn your back on any scientific hypothesis because you're afraid of what it might show. . . . If you know that susceptible group, you can save those children. If you turn your back on the notion there is a susceptible group . . . what can I say?*"4 Also commendable is the new 5-year research plan of the National Vaccine Advisory Committee, which will entail the study of minority subpopulations, including patients with mitochondrial disorders.5

A strong, safe vaccination program is a cornerstone of public health. Misrepresenting Hannah Poling v. HHS to the medical profession does not improve confidence in the immunization program or advance science toward an understanding of how and why regressive encephalopathy with autistic features follows vaccination in susceptible children.

Jon S. Poling, M.D., Ph.D.
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Dr. Poling is the father of Hannah Poling and reports receiving consulting or lecture fees from Pfizer, Eisai, Ortho-McNeil, Biogen, Teva, Immunex, and Allergan. No other potential conflict of interest relevant to this letter was reported.

References

1. Offit PA. Vaccines and autism revisited -- the Hannah Poling case. N Engl J Med 2008;358:2089-2091. [Free Full Text]
2. Oliveira G, Ataíde A, Marques C, et al. Epidemiology of autism spectrum disorder in Portugal: prevalence, clinical characterization, and medical conditions. Dev Med Child Neurol 2007;49:726-733. [ISI][Medline]
3. Brady MT. Immunization recommendations for children with metabolic disorders: more data would help. Pediatrics 2006;118:810-813. [Free Full Text]
4. CBS News. The "open question" on vaccines and autism. May 2008. (Accessed July 18, 2008, at http://www.cbsnews.com/blogs/2008/05/12/couricandco/entry4090144.shtml.)
5. Draft ISO Scientific Agenda for NVAC Vaccine Safety Working Group. Centers for Disease Control and Prevention's Immunization Safety Office scientific agenda: draft recommendations. April 4, 2008. In: Scientific review. Washington, DC: National Vaccine Advisory Committee Vaccine Safety Working Group, April 11, 2008:30. (Accessed July 18, 2008, at http://www.cdc.gov/vaccinesafety/00_pdf/draft_agenda_recommendations_080404.pdf.)

The author replies: Poling implies that by omitting his phrase "*many in the autism community and their champions*," I unfairly attributed the notion that vaccines might cause autism to him alone. However, Dr. Poling's public announcement of the DHHS concession to the press and his subsequent appearances on national television and at autism conferences suggest that he is, at the very least, a vocal centerpiece of that community.

Poling claims that I didn't have access to his daughter's medical records. My information was based on a verbatim transcript of the DHHS concession, which stated that his daughter had had frequent ear infections and a series of viral infections early in life. These infections, which are a far greater immunologic challenge than attenuated or inactivated vaccines, are not in dispute.

Poling states that my assertion that the administration of multiple vaccines is safe is an "*opinion . . . unsupported by clinical trials*." But studies of concomitant use, which are required by the Food and Drug Administration before licensure to show that new vaccines do not affect the safety or immunogenicity of existing vaccines or vice versa, have clearly shown that multiple vaccines can be administered safely.

Poling agrees with Healy that "*you should [n]ever turn your back on any scientific hypothesis because you're afraid of what it might show.*" However, scientists have not been afraid to test the hypothesis that vaccines might cause autism. Far from it: the ill-founded notion that the measles–mumps–rubella (MMR) vaccine caused autism was tested in 10 epidemiologic studies. Unfortunately, the public airing of that hypothesis caused thousands of parents to avoid the MMR; many children were hospitalized and several died from measles as a result.1,2,3,4 Now, Poling and Healy are standard-bearers for the poorly conceived hypothesis that children receive too many vaccines too early. As a consequence, some parents are choosing to delay, withhold, or separate vaccines. The problem here is not a failure of scientists to consider hypotheses; rather, it is a failure of the media and the public to distinguish hypotheses from scientific evidence.

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www.ageofautism.com/2008/08/dr-paul-offit-a.html

“Younger ages at diagnosis, differential migration, changes in diagnostic criteria, and inclusion of milder cases do not fully explain the observed increases.”

Epidemiology • January 2009

The Rise in Autism and the Role of Age at Diagnosis

Hertz-Picciotto, Irvaa,b; Delwiche, Loraa

Abstract

Background

Autism prevalence in California, based on individuals eligible for state-funded services, rose throughout the 1990s. The extent to which this trend is explained by changes in age at diagnosis or inclusion of milder cases has not been previously evaluated.

Methods

Autism cases were identified from 1990 through 2006 in databases of the California Department of Developmental Services, which coordinates services for individuals with specific developmental disorders. The main outcomes were population incident cases younger than age 10 years for each quarter, cumulative incidence by age and birth year, age-specific incidence rates stratified by birth year, and proportions of diagnoses by age across birth years.

Results

Autism incidence in children rose throughout the period. Cumulative incidence to 5 years of age per 10,000 births rose consistently from 6.2 for 1990 births to 42.5 for 2001 births. Age-specific incidence rates increased most steeply for 2- and 3-year olds. The proportion diagnosed by age 5 years increased only slightly, from 54% for 1990 births to 61% for 1996 births. Changing age at diagnosis can explain a 12% increase, and inclusion of milder cases, a 56% increase.

Conclusions

Autism incidence in California shows no sign yet of plateauing. Younger ages at diagnosis, differential migration, changes in diagnostic criteria, and inclusion of milder cases do not fully explain the observed increases. Other artifacts have yet to be quantified, and as a result, the extent to which the continued rise represents a true increase in the occurrence of autism remains unclear.

http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4113600/

Journal Of Neuroimmunology • February 2009

Elevated immune response in the brain of autistic patients

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Abstract

This study determined immune activities in the brain of ASD patients and matched normal subjects by examining cytokines in the brain tissue. Our results showed that proinflammatory cytokines (TNF-alpha, IL-6 and GM-CSF), Th1 cytokine (IFN-gamma) and chemokine (IL-8) were significantly increased in the brains of ASD patients compared with the controls. However the Th2 cytokines (IL-4, IL-5 and IL-10) showed no significant difference. The Th1/Th2 ratio was also significantly increased in ASD patients.

CONCLUSION

ASD patients displayed an increased innate and adaptive immune response through the Th1 pathway, suggesting that localized brain inflammation and autoimmune disorder may be involved in the pathogenesis of ASD.

Full Report

http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2770268/

“ASD patients displayed an increased innate and adaptive immune response through the Th1 pathway, suggesting that localized brain inflammation and autoimmune disorder may be involved in the pathogenesis of ASD.”

Current Medicinal Chemistry • July 2009

Immune-glutamatergic dysfunction as a central mechanism of the autism spectrum disorders

Author information

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Abstract

Despite the great number of observations being made concerning cellular and the molecular dysfunctions associated with autism spectrum disorders (ASD), the basic central mechanism of these disorders has not been proposed in the major scientific literature. Our review brings evidence that most heterogeneous symptoms of ASD have a common set of events closely connected with dysregulation of glutamatergic neurotransmission in the brain with enhancement of excitatory receptor function by pro-inflammatory immune cytokines as the underlying mechanism. We suggest that environmental and dietary excitotoxins, mercury, fluoride, and aluminum can exacerbate the pathological and clinical problems by worsening excitotoxicity and by microglial priming. In addition, each has effects on cell signaling that can affect neurodevelopment and neuronal function. Our hypothesis opens the door to a number of new treatment modes, including the nutritional factors that naturally reduce excitotoxicity and brain inflammation.

http://www.ncbi.nlm.nih.gov/pubmed/?term=19149568

“... environmental and dietary excitotoxins, mercury, fluoride, and aluminum can exacerbate the pathological and clinical problems by worsening excitotoxicity and by microglial priming. In addition, each has effects on cell signaling that can affect neurodevelopment and neuronal function.”

Journal Of Toxicology • August 2009

The severity of autism is associated with toxic metal body burden and red blood cell glutathione levels

Author information

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Abstract

This study investigated the relationship of children's autism symptoms with their toxic metal body burden and red blood cell (RBC) glutathione levels. In children ages 3-8 years, the severity of autism was assessed using four tools: ADOS, PDD-BI, ATEC, and SAS. Toxic metal body burden was assessed by measuring urinary excretion of toxic metals, both before and after oral dimercaptosuccinic acid (DMSA). Multiple positive correlations were found between the severity of autism and the urinary excretion of toxic metals. Variations in the severity of autism measurements could be explained, in part, by regression analyses of urinary excretion of toxic metals before and after DMSA and the level of RBC glutathione (adjusted R(2) of 0.22-0.45, $P < .005$ in all cases). This study demonstrates a significant positive association between the severity of autism and the relative body burden of toxic metals.

http://www.ncbi.nlm.nih.gov/pubmed/?term=20107587

"Multiple positive correlations were found between the severity of autism and the urinary excretion of toxic metals."

Journal Of Cellular And Molecular Medicine • October 2009

One carbon metabolism disturbances and the C677T MTHFR gene polymorphism in children with autism spectrum disorders

Author information

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Abstract

Autism spectrum disorders (ASDs), which include the prototypic autistic disorder (AD), Asperger's syndrome (AS) and pervasive developmental disorders not otherwise specified (PDD-NOS), are complex neurodevelopmental conditions of unknown aetiology. The current study investigated the metabolites in the methionine cycle, the transsulphuration pathway, folate, vitamin B(12) and the C677T polymorphism of the MTHFR gene in three groups of children diagnosed with AD (n= 15), AS (n= 5) and PDD-NOS (n= 19) and their age- and sex-matched controls (n= 25). No metabolic disturbances were seen in the AS patients, while in the AD and PDD-NOS groups, lower plasma levels of methionine (P= 0.01 and P= 0.03, respectively) and alpha-aminobutyrate were observed (P= 0.01 and P= 0.001, respectively). Only in the AD group, plasma cysteine (P= 0.02) and total blood glutathione (P= 0.02) were found to be reduced. Although there was a trend towards lower levels of serine, glycine, N, N-dimethylglycine in AD patients, the plasma levels of these metabolites as well as the levels of homocysteine and cystathionine were not statistically different in any of the ASDs groups. The serum levels of vitamin B(12) and folate were in the normal range. The results of the MTHFR gene analysis showed a normal distribution of the C677T polymorphism in children with ASDs, but the frequency of the 677T allele was slightly more prevalent in AD patients. Our study indicates a possible role for the alterations in one carbon metabolism in the pathophysiology of ASDs and provides, for the first time, preliminary evidence for metabolic and genetic differences between clinical subtypes of ASDs.

Full Report

http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4496129/

"Our study indicates a possible role for the alterations in one carbon metabolism in the pathophysiology of ASDs and provides, for the first time, preliminary evidence for metabolic and genetic differences between clinical subtypes of ASDs."

Current Medicinal Chemistry • 2009

Immune-glutamatergic dysfunction as a central mechanism of the autism spectrum disorders

Author information

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Abstract

Despite the great number of observations being made concerning cellular and the molecular dysfunctions associated with autism spectrum disorders (ASD), the basic central mechanism of these disorders has not been proposed in the major scientific literature. Our review brings evidence that most heterogeneous symptoms of ASD have a common set of events closely connected with dysregulation of glutamatergic neurotransmission in the brain with enhancement of excitatory receptor function by pro-inflammatory immune cytokines as the underlying mechanism. We suggest that environmental and dietary excitotoxins, mercury, fluoride, and aluminum can exacerbate the pathological and clinical problems by worsening excitotoxicity and by microglial priming. In addition, each has effects on cell signaling that can affect neurodevelopment and neuronal function. Our hypothesis opens the door to a number of new treatment modes, including the nutritional factors that naturally reduce excitotoxicity and brain inflammation.

http://www.ncbi.nlm.nih.gov/pubmed/?term=19149568

“We suggest that environmental and dietary excitotoxins, mercury, fluoride, and aluminum can exacerbate the pathological and clinical problems by worsening excitotoxicity and by microglial priming. In addition, each has effects on cell signaling that can affect neurodevelopment and neuronal function.”

Acta Neurobiologiea Experimentalis • 2010

The review of most frequently occurring medical disorders related to aetiology of autism and the methods of treatment

Author information

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Abstract

The medical understanding of autism has changed since it was first defined by Kanner. Nowadays medicine identifies many medical abnormalities and diseases, which may underline or aggravate the cognitive aspect, behavioural issues and general health in autists. This includes chronic inflammation of gastrointestinal tract, dysbiosis, maldigestion, malabsorption, malnutrition, food intolerance, allergies, chronic viral, fungal and bacterial infections, impaired kidney function, impaired detoxification of endo- and exotoxins, disorders of metal ion transportation. Treatment of the above mentioned conditions combined with improving detoxification mechanisms, followed by a special diet and individually customized supplementation of nutritional deficiencies may lead to the improvement of the functioning of these patients, changing their level of functioning and self-dependence. The aim of this paper is to present medical problems of children with autism which may be identified and treated by general practitioners as a review of current medical papers related to Autism Spectrum Disorder, in the context of author's professional experience, based on the medical cases from author's practice.

http://www.ncbi.nlm.nih.gov/pubmed/?term=20628438

"This includes chronic inflammation of gastrointestinal tract, dysbiosis, maldigestion, malabsorption, malnutrition, food intolerance, allergies, chronic viral, fungal and bacterial infections, impaired kidney function, impaired detoxification of endo- and exotoxins, disorders of metal ion transportation."

Neurobiologiae Experimentalis • 2010

Age-dependent lower or higher levels of hair mercury in autistic children than in healthy controls

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Abstract

An association between autism and early life exposure to mercury is a hotly debated issue. In this study, 91 autistic Polish children, male and female, 3-4 and 7-9 years old, were compared to 75 age- and sex-matched healthy children with respect to: demographic, perinatal, clinical and developmental measures, parental age, birth order, morphometric measures, vaccination history, and hair mercury content. In demographic and perinatal measures there were no consistent differences between the autistic and control groups. Autistic children had a significantly greater prevalence of adverse reactions after vaccinations and abnormal development than controls. Between 45 and 80% of autistic children experienced developmental regress. Autistic children significantly differed from healthy peers in the concentrations of mercury in hair: younger autistics had lower levels, while older - higher levels than their respective controls. The results suggest that autistic children differ from healthy children in metabolism of mercury, which seems to change with age.

https://app.box.com/s/938bs6e55098v78c4tnuyca38p2xnnqu

“The results suggest that

autistic children differ from healthy children

in metabolism of mercury ...”

Neurobiologiae Experimentalis • 2010

Sorting out the spinning of autism: heavy metals and the question of incidence

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Abstract

The reasons for the rise in autism prevalence are a subject of heated professional debate. Featuring a critical appraisal of some research used to question whether rising levels of autism are related to environmental exposure to toxins (Soden et al. 2007, Barbaresi et al. 2009, Thompson et al. 2007) we aim to evaluate the actual state of scientific knowledge. In addition, we surveyed the empirical research on the topic of autism and heavy metal toxins. In our opinion empirical investigations are finding support for a link with heavy metal toxins. The various causes that have led to the increase in autism diagnosis are likely multi-faceted, and understanding the causes is one of the most important health topics today. We argue that scientific research does not support rejecting the link between the neurodevelopmental disorder of autism and toxic exposures.

https://app.box.com/s/rs4j52jgdbjvj0a7qroo8sgxv7t06ly9

“We argue that scientific research does not support rejecting the link between the neurodevelopmental disorder of autism and toxic exposures.”

Journal Of Neurovirology • March 2010

Association of autism with polyomavirus infection in postmortem brains

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Abstract

Autism is a highly heritable behavioral disorder. Yet, two decades of genetic investigation have unveiled extremely few cases that can be solely explained on the basis of de novo mutations or cytogenetic abnormalities. Vertical viral transmission represents a nongenetic mechanism of disease compatible with high parent-to-offspring transmission and with low rates of disease-specific genetic abnormalities. Vertically transmitted viruses should be found more frequently in the affected tissues of autistic individuals compared to controls. Our initial step was thus to assess by nested polymerase chain reaction (PCR) and DNA sequence analysis the presence of cytomegalovirus (CMV), Epstein-Barr virus (EBV), herpes simplex virus type 1 (HSV1), herpes simplex virus type 2 (HSV2), human herpes virus 6 (HHV6), BK virus (BKV), JC virus (JCV), and simian virus 40 (SV40) in genomic DNA extracted from postmortem temporocortical tissue (Brodmann areas 41/42) belonging to 15 autistic patients and 13 controls. BKV, JCV, and SV40 combined are significantly more frequent among autistic patients compared to controls (67% versus 23%, respectively; P < .05). The majority of positives yielded archetypal sequences, whereas six patients and two controls unveiled single-base pair changes in two or more sequenced clones. No association is present with the remaining viruses, which are found in relatively few individuals (N <or= 3). Also polyviral infections tend to occur more frequently in the brains of autistic patients compared to controls (40% versus 7.7%, respectively; P = .08). Follow-up studies exploring vertical viral transmission as a possible pathogenetic mechanism in autistic disorder should focus on, but not be limited to, the role of polyomaviruses.

http://www.ncbi.nlm.nih.gov/pubmed/20345322

“BKV, JCV, and SV40 [viruses] combined are significantly more frequent among autistic patients compared to controls (67% versus 23%, respectively; P < .05).”

Journal Of Pediatrics • April 2010

Autism spectrum disorders in extremely preterm children

Author information

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Abstract

OBJECTIVES
To investigate the prevalence, correlates, and antecedents of autism spectrum disorders (ASD) in extremely preterm children.

STUDY DESIGN
We conducted a prospective study of all births <26 weeks gestation in the United Kingdom and Ireland in 1995. Of 307 survivors at 11 years, 219 (71%) were assessed and compared with 153 term-born classmates. Parents completed the Social Communication Questionnaire (SCQ) to assess autism spectrum symptoms, and ASD were diagnosed by using a psychiatric evaluation. An IQ test and clinical evaluation were also administered. Longitudinal outcome data were available for extremely preterm children.

RESULTS
Extremely preterm children had significantly higher SCQ scores than classmates (mean difference, 4.6 points; 95% CI, 3.4-5.8). Sixteen extremely preterm children (8%) were assigned an ASD diagnosis, compared with none of the classmates. By hospital discharge, male sex, lower gestation, vaginal breech delivery, abnormal cerebral ultrasound scanning results, and not having had breast milk were independently associated with autism spectrum symptoms. By 6 years, independent associates were cognitive impairment, inattention and peer problems, withdrawn behavior at 2.5 years, and not having had breast milk.

CONCLUSIONS
Extremely preterm children are at increased risk for autism spectrum symptoms and ASD in middle childhood. These symptoms and disorders were associated with neurocognitive outcomes, suggesting that ASD may result from abnormal brain development in this population.

http://www.ncbi.nlm.nih.gov/pubmed/?term=20056232

"Extremely preterm children are at increased risk for autism spectrum symptoms and ASD in middle childhood."

Journal Of Pediatrics • April 2010

Autism spectrum disorders in extremely preterm children

Author information

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Abstract

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Extremely preterm children are at increased risk for autism spectrum symptoms and ASD in middle childhood. These symptoms and disorders were associated with neurocognitive outcomes, suggesting that ASD may result from abnormal brain development in this population.

http://www.ncbi.nlm.nih.gov/pubmed/?term=20056232

Journal Of Toxicology And Environmental Health Part A • June 2010

Porphyrinuria in Korean children with autism: correlation with oxidative stress

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Abstract

Autism spectrum disorder (ASD) is a neurodevelopmental disorder believed to be associated with heavy metal exposure, especially mercury (Hg), and is characterized by disturbances in metal elimination. Various studies correlated elevated heavy metal body burden with ASD diagnoses as evidenced by increased urinary porphyrin levels in patients. Urinary porphyrins were also determined in Korean patients diagnosed with ASD (n = 65) who visited AK Eastern Medicinal Clinic in Kangnam-gu, Seoul, from June 2007 to September 2008, compared to controls (n = 9) residing in the same area, by means of Metametrix (CLIA-approved) laboratory testing. Further, urinary organic acids as indicators of hepatic detoxification/oxidative stress were also analyzed among patients diagnosed with ASD. Significant increases were found in patients diagnosed with ASD for proporphyrins, pentacarboxyporphyrin, precoproporphyrin, coproporphyrins, and total porphyrins. Significant correlations were observed between hepatic detoxification/oxidative stress markers and urinary porphyrins. In agreement with published data, the present results demonstrated that measurement of porphyrins serves as a reliable tool for diagnosis of heavy metal involvement in ASD.

http://www.ncbi.nlm.nih.gov/pubmed/?term=20391113

“Autism spectrum disorder (ASD) is a neurodevelopmental disorder believed to be associated with heavy metal exposure, especially mercury (Hg), and is characterized by disturbances in metal elimination. Significant correlations were observed between hepatic detoxification/oxidative stress markers and urinary porphyrins. In agreement with published data, the present results demonstrated that measurement of porphyrins serves as a reliable tool for diagnosis of heavy metal involvement in Autistic Spectrum Disorder.”

Acta Neurobiologiea Experimentalis • 2010

The biological basis of autism spectrum disorders: Understanding causation and treatment by clinical geneticists

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Abstract

Autism spectrum disorders (ASDs) also known as pervasive developmental disorders (PDD) are a behaviorally defined group of neurodevelopmental disorders that are usually diagnosed in early childhood. ASDs disproportionately affect male children. Mercury (Hg) a heavy metal, is widespread and persistent in the environment. Mercury is a ubiquitous source of danger in fish, drugs, fungicides/herbicides, dental fillings, thermometers, and many other products. Elevated Hg concentrations may remain in the brain from several years to decades following exposure. This is important because investigators have long recognized that Hg is a neurodevelopmental poison; it can cause problems in neuronal cell migration and division, and can ultimately cause cell degeneration and death. Case-reports of patients have described developmental regressions with ASD symptoms following fetal and/or early childhood Hg exposure, and epidemiological studies have linked exposure to Hg with an elevated risk of a patient being diagnosed with an ASD. Immune, sensory, neurological, motor, and behavioral dysfunctions similar to traits defining or associated with ASDs were reported following Hg intoxication with similarities extending to neuroanatomy, neurotransmitters, and biochemistry. The sexual dimorphism of ASDs may result from synergistic neurotoxicity caused by the interaction of testosterone and Hg; in contrast, estrogen is protective, mitigating the toxicity of Hg. Mercury exposure may significantly increase androgen levels, and as a result, patients diagnosed with an ASD may significantly benefit from anti-androgen therapy. Finally, the clinical geneticist has a wealth of biomarkers to evaluate and treat patients diagnosed with an ASD.

http://www.ncbi.nlm.nih.gov/pubmed/20628444

Journal Of Immunotoxicology • January 2011

Theoretical aspects of autism: causes—a review

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Abstract

Autism, a member of the pervasive developmental disorders (PDDs), has been increasing dramatically since its description by Leo Kanner in 1943. First estimated to occur in 4 to 5 per 10,000 children, the incidence of autism is now 1 per 110 in the United States, and 1 per 64 in the United Kingdom, with similar incidences throughout the world. Searching information from 1943 to the present in PubMed and Ovid Medline databases, this review summarizes results that correlate the timing of changes in incidence with environmental changes. Autism could result from more than one cause, with different manifestations in different individuals that share common symptoms. Documented causes of autism include genetic mutations and/or deletions, viral infections, and encephalitis following vaccination. Therefore, autism is the result of genetic defects and/or inflammation of the brain. The inflammation could be caused by a defective placenta, immature blood-brain barrier, the immune response of the mother to infection while pregnant, a premature birth, encephalitis in the child after birth, or a toxic environment.

http://www.ncbi.nlm.nih.gov/pubmed/21299355

Pediatrics • June 2011

Trends in the prevalence of developmental disabilities in US children, 1997-2008

Author information

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Abstract

OBJECTIVE

To fill gaps in crucial data needed for health and educational planning, we determined the prevalence of developmental disabilities in US children and in selected populations for a recent 12-year period.

PARTICIPANTS AND METHODS

We used data on children aged 3 to 17 years from the 1997-2008 National Health Interview Surveys, which are ongoing nationally representative samples of US households. Parent-reported diagnoses of the following were included: attention deficit hyperactivity disorder; intellectual disability; cerebral palsy; autism; seizures; stuttering or stammering; moderate to profound hearing loss; blindness; learning disorders; and/or other developmental delays.

RESULTS

Boys had a higher prevalence overall and for a number of select disabilities compared with girls. Hispanic children had the lowest prevalence for a number of disabilities compared with non-Hispanic white and black children. Low income and public health insurance were associated with a higher prevalence of many disabilities. Prevalence of any developmental disability increased from 12.84% to 15.04% over 12 years. Autism, attention deficit hyperactivity disorder, and other developmental delays increased, whereas hearing loss showed a significant decline. These trends were found in all of the sociodemographic subgroups, except for autism in non-Hispanic black children.

CONCLUSIONS

Developmental disabilities are common and were reported in ~1 in 6 children in the United States in 2006-2008. The number of children with select developmental disabilities (autism, attention deficit hyperactivity disorder, and other developmental delays) has increased, requiring more health and education services. Additional study of the influence of risk-factor shifts, changes in acceptance, and benefits of early services is needed.

http://www.ncbi.nlm.nih.gov/pubmed/21606152

“Developmental disabilities are common and were reported in 1 in 6 children in the United States in 2006-2008. The number of children with select developmental disabilities (autism, attention deficit hyperactivity disorder, and other developmental delays) has increased, requiring more health and education services.”

Surveillance Summaries • March 30, 2012

Prevalence of Autism Spectrum Disorders

Autism and Developmental Disabilities Monitoring Network • 14 Sites USA
Autism and Developmental Disabilities Monitoring Network Surveillance Year 2008

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Abstract

Problem/Condition

Autism spectrum disorders (ASDs) are a group of developmental disabilities characterized by impairments in social interaction and communication and by restricted, repetitive, and stereotyped patterns of behavior. Symptoms typically are apparent before age 3 years. The complex nature of these disorders, coupled with a lack of biologic markers for diagnosis and changes in clinical definitions over time, creates challenges in monitoring the prevalence of ASDs. Accurate reporting of data is essential to understand the prevalence of ASDs in the population and can help direct research.

Period Covered

2008

Description of System

The Autism and Developmental Disabilities Monitoring (ADDM) Network is an active surveillance system that estimates the prevalence of ASDs and describes other characteristics among children aged 8 years whose parents or guardians reside within 14 ADDM sites in the United States. ADDM does not rely on professional or family reporting of an existing ASD diagnosis or classification to ascertain case status. Instead, information is obtained from children's evaluation records to determine the presence of ASD symptoms at any time from birth through the end of the year when the child reaches age 8 years. ADDM focuses on children aged 8 years because a baseline study conducted by CDC demonstrated that this is the age of identified peak prevalence. A child is included as meeting the surveillance case definition for an ASD if he or she displays behaviors (as described on a comprehensive evaluation completed by a qualified professional) consistent with the American Psychiatric Association's Diagnostic and Statistical Manual-IV, Text Revision (DSM-IV-TR) diagnostic criteria for any of the following conditions: Autistic Disorder; Pervasive Developmental Disorder–Not Otherwise Specified (PDD-NOS, including Atypical Autism); or Asperger Disorder. The first phase of the ADDM methodology involves screening and abstraction of comprehensive evaluations completed by professional providers at multiple data sources in the community. Multiple data sources are included, ranging from general pediatric health clinics to specialized programs for children with developmental disabilities. In addition, many ADDM sites also review and abstract records of children receiving special education services in public schools. In the second phase of the study, all abstracted evaluations are reviewed by trained clinicians to determine ASD case status. Because the case definition and surveillance methods have remained consistent across all ADDM surveillance years to date, comparisons to results for earlier surveillance years can be made. This report provides updated ASD prevalence estimates from the 2008 surveillance year, representing 14 ADDM areas in the United States. In addition to prevalence estimates, characteristics of the population of children with ASDs are described, as well as detailed comparisons of the 2008 surveillance year findings with those for the 2002 and 2006 surveillance years.

Results

For 2008, the overall estimated prevalence of ASDs among the 14 ADDM sites was 11.3 per 1,000 (one in 88) children aged 8 years who were living in these communities during 2008. Overall ASD prevalence estimates varied widely across all sites (range: 4.8–21.2 per 1,000 children aged 8 years). ASD prevalence estimates also varied widely by sex and by racial/ethnic group. Approximately one in 54 boys and one in 252 girls living in the ADDM Network communities were identified as having ASDs. Comparison of 2008 findings with those for earlier surveillance years indicated an increase in estimated ASD prevalence of 23% when the 2008 data were compared with the data for 2006 (from 9.0 per 1,000 children aged 8 years in 2006 to 11.0 in 2008 for the 11 sites that provided data for both surveillance years) and an estimated increase of 78% when the 2008 data were compared with the data for 2002 (from 6.4 per 1,000 children aged 8 years in 2002 to 11.4 in 2008 for the 13 sites that provided data for both surveillance years). Because the ADDM Network sites do not make up a nationally representative sample, these combined prevalence estimates should not be generalized to the United States as a whole.

"For 2008, the overall estimated prevalence of Autistic Spectrum Disorder among the 14 ADDM sites was 11.3 per 1,000 (one in 88) ..."

http://www.cdc.gov/mmwr/preview/mmwrhtml/ss6103a1.htm

Molecular Psychiatry • April 2012

A review of research trends in physiological abnormalities in autism spectrum disorders: immune dysregulation, inflammation, oxidative stress, mitochondrial dysfunction and environmental toxicant exposures

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Abstract

Recent studies have implicated physiological and metabolic abnormalities in autism spectrum disorders (ASD) and other psychiatric disorders, particularly immune dysregulation or inflammation, oxidative stress, mitochondrial dysfunction and environmental toxicant exposures ('four major areas'). The aim of this study was to determine trends in the literature on these topics with respect to ASD. A comprehensive literature search from 1971 to 2010 was performed in these four major areas in ASD with three objectives. First, publications were divided by several criteria, including whether or not they implicated an association between the physiological abnormality and ASD. A large percentage of publications implicated an association between ASD and immune dysregulation/inflammation (416 out of 437 publications, 95%), oxidative stress (all 115), mitochondrial dysfunction (145 of 153, 95%) and toxicant exposures (170 of 190, 89%). Second, the strength of evidence for publications in each area was computed using a validated scale. The strongest evidence was for immune dysregulation/inflammation and oxidative stress, followed by toxicant exposures and mitochondrial dysfunction. In all areas, at least 45% of the publications were rated as providing strong evidence for an association between the physiological abnormalities and ASD. Third, the time trends in the four major areas were compared with trends in neuroimaging, neuropathology, theory of mind and genetics ('four comparison areas'). The number of publications per 5-year block in all eight areas was calculated in order to identify significant changes in trends. Prior to 1986, only 12 publications were identified in the four major areas and 51 in the four comparison areas (42 for genetics). For each 5-year period, the total number of publications in the eight combined areas increased progressively. Most publications (552 of 895, 62%) in the four major areas were published in the last 5 years (2006-2010). Evaluation of trends between the four major areas and the four comparison areas demonstrated that the largest relative growth was in immune dysregulation/inflammation, oxidative stress, toxicant exposures, genetics and neuroimaging. Research on mitochondrial dysfunction started growing in the last 5 years. Theory of mind and neuropathology research has declined in recent years. Although most publications implicated an association between the four major areas and ASD, publication bias may have led to an overestimation of this association. Further research into these physiological areas may provide insight into general or subset-specific processes that could contribute to the development of ASD and other psychiatric disorders.

Full Report

http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3317062/

[the state of autism research]

PLoS One • April 2012

The co-morbidity burden of children and young adults with autism spectrum disorders

Author information

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Abstract

OBJECTIVES

Use electronic health records Autism Spectrum Disorder (ASD) to assess the comorbidity burden of ASD in children and young adults.

STUDY DESIGN

A retrospective prevalence study was performed using a distributed query system across three general hospitals and one pediatric hospital. Over 14,000 individuals under age 35 with ASD were characterized by their co-morbidities and conversely, the prevalence of ASD within these comorbidities was measured. The comorbidity prevalence of the younger (Age<18 years) and older (Age 18-34 years) individuals with ASD was compared.

RESULTS

19.44% of ASD patients had epilepsy as compared to 2.19% in the overall hospital population (95% confidence interval for difference in percentages 13.58-14.69%), 2.43% of ASD with schizophrenia vs. 0.24% in the hospital population (95% CI 1.89-2.39%), inflammatory bowel disease (IBD) 0.83% vs. 0.54% (95% CI 0.13-0.43%), bowel disorders (without IBD) 11.74% vs. 4.5% (95% CI 5.72-6.68%), CNS/cranial anomalies 12.45% vs. 1.19% (95% CI 9.41-10.38%), diabetes mellitus type I (DM1) 0.79% vs. 0.34% (95% CI 0.3-0.6%), muscular dystrophy 0.47% vs 0.05% (95% CI 0.26-0.49%), sleep disorders 1.12% vs. 0.14% (95% CI 0.79-1.14%). Autoimmune disorders (excluding DM1 and IBD) were not significantly different at 0.67% vs. 0.68% (95% CI -0.14-0.13%). Three of the studied comorbidities increased significantly when comparing ages 0-17 vs 18-34 with $p<0.001$: Schizophrenia (1.43% vs. 8.76%), diabetes mellitus type I (0.67% vs. 2.08%), IBD (0.68% vs. 1.99%) whereas sleeping disorders, bowel disorders (without IBD) and epilepsy did not change significantly.

CONCLUSIONS

The comorbidities of ASD encompass disease states that are significantly overrepresented in ASD with respect to even the patient populations of tertiary health centers. This burden of comorbidities goes well beyond those routinely managed in developmental medicine centers and requires broad multidisciplinary management that payors and providers will have to plan for.

Full Report

http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3325235/

[autism encompasses far more than just neurological disorders. Autism includes epilepsy, schizophrenia, inflammatory bowel disease, bowel disorders, cranial anomalies, diabetes mellitus type 1, muscular dystrophy, sleep disorders, autoimmune disorders and more...]

European Journal Of Paediatric Neurology • November 2012

Observed prevalence of autism spectrum disorders in two Norwegian counties

Author information

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Abstract

BACKGROUND
The prevalence of autism spectrum disorders (ASD) has previously been reported to be increasing dramatically in European and non-European countries. No similar increase in prevalence rates has been documented in Norway to date. The current study reports on ASD prevalence rates in two Norwegian counties.

METHODS
The population comprised 31,015 children, ages six to 12. Information about special needs services was provided by the school authorities and the public health service. Multiple search strategies were applied to identify children at risk of ASD or diagnosed with ASD. Hospital registers were searched and a mapping tool was used in all local schools.

RESULTS
The total number of patients with ASD found in the population was 158. This gives a prevalence of 51 per 10,000 (95% CI, 0.43-0.59).

CONCLUSION
Compared with the previously reported prevalence of ASD in Norway, there has been almost a fourfold increase in the occurrence of childhood autism and a tenfold increase in the occurrence of all ASD groups. These findings have significant implications for designing and dimensioning appropriate intervention programmes for children with ASD and their families.

http://www.ncbi.nlm.nih.gov/pubmed/?term=22342070

“there has been almost a fourfold increase in the occurrence of childhood autism and a tenfold increase in the occurrence of all ASD groups.”

International Journal Of Environmental Research And Public Health • December 2012

Hair toxic metal concentrations and autism spectrum disorder severity in young children

Author information

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Abstract

Previous studies have found a higher body-burden of toxic metals, particularly mercury (Hg), among subjects diagnosed with an autism spectrum disorder (ASD) in comparison to neurotypical controls. Moreover, Hg body-burden was associated with ASD severity. This cross-sectional study examined the potential correlation between hair toxic metal concentrations and ASD severity in a prospective cohort of participants diagnosed with moderate to severe ASD. The Institutional Review Board at the University of Texas Southwestern Medical Center at Dallas (Dallas, TX) approved the present study. Qualifying study participants (n = 18) were evaluated for ASD severity using the Childhood Autism Rating Scale (CARS) and quantitatively for arsenic, Hg, cadmium, lead, chromium, cobalt, nickel, aluminum, tin, uranium, and manganese using hair toxic element testing by Doctor's Data (a CLIA-approved laboratory). CARS scoring and hair toxic element testing were blinded to one another. Increasing hair Hg concentrations significantly correlated with increased ASD severity. In contrast, no significant correlations were observed between any other of the hair toxic metals examined and ASD severity. This study helps to provide additional mechanistic support for Hg in the etiology of ASD severity, and is supported by an increasing number of recent critical reviews that provide biological plausibility for the role of Hg exposure in the pathogenesis of ASDs.

Full Report

http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3546773/

"This study helps to provide additional mechanistic support for Hg [ethyl mercury or thimerosal] in the etiology of Autistic Spectrum Disorder [ASD] severity, and is supported by an increasing number of recent critical reviews that provide biological plausibility for the role of ethyl mercuty [Hg] exposure in the pathogenesis of Autistic Spectrum Disorder"

Acta Neurobiologia Experimentalis • 2012

Evidence of parallels between mercury intoxication and the brain pathology in autism

Author information

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Abstract

The purpose of this review is to examine the parallels between the effects mercury intoxication on the brain and the brain pathology found in autism spectrum disorder (ASD). This review finds evidence of many parallels between the two, including: (1) microtubule degeneration, specifically large, long-range axon degeneration with subsequent abortive axonal sprouting (short, thin axons); (2) dentritic overgrowth; (3) neuroinflammation; (4) microglial/astrocytic activation; (5) brain immune response activation; (6) elevated glial fibrillary acidic protein; (7) oxidative stress and lipid peroxidation; (8) decreased reduced glutathione levels and elevated oxidized glutathione; (9) mitochondrial dysfunction; (10) disruption in calcium homeostasis and signaling; (11) inhibition of glutamic acid decarboxylase (GAD) activity; (12) disruption of GABAergic and glutamatergic homeostasis; (13) inhibition of IGF-1 and methionine synthase activity; (14) impairment in methylation; (15) vascular endothelial cell dysfunction and pathological changes of the blood vessels; (16) decreased cerebral/cerebellar blood flow; (17) increased amyloid precursor protein; (18) loss of granule and Purkinje neurons in the cerebellum; (19) increased pro-inflammatory cytokine levels in the brain (TNF-□, IFN-□, IL-1□, IL-8); and (20) aberrant nuclear factor kappa-light-chain-enhancer of activated B cells (NF-kappaB). This review also discusses the ability of mercury to potentiate and work synergistically with other toxins and pathogens in a way that may contribute to the brain pathology in ASD. The evidence suggests that mercury may be either causal or contributory in the brain pathology in ASD, possibly working synergistically with other toxic compounds or pathogens to produce the brain pathology observed in those diagnosed with an ASD.

Full Report

http://www.ncbi.nlm.nih.gov/pubmed/22810216

“The evidence suggests that mercury may be either causal or contributory in the brain pathology in Autistic Spectrum Disorder, possibly working synergistically with other toxic compounds or pathogens to produce the brain pathology observed in those diagnosed with an Autistic Spectrum Disorder”

Translational Neurodegeneration • August 2013

Evidence of neurodegeneration in autism spectrum disorder

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Abstract

Autism spectrum disorder (ASD) is a neurological disorder in which a significant number of children experience a developmental regression characterized by a loss of previously-acquired skills and abilities. Loss of neurological function in ASD, as observed in affected children who have regressed, can be explained as neurodegeneration. Although there is research evidence of neurodegeneration or progressive encephalopathy in ASD, the issue of neurodegeneration in ASD is still under debate. Evidence of neurodegeneration in the brain in ASD includes: (1) neuronal cell loss, (2) activated microglia and astrocytes, (3) proinflammatory cytokines, (4) oxidative stress, and (5) elevated 8-oxo-guanosine levels. The evidence from this review suggests that neurodegeneration underlies the loss of neurological function in children with ASD who have experienced regression and loss of previously acquired skills and abilities, and that research into treatments to address the issue of neurodegeneration in ASD are warranted.

http://www.ncbi.nlm.nih.gov/pubmed/23925007

“Evidence of neurodegeneration in the brain in ASD [autistic spectrum disorder] includes:

(1) neuronal cell loss,

(2) activated microglia and astrocytes,

(3) proinflammatory cytokines,

(4) oxidative stress, and

(5) elevated 8-oxo-guanosine levels.”

Journal on Developmental Disabilities • 2012

Autism

Author Information

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Abstract

Autism is a multisystem developmental disorder characterized by dysfunctional immunity and impaired brain function. Although autism is partly determined by genetic susceptibility factors, reported dramatic increases in the prevalence of autism in developed countries have intensified scientific focus on environmental exposures. Pre- and perinatal immunotoxic insults are now strongly suspected as contributors to this increase. Mercury (Hg) is both a neuro- and an immunotoxin and continues to be used in some pediatric vaccines in the form of the preservative thimerosal. Although currently there are no direct human studies on the risks of Hg exposure from thimerosal-containing vaccines (TCVs), animal studies show that doses relevant to human TCV exposure can result in adverse neurodevelopmental outcomes. To date, TCVs continue to be administered on a regular basis to potentially the most vulnerable populations: pregnant women and children. In light of existing experimental evidence, the rationale for using this known immunotoxic and neurotoxic substance in human vaccines should be reconsidered.

http://connection.ebscohost.com/c/articles/79268607/commentary-link-between-mercury-exposure-autism-spectrum-disorder-other-neurodevelopmental-disorders-implications-thimerosal-containing-vaccines

Brain • September 2013

Early brain enlargement and elevated extra-axial fluid in infants who develop autism spectrum disorder

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Abstract

Prospective studies of infants at risk for autism spectrum disorder have provided important clues about the early behavioural symptoms of autism spectrum disorder. Diagnosis of autism spectrum disorder, however, is not currently made until at least 18 months of age. There is substantially less research on potential brain-based differences in the period between 6 and 12 months of age. Our objective in the current study was to use magnetic resonance imaging to identify any consistently observable brain anomalies in 6-9 month old infants who would later develop autism spectrum disorder. We conducted a prospective infant sibling study with longitudinal magnetic resonance imaging scans at three time points (6-9, 12-15, and 18-24 months of age), in conjunction with intensive behavioural assessments. Fifty-five infants (33 'high-risk' infants having an older sibling with autism spectrum disorder and 22 'low-risk' infants having no relatives with autism spectrum disorder) were imaged at 6-9 months; 43 of these (27 high-risk and 16 low-risk) were imaged at 12-15 months; and 42 (26 high-risk and 16 low-risk) were imaged again at 18-24 months. Infants were classified as meeting criteria for autism spectrum disorder, other developmental delays, or typical development at 24 months or later (mean age at outcome: 32.5 months). Compared with the other two groups, infants who developed autism spectrum disorder (n = 10) had significantly greater extra-axial fluid at 6-9 months, which persisted and remained elevated at 12-15 and 18-24 months. Extra-axial fluid is characterized by excessive cerebrospinal fluid in the subarachnoid space, particularly over the frontal lobes. The amount of extra-axial fluid detected as early as 6 months was predictive of more severe autism spectrum disorder symptoms at the time of outcome. Infants who developed autism spectrum disorder also had significantly larger total cerebral volumes at both 12-15 and 18-24 months of age. This is the first magnetic resonance imaging study to prospectively evaluate brain growth trajectories from infancy in children who develop autism spectrum disorder. The presence of excessive extra-axial fluid detected as early as 6 months and the lack of resolution by 24 months is a hitherto unreported brain anomaly in infants who later develop autism spectrum disorder. This is also the first magnetic resonance imaging evidence of brain enlargement in autism before age 2. These findings raise the potential for the use of structural magnetic resonance imaging to aid in the early detection of children at risk for autism spectrum disorder or other neurodevelopmental disorders.

Full Report

http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3754460/

Journal Of Mental Health Research And Intellectual Disability • October 2013

A Comparison of the Autism Treatment Evaluation Checklist (ATEC) and the Childhood Autism Rating Scale (CARS) for the Quantitative Evaluation of Autism

Author information

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Abstract

The purpose of this study was to evaluate scores generated from the Autism Treatment Evaluation Checklist (ATEC), a parent-rated measure, and those derived from professionally completed Childhood Autism Rating Scale (CARS) evaluations. A cohort of 56 participants diagnosed with an autism spectrum disorder was used for the study, and each child was evaluated independently by the parent using the ATEC and a health care professional using the CARS. The Spearman's rank correlation statistic □ was used to evaluate the correlation between ATEC and CARS scores. It was observed that there was a significant correlation between total ATEC and CARS scores (□ = .71). Specific domains in the ATEC evaluation significantly correlated with CARS scores. Sensitivity, specificity, and receiver operating characteristic confirmed the association between CARS and ATEC domains. The results help to validate the utility of the parentally completed ATEC in comparison with an established, professional-related measure of autism.

http://www.ncbi.nlm.nih.gov/pubmed/23914277

"The results help to validate the utility of the parentally completed ATEC in comparison with an established, professional-related measure of autism."

Current Neuropharmacology • March 2014

Redox Regulation and the Autistic Spectrum: Role of Tryptophan Catabolites, Immuno-inflammation, Autoimmunity and the Amygdala

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Abstract

The autistic spectrum disorders (ASD) form a set of multi-faceted disorders with significant genetic, epigenetic and environmental determinants. Oxidative and nitrosative stress (O&NS), immuno-inflammatory pathways, mitochondrial dysfunction and dysregulation of the tryptophan catabolite (TRYCATs) pathway play significant interactive roles in driving the early developmental etiology and course of ASD. O&NS interactions with immuno-inflammatory pathways mediate their effects centrally via the regulation of astrocyte and microglia responses, including regional variations in TRYCATs produced. Here we review the nature of these interactions and propose an early developmental model whereby different ASD genetic susceptibilities interact with environmental and epigenetic processes, resulting in glia biasing the patterning of central interarea interactions. A role for decreased local melatonin and N-acetylserotonin production by immune and glia cells may be a significant treatment target.

Full Report

http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3964746/

Pediatrics • May 2014

Parental obesity and risk of autism spectrum disorder

Author information

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Abstract

OBJECTIVES

The objective of the study was to investigate the associations among maternal prepregnancy BMI, paternal BMI, and the risk of autism spectrum disorders (ASDs) in children.

METHODS

The study sample of 92 909 children was derived from the population-based, prospective Norwegian Mother and Child Cohort Study. The age range was 4.0 through 13.1 (mean 7.4) years. Relative risks of ASDs were estimated by odds ratios (ORs) and 95% confidence intervals (CIs) from logistic regression models.

RESULTS

At the end of follow-up on December 31, 2012, 419 children in the study sample had been diagnosed with ASDs: 162 with autistic disorder, 103 with Asperger disorder, and 154 with pervasive developmental disorder not otherwise specified. Maternal obesity (BMI ≥30) was only weakly associated with ASD risk, whereas paternal obesity was associated with an increased risk of autistic disorder and Asperger disorder. The risk of autistic disorder was 0.27% (25 of 9267) in children of obese fathers and 0.14% (59 of 41 603) in children of fathers with normal weight (BMI <25), generating an adjusted OR of 1.73 (95% CI: 1.07-2.82). For Asperger disorder, analyses were limited to children aged ≥7 years (n = 50 116). The risk was 0.38% (18 of 4761) in children of obese fathers and 0.18% (42 of 22 736) in children of normal-weight fathers, and the adjusted OR was 2.01 (95% CI: 1.13-3.57). No associations were found for pervasive developmental disorder not otherwise specified.

CONCLUSIONS

Paternal obesity is an independent risk factor for ASDs in children. The associations should be investigated further in genetic and epigenetic studies.

http://www.ncbi.nlm.nih.gov/pubmed/24709932

“Several of these influences, including polybrominated diphenyl ethers, aluminum adjuvants, the herbicide glyphosate, and obesity among U.S. women, have increasing trends that are positively correlated to the rise in autism. However, most of the toxins surveyed, including lead, PCBs, organochlorine pesticides, vehicular emissions and air pollution, have flat or declining trends, making it less likely that they can be driving the increase in diagnosed autism seen over the 35-year period of the composite data set.”

Environmental Health • September 2014

A comparison of temporal trends in United States autism prevalence to trends in suspected environmental factors

Cynthia D Nevison

Abstract

Background

The prevalence of diagnosed autism has increased rapidly over the last several decades among U.S. children. Environmental factors are thought to be driving this increase and a list of the top ten suspected environmental toxins was published recently.

Methods

Temporal trends in autism for birth years 1970–2005 were derived from a combination of data from the California Department of Developmental Services (CDDS) and the United States Individuals with Disabilities Education Act (IDEA). Temporal trends in suspected toxins were derived from data compiled during an extensive literature survey. Toxin and autism trends were compared by visual inspection and computed correlation coefficients. Using IDEA data, autism prevalence vs. birth year trends were calculated independently from snapshots of data from the most recent annual report, and by tracking prevalence at a constant age over many years of reports. The ratio of the snapshot:tracking trend slopes was used to estimate the “real” fraction of the increase in autism.

Results

The CDDS and IDEA data sets are qualitatively consistent in suggesting a strong increase in autism prevalence over recent decades. The quantitative comparison of IDEA snapshot and constant-age tracking trend slopes suggests that ~75-80% of the tracked increase in autism since 1988 is due to an actual increase in the disorder rather than to changing diagnostic criteria. Most of the suspected environmental toxins examined have flat or decreasing temporal trends that correlate poorly to the rise in autism. Some, including lead, organochlorine pesticides and vehicular emissions, have strongly decreasing trends. Among the suspected toxins surveyed, polybrominated diphenyl ethers, aluminum adjuvants, and the herbicide glyphosate have increasing trends that correlate positively to the rise in autism.

Conclusions

Diagnosed autism prevalence has risen dramatically in the U.S over the last several decades and continued to trend upward as of birth year 2005. The increase is mainly real and has occurred mostly since the late 1980s. In contrast, children’s exposure to most of the top ten toxic compounds has remained flat or decreased over this same time frame. Environmental factors with increasing temporal trends can help suggest hypotheses for drivers of autism that merit further investigation.

Summary

Temporal trends in autism were constructed both by tracking prevalence at a constant age in a series of historical IDEA reports and by computing prevalence from age-resolved snapshots in individual, recent IDEA reports. Both the snapshot and tracking approaches suggest a strong increase in autism that took off in the late 1980s and was ongoing as of birth year 2005. The ratio of the snapshot:tracking slopes suggests that among states with the most reliable data, about 75 to 80% of the tracked increase in IDEA autism since 1988 is due to a real increase in the disorder rather than just to better or expanded diagnosis. The trend in California IDEA autism prevalence was shown to be broadly representative of the mean United States trend and was extended to span birth years 1970–2005 using a composite CDDS plus IDEA dataset. The composite dataset, which shows that a more gradual increase in autism had begun already by 1980, was compared to the corresponding trends in a list of suspected toxins and environmental influences. Several of these influences, including polybrominated diphenyl ethers, aluminum adjuvants, the herbicide glyphosate, and obesity among U.S. women, have increasing trends that are positively correlated to the rise in autism. However, most of the toxins surveyed, including lead, PCBs, organochlorine pesticides, vehicular emissions and air pollution, have flat or declining trends, making it less likely that they can be driving the increase in diagnosed autism seen over the 35-year period of the composite data set.

http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4177682/

Molecular Autism • September 2014

Dysregulation of estrogen receptor beta (ERß), aromatase (CYP19A1), and ER co-activators in the middle frontal gyrus of autism spectrum disorder subjects

Author information

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Abstract

BACKGROUND

Autism spectrum disorders (ASD) are much more common in males than in females. Molecular alterations within the estrogen receptor (ER) signaling pathway may contribute to the sex difference in ASD, but the extent of such abnormalities in the brain is not known.

METHODS

Postmortem middle frontal gyrus tissues (13 ASD and 13 control subjects) were used. The protein levels were examined by western blotting. The gene expression was determined by qRT-PCR.

RESULTS

Gene expression analysis identified a 35% decrease in ER□ mRNA expression in the middle frontal gyrus of ASD subjects. In addition, a 38% reduction in aromatase (CYP19A1) mRNA expression was observed in ASD subjects. We also found significant decreases in ER co-activators that included a 34% decrease in SRC-1, a 77% decrease in CBP, and a 52% decrease in P/CAF mRNA levels in ASD subjects relative to controls. There were no differences in the mRNA levels of TIF-2, AIB-1 (ER co-activators), ER co-repressors (SMRT and nCoR) and ERß in the middle frontal gyrus of ASD subjects as compared to controls. We observed significant correlations between ERß, CYP19A1, and co-activators in the study subjects. Immunoblot analysis further confirmed the changes in ERß and aromatase at the protein level in the control and ASD subjects.

http://www.ncbi.nlm.nih.gov/pubmed/25221668

Journal of Public Health and Epidemiology • September 2014

Impact of environmental factors on the prevalence of autistic disorder after 1979

Author Information

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Abstract

The aim of this study was to investigate a previously overlooked, universally introduced environmental factor, fetal and retroviral contaminants in childhood vaccines, absent prior to change points (CPs) in autistic disorder (AD) prevalence with subsequent dose-effect evidence and known pathologic mechanisms of action. Worldwide population based cohort study was used for the design of this study. The United States, Western Australia, United Kingdom and Denmark settings were used. All live born infants who later developed autistic disorder delivered after 1 January 1970, whose redacted vaccination and autistic disorder diagnosis information is publicly available in databases maintained by the US Federal Government, Western Australia, UK, and Denmark. The live births, grouped by father's age, were from the US and Australia. The children vaccinated with MMRII, Varicella and Hepatitis A vaccines varied from 19 to 35 months of age at the time of vaccination. Autistic disorder birth year change points were identified as 1980.9, 1988.4 and 1996 for the US, 1987 for UK, 1990.4 for Western Australia, and 1987.5 for Denmark. Change points in these countries corresponded to introduction of or increased doses of human fetal cell line-manufactured vaccines, while no relationship was found between paternal age or Diagnostic and Statistical Manual (DSM) revisions and autistic disorder diagnosis. Further, linear regression revealed that Varicella and Hepatitis A immunization coverage was significantly correlated to autistic disorder cases. R software was used to calculate change points. Autistic disorder change points years are coincident with introduction of vaccines manufactured using human fetal cell lines, containing fetal and retroviral contaminants, into childhood vaccine regimens. This pattern was repeated in the US, UK, Western Australia and Denmark. Thus, rising autistic disorder prevalence is directly related to vaccines manufactured utilizing human fetal cells. Increased paternal age and DSM revisions were not related to rising autistic disorder prevalence.

http://soundchoice.org/scpiJournalPubHealthEpidem092014.pdf

"R software was used to calculate change points. Autistic disorder change points years are coincident with introduction of vaccines manufactured using human fetal cell lines, containing fetal and retroviral contaminants, into childhood vaccine regimens ... rising autistic disorder prevalence is directly related to vaccines manufactured utilizing human fetal cells."

Environmental Toxicology And Pharmacology • November 2014

Autism: a form of lead and mercury toxicity

Author information

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Abstract

AIM

Autism is a developmental disability characterized by severe deficits in social interaction and communication. The definite cause of autism is still unknown. The aim of this study is to find out the relation between exposure to Lead and/or mercury as heavy metals and autistic symptoms, dealing with the heavy metals with chelating agents can improve the autististic symptoms.

METHOD

Blood and hair samples were obtained from 45 children from Upper Egypt with autism between the ages of 2 and 10 years and 45 children served as controls in the same age range, after taken an informed consent and fill a questionnaire to assess the risk factors. The samples were analyzed blindly for lead and mercury by using atomic absorption and ICP-MS. Data from the two groups were compared, then follow up of the autistic children after treatment with chelating agents were done.

RESULTS

The results obtained showed significant difference among the two groups, there was high level of mercury and lead among those kids with autism. Significant decline in the blood level of lead and mercury with the use of DMSA as a chelating agent. In addition, there was decline in the autistic symptoms with the decrease in the lead and mercury level in blood.

CONCLUSION

Lead and mercury considered as one of the main causes of autism. Environmental exposure as well as defect in heavy metal metabolism is responsible for the high level of heavy metals. Detoxification by chelating agents had great role in improvement of those kids.

http://www.ncbi.nlm.nih.gov/pubmed/25461563

“Lead and mercury considered as one of the main causes of autism. Environmental exposure as well as defect in heavy metal metabolism is responsible for the high level of heavy metals.”

Current Problems In Pediatric And Adolescent Health Care • November 2014

Environmental chemical exposures and autism spectrum disorders: a review of the epidemiological evidence

Author information

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Abstract

In the past decade, the number of epidemiological publications addressing environmental chemical exposures and autism has grown tremendously. These studies are important because it is now understood that environmental factors play a larger role in causing autism than previously thought and because they address modifiable risk factors that may open up avenues for the primary prevention of the disability associated with autism. In this review, we covered studies of autism and estimates of exposure to tobacco, air pollutants, volatile organic compounds and solvents, metals (from air, occupation, diet, dental amalgams, and thimerosal-containing vaccines), pesticides, and organic endocrine-disrupting compounds such as flame retardants, non-stick chemicals, phthalates, and bisphenol A. We included studies that had individual-level data on autism, exposure measures pertaining to pregnancy or the 1st year of life, valid comparison groups, control for confounders, and adequate sample sizes. Despite the inherent error in the measurement of many of these environmental exposures, which is likely to attenuate observed associations, some environmental exposures showed associations with autism, especially traffic-related air pollutants, some metals, and several pesticides, with suggestive trends for some volatile organic compounds (e.g., methylene chloride, trichloroethylene, and styrene) and phthalates. Whether any of these play a causal role requires further study. Given the limited scope of these publications, other environmental chemicals cannot be ruled out, but have not yet been adequately studied. Future research that addresses these and additional environmental chemicals, including their most common routes of exposures, with accurate exposure measurement pertaining to several developmental windows, is essential to guide efforts for the prevention of the neurodevelopmental damage that manifests in autism symptoms.

http://www.ncbi.nlm.nih.gov/pubmed/25199954

Journal Of Developmental Physical Disability • February 2015

A Review of the Differences in Developmental, Psychiatric, and Medical Endophenotypes Between Males and Females with Autism Spectrum Disorder

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Abstract

Autism spectrum disorder (ASD) is over four times more prevalent in males compared to females. Increased understanding of sex differences in ASD endophenotypes could add insight into possible etiologies and the assessment and management of the disorder. Consequently, the purpose of this review is to describe current literature regarding sex differences in the developmental, psychiatric, and medical endophenotypes of ASD in order to illustrate current knowledge and areas in need of further research. Our review found that repetitive behaviors and restricted interests are more common in males than females with ASD. Intellectual disability is more common in females than males with ASD. Attention to detail may be more common in males than females with ASD and epilepsy may be more common in females than males with ASD, although limited research in these areas prevent definitive conclusions from being drawn. There does not appear to be a sex difference in other developmental, psychiatric, and medical symptoms associated with ASD, or the research was contradictory or too sparse to establish a sex difference. Our review is unique in that it offers detailed discussion of sex differences in three major endophenotypes of ASD. Further research is needed to better understand why sex differences exist in certain ASD traits and to evaluate whether phenotypic sex differences are related to different pathways of development, assessment, and treatment of the disorder.

http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4490156/

“Further research is needed to better understand why sex differences exist in certain ASD traits and to evaluate whether phenotypic sex differences are related to different pathways of development, assessment, and treatment of the disorder.”

Journal Of Attention Disorders • September 2015

Are ASD and ADHD a Continuum? A Comparison of Pathophysiological Similarities Between the Disorders

Author information

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Abstract

OBJECTIVE

The objective of this study was to review and compare the similarities between autism spectrum disorder (ASD) and ADHD with regard to symptomatology, neurological deficits, metabolic and endocrine-related conditions, and brain pathology.

METHOD

A comprehensive review of the relevant research literature was carried out.

RESULTS

A number of important similarities between ASD and ADHD were identified, including recent increases in prevalence, male-biased incidence, shared involvement of sensory processing, motor and impulse control, abnormal patterns of neural connectivity, and sleep disturbances. Studies suggest involvement of androgen metabolism, impaired methylation, and heavy metal toxicity as possible contributing factors for both disorders.

CONCLUSION

ASD and ADHD share a number of features and pathophysiological conditions, which suggests that the two disorders may be a continuum and have a common origin.

http://www.ncbi.nlm.nih.gov/pubmed/23074304

“ASD and ADHD share a number of features and pathophysiological conditions, which suggests that the two disorders may be a continuum and have a common origin.”

International Journal of Emergency Mental Health and Human Resilience • September 2015

Autism Spectrum Disorder in the Emergency Department: Looking Beyond Behavior

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Abstract

Autism spectrum disorder (ASD) is a complex neurodevelopmental condition that is behaviorally defined by its well-recognized impairments in verbal and non-verbal communication and social interactions in addition to distinctive restrictive and repetitive behaviors (APA, 1994). Over the past decades the incidence of this disorder has dramatically increased. Although the reason or reasons for this increase is still up for debate, the fact remains that ASD is now estimated to affect 1 in 68 children in the United States (Developmental Disabilities Monitoring Network Surveillance Year Principal, Centers for Disease, & Prevention, 2014). ASD is defined by behavioral manifestations, yet children with ASD have a high prevalence of many medical conditions including recurrent infections (Doshi-Velez, Ge, & Kohane, 2014), gastrointestinal (GI) disturbances (Chaidez, Hansen, & Hertz-Picciotto, 2013), seizures and epilepsy (Frye et al., 2013), anxiety (Sukhodolsky, Bloch, Panza, & Reichow, 2013), allergies (Angelidou et al., 2011) and metabolic disorders (Frye & James, 2014; Frye & Rossignol, 2012) including mitochondrial disease (Frye & Rossignol, 2011; Rossignol & Frye, 2012). With the increase in prevalence and the significant co-morbidity of medical problems, it is likely that medical professionals in the emergency and urgent care facilities will have increasing exposure to individuals with ASD for urgent medical management, particularly acute behavioral dysregulation. When this occurs it will be important to consider their special needs and understand the unique manner in which common medical problem may present in individuals with ASD. Indeed, children without typical communication skills, aberrant behaviors may be the manner in which the child is communicating the need for medical attention (Buie et al., 2010).

ASD is associated with a wide spectrum of behavioral manifestations. Some of the most disruptive behaviors, referred to as aberrant behaviors, can cause significant disability and distress to the patient and caregiver (Baghdadli, Pry, Michelon, & Rattaz, 2014). Aberrant behavior is divided into subcategories by the Aberrant Behavior Checklist (Slosson Educational Publications Inc, East Aurora, NY). These categories include Irritability, Social Withdrawal, Stereotypy, Hyperactivity and Inappropriate Speech. Irritability, which includes severe tantrums, aggression, and self-injury, is one of the major and most disruptive aberrant behaviors (Stigler, 2014). Irritability is commonly treated with antipsychotic medication with or without behavior therapy (Aman et al., 2009). Treating with a medication to suppression symptoms rather than understanding if there is an underlying medical cause for such behaviors can be problematic for several reasons. First, treating symptoms instead of identifying a cause can lead to increased morbidity and mortality from an undiagnosed disorder. Second, antipsychotic medications can detrimentally affect glucose, cholesterol and lipids and weight, even in the short-term (Correll et al., 2009; Wink et al., 2014) and long-term anti-psychotic use increases the risk for type II diabetes (Bobo et al., 2013) and can result in tardive dyskinesia, a potentially permanent movement disorder (Correll & Kane, 2007). Thus, it may be best to look beyond the obvious of controlling behavior and understanding what the behavior means in order to solve potentially important medical conditions to improve the long-term health of a child with ASD. Several examples are given below of the medical condition that can present as behavioral dysregulation in children with ASD.

GI disturbances have been reported to occur in 9% to 70% of children with ASD, with high quality studies suggesting that GI symptoms are very prevalent. GI symptoms commonly manifest as behavioral manifestations in children with ASD (Buie et al., 2010). For example, abdominal pain, gastroesophageal reflux disease and/ or constipation can manifest as vocal symptoms such as frequent repetitive throat clearing or swallowing and/or screaming, crying, whining or sobbing for no reason; motor behaviors such as facial grimacing, teeth grinding, chewing on clothes or other objects, applying pressure to the abdomen or aggressive or self-injurious behavior; and/or general behaviors such sleep disturbance or irritability (Buie et al., 2010). Thus, it is important to obtain a GI history, including symptoms of gastroesophageal reflux, stool frequency and consistency, and perform a careful GI examination to look for abdominal distention and/or impaction.
Many of the GI symptoms may drive aberrant behavior through causing pain. When a child cannot communicate verbally, aberrant and unusual behaviors may be the only manner in which the child can communicate that pain exists. Thus, the clinician needs to have a high index of suspicion for obvious and non-obvious sources of pain. For example, head banging is sometimes associated with headache. Other sources of pain not uncommon in childhood such as pharyngitis, sinusitis, otitis media and dental caries, just to name a few, must also be considered. A trial of analgesics might be appropriate if pain is believed to be driving the behavior. Interestingly celecoxib has been shown to be an effective adjunctive treatment to risperidone for irritability in a double-blind placebo-controlled trial.
(Asadabadi et al., 2013).

Full Report With References

http://www.omicsonline.com/open-access/autism-spectrum-disorder-in-the-emergency-department-looking-beyond-behavior-1522-4821-1000253.php?aid=61163

Sleep disruption is estimated to affect from 44% to 83% of individuals with ASD, with delayed sleep onset and nighttime wakening being the most predominant symptoms (Krakowiak et al., 2008). Several studies have demonstrated that disruption in sleep patterns is associated with problem behaviors during the day, particularly in low-functioning ASD individuals (Cohen et al., 2014), and lower overall functioning in several measures of development including greater problems with language and communication (Taylor, Schreck, & Mulick, 2012). Melatonin is a safe and effective treatment sleep duration and sleep onset latency but is less effective for night time wakening (Rossignol & Frye, 2011) and has been shown to improve daytime behavior and parenting stress (Malow et al., 2012). In addition, a case series reported that the selective melatonin receptor agonist ramelteon can also be effective for improving sleep and daytime behavior (Kawabe, Horiuchi, Oka, & Ueno, 2014). Thus, a careful focused sleep history may provide important information which can lead to appropriate evaluation and treatment.

Anxiety is very common in ASD (Vasa & Mazurek, 2015), particularly in high-functioning ASD children (Chandler et al., 2015). Anxiety is related to aggressive behavior (Pugliese, White, White, & Ollendick, 2013), more severe repetitive behaviors and lower overall development (Magiati et al., 2015) and sleep disruption (Mazurek & Petroski, 2015). A wide variety of treatments for anxiety have been studied in individuals with ASD. The best studied treatments for anxiety in ASD include intranasal oxytocin (Hofmann, Fang, & Brager, 2015) and cognitive-behavioral therapy (Ung, Selles, Small, & Storch, 2015). Although selective serotonin reuptake inhibitors were previously considered useful in the ASD population, such medications may increase the risk of behavioral activation (Vasa & Mazurek, 2015) and may be best suited for treating repetitive behavior (Hollander et al., 2012). Thus, it is important to screen for symptoms of anxiety as such a significant psychiatric comorbidity could be driving disruptive behavior.

There appears to be a wide range of behavioral manifestations that are related to immune dysregulation, although the treatments for these disorders are not well studied. Pediatric Autoimmune Neuropsychiatric Disorders Associated With Streptococcal Infections (PANDAS), a disorder which can result in sudden onset obsessive compulsive behavior, tics and Tourette like behavior (Martino, Defazio, & Giovannoni, 2009), is associated with ASD (Libbey & Fujinami, 2010). Recently PANDAS has been brought in under the umbrella of Pediatric Acute-Onset Neuropsychiatric Syndrome (PANS) and recommendation for diagnostic workup have been outlined in a consensus conference (Chang et al., 2015). The recent recognition of the association of PANDAS/PANS with specific antibodies titers to basal ganglia has provided a medical test to help with diagnosis of these patients (Cox et al., 2015). Other immune abnormalities, which are less well-studied, have been reported. These include the associated between depressed plasma immunoglobulin concentrations with aberrant behavior (Heuer et al., 2008) and the recognition of a subset of children with ASD with behavioral dysregulation following episodes of immune activation (Jyonouchi, Geng, Streck, & Toruner, 2012). Although treatments for immune abnormalities are not well studied, identifying immune abnormalities can result in appropriate referral and treatment.

A disorder related to depressed folate concentration in the brain appears to be rather common is ASD and may be related to behavioral dysregulation. The folate receptor alpha autoantibody is prevalent in ASD with up to 75% of ASD patients being positive for the blocking or binding autoantibody (Frye et al., 2013). Autoantibody titers are directly correlated with increased aggressive behavior (Ramaekers et al., 2007). Titers are increased by the ingestion of milk and behavior can be improved with the treatment of a milk free diet (Ramaekers, Sequeira, Blau, & Quadros, 2008). Since this autoantibody blocks the ability of folate from crossing the blood-brain barrier, an alternative form of folate, high-dose folinic acid, can improve behavior in ASD patient with folate receptor alpha autoantibodies (Frye et al., 2013; Moretti et al., 2005).

These medical conditions which are associated with behavioral dysregulation are under recognized across many medical settings, but it is of the upmost importance for medical professional in the emergency and urgent care departments to recognize these potential medical conditions since many children with ASD will arrive in the emergency department when behavior suddenly escalates. Unfortunately, the evaluation of children with ASD and behavioral dysregulation has not been standardized and many of the medical abnormalities associated with behavioral dysregulation have not been well studied, especially in regards to treatment. Recognition of these conditions can lead to appropriate management and referrals. With the rising number of children with ASD it is important for front line medical professional to be comfortable with evaluating children with ASD and to consider the medical complexities associated with ASD.

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Assessment of Hair Aluminum, Lead, and Mercury in a Sample of Autistic Egyptian Children: Environmental Risk Factors of Heavy Metals in Autism

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Abstract

Background and Aims. The etiological factors involved in the etiology of autism remain elusive and controversial, but both genetic and environmental factors have been implicated. The aim of this study was to assess the levels and possible environmental risk factors and sources of exposure to mercury, lead, and aluminum in children with autism spectrum disorder (ASD) as compared to their matched controls.

Methods. One hundred ASD children were studied in comparison to 100 controls. All participants were subjected to clinical evaluation and measurement of mercury, lead, and aluminum through hair analysis which reflects past exposure.

Results. The mean Levels of mercury, lead, and aluminum in hair of the autistic patients were significantly higher than controls. Mercury, lead, and aluminum levels were positively correlated with maternal fish consumptions, living nearby gasoline stations, and the usage of aluminum pans, respectively.

Conclusion. Levels of mercury, lead, and aluminum in the hair of autistic children are higher than controls. Environmental exposure to these toxic heavy metals, at key times in development, may play a causal role in autism.

http://www.ncbi.nlm.nih.gov/pubmed/?term=26508811

“Levels of mercury, lead, and aluminum in the hair of autistic children are higher than controls. Environmental exposure to these toxic heavy metals, at key times in development, may play a causal role in autism.”

Chapter Seven
Short Essays On Vaccination

Herd Immunity:
Can Infectious Diseases be Prevented by High Vaccination Coverage?

By Lucija Tomljenovic, PhD

The frequent statement that high levels of vaccination prevent disease outbreaks is not accurate as infectious diseases do in fact occur even in fully vaccinated populations [1] as well as individuals. [2] (See Table 1 for more examples)

The likely reason for this is that vaccines primarily stimulate humoral immunity (antibody-based or Th2 responses) while they have little or no effect on cellular immunity (cytotoxic T-cells, Th1 responses), which is absolutely crucial for protection against viral as well as some bacterial pathogens. [3]

This may be the reason why vaccine-induced immunities are transient, requiring booster shots; while naturally acquired immunity conferred by the cellular immune system tends to be permanent in the absence of vaccination.
Taken together, these observations may explain why outbreaks of allegedly vaccine-preventable diseases do occur in fully vaccinated populations and why, immunity (or its absence) cannot be reliably determined by measuring antibody levels, [4] which is the most common measure of vaccine efficacy in clinical trials. [5-7]

It should be noted that there is an instance where vaccinations can induce T-cell (Th1) responses. This is possible in the case of repetitive immunizations with the same antigen (i.e., closely spaced “booster shoots”).

However, the induction of such immune responses is deleterious as demonstrated by Tsumiyama et al. [8] who showed that CD4+ T cells from repeatedly-immunized mice acquire the ability to induce autoantibodies which result in autoimmune tissue injury akin to that seen in human autoimmune diseases.

From these experiments Tsumiyama et al. [8] concluded that systemic autoimmunity appears to be the inevitable consequence of over-stimulating the host’s immune ‘system’ by repeated immunization with antigen.

Full Report

http://sanevax.org/wp-content/uploads/2015/05/Herd-Immunity-.pdf

Forced Vaccinations: For the Greater Good?

by Lucija Tomljenovic, PhD

Full Report

http://vaccinechoicecanada.com/wp-content/uploads/Forced-Vaccinations-For-the-Greater-Good-Tomljenovic.pdf

Dr. Lucija Tomljenovic was awarded a PhD in 2009 in Biochemistry from the Comparative Genomics Centre at James Cook University in Townsville, Australia. In 2010, she joined the Neural Dynamics Research Group at the University of British Columbia (Chris Shaw's lab) and is currently researching the neurotoxic effects of aluminium vaccine adjuvants.

Lawsuits claiming Merck lied about mumps vaccine efficacy headed to trial

September 9, 2014 by Carly Helfand

Two lawsuits claiming Merck ($MRK) lied about the efficacy of its mumps vaccine won't be going away anytime soon. A federal judge in Pennsylvania refused to dismiss the suits, filed by a pair of whistleblowers and a group of doctors and payers, and now, they're on their way to trial.

On Thursday, U.S. District Judge C. Darnell Jones II ruled that the whistleblowers--two former Merck virologists--had sufficiently showed that the company may have misstated the vaccine's efficacy to the government, Law360 reports. And the direct purchasers produced enough evidence to establish that those false statements could have helped give Merck a monopoly, the judge said. Now, the plaintiffs will have to prove their cases at trial.

Merck has been the sole manufacturer with an FDA license to produce mumps vaccine since 1967, the news service points out, and the company has long touted a 95% efficacy rate for the shot. The drugmaker brought in $621 million on mumps vaccine sales last year, between its M-M-R II vaccine and ProQuad, a pediatric combo jab.

But rather than using the "gold standard" approach and testing the vaccine against a wild-type mumps virus, Merck tested it against the attenuated virus strain that had created the vaccine in the 1960s--likely overstating the vaccine's effectiveness, the whistleblowers claim, according to the judge's memorandum. And if Merck "fraudulently misled the government and omitted, concealed, and adulterated material information regarding the efficacy of its mumps vaccine" in violation of the False Claims Act, as they allege, it may have discouraged competition.

"As with the market for any product, a potential competitor's decision to enter a market hinges on whether its product can compete with those products already being sold in the market," the complaint reads, as quoted by Law360. "If an existing vaccine is represented as safe and at least 95% effective, as Merck has falsely represented its vaccine to be, it would be economically irrational for a potential competitor to bring a new mumps vaccine to the relevant market," the suit claims.

The way Merck sees it, whether it misstated the vaccine's efficacy is a matter for the FDA to investigate. The company argued that the whistleblowers' claims "rest on a finding that the vaccine label is misbranded, a determination which should fall squarely under the 'scientific expertise' and 'regulatory discretion'" of the agency, the memorandum says.
But Jones didn't agree, and now it'll be up to the courts to decide--a prospect that pleases Constantine Cannon, which is representing the whistleblowers, and Robins Kaplan Miller & Ciresi, representing the direct purchasers. "This decision brings us one step closer to shining a light on Merck's deceptive business practices so that new and more effective vaccines will ultimately be developed in the future," Robins Kaplan Miller & Ciresi lawyer Kellie Lerner said in a statement.

Read the judges Memorandum

http://assets.fiercemarkets.net/public/merckmemo.pdf

CDC Responds to Allegation it Omitted Vaccine-Autism Study Link

by Sharyl Attkisson • August 28, 2014

The Centers for Disease Control and Prevention (CDC) is responding to a charge from one of its own senior scientists that it omitted key data in a 2004 study that would have revealed a link between autism and a commonly-required childhood vaccine, MMR (Measles, Mumps, Rubella).

The allegation was made by CDC epidemiologist William Thompson in a statement this week issued through his attorney. It states: "I regret that my coauthors and I omitted statistically significant information in our 2004 article published in the journal Pediatrics. The omitted data suggested that African American males who received the MMR vaccine before age 36 months were at increased risk for autism."

It is highly unusual, if not unprecedented, for a sitting CDC senior scientist to blow the whistle on alleged scientific misconduct involving a study article that he co-authored. In this instance, the impact of the charge is magnified by more than a decade of allegations from autism advocates who say the federal government and pharmaceutical interests have worked to downplay or hide associations between vaccines and autism.

Dr. Frank DeStefano, CDC Director of Immunization Safety

A spokesman for the journal Pediatrics today said the publication stands by the study despite the news. "There's a standard process that journals follow when an article is questioned," said the spokesman. "Those discussions took place between the editors of Pediatrics and the authors of this study, and the editors concluded the research was appropriately conducted." Pediatrics is published by the American Academy of Pediatrics, which accepts vaccine industry funding.

The Director of the CDC Immunization Safety Office, Dr. Frank DeStefano, is a co-author of the now-questioned study which has been widely-cited to dispel an MMR-autism link. DeStefano is frequently quoted as an expert who debunks vaccine-autism ties.

"I stand by the research and the conclusions in our 2004 paper, and I'll reiterate that the evidence, thus far, the weight of the evidence, is against a causal association between vaccines and autism," DeStefano told me in a telephone interview this week.

"Lowest Point in my Career"

Thompson is a PhD who works in the National Immunization Program at the CDC where he has been employed for 16 years. His revelations were first made public after he reportedly made wide-ranging claims and confessions in a series of telephone conversations with autism advocate and researcher Brian Hooker of Focus Autism. Hooker, also a PhD, is an assistant professor of biology and the parent of an autistic teenager. Because of the significance of Thompson's allegations, Hooker began recording some of the conversations without Thompson's knowledge.

"It's the lowest point in my career that I went along with that paper," Thompson tells Hooker in a recording played on the online Autism Media Channel. "I went along with this, we didn't report significant findings."

The CDC's DeStefano acknowledges that he and his study co-authors changed their study analysis plan mid-stream, which resulted in reducing the statistical vaccine-autism link among black boys. But he says they did so for good scientific reason.

"[Vaccine] exposure around [three years of age] is just not biologically plausible to have a causal association with autism," DeStefano says. "I mean autism would've already started by then…it probably starts in the womb. So I think from a biological argument, it's implausible this was a causal association."

Highly-Charged Issue

The issue is highly-charged for several reasons: public health officials fear that the public will panic and stop vaccinating if they believe there are links between vaccines and autism. That could lead to resurgence in serious infectious diseases.

Also, vaccination is a multi-billion dollar global industry that employs law firms and public relations agents to engage in a variety of high-powered PR efforts. These efforts include: lobbying members of Congress to prevent hearings exploring vaccine safety, holding private meetings with news executives to discourage reporting on vaccines and autism, and financing nonprofits which take favorable positions on vaccine safety issues. Because pharmaceutical companies that produce vaccines spend millions of dollars each year buying advertising on television, print and online, critics argue they may be given undue influence over content of the reporting media.

Pharmaceutical interests and their surrogates routinely falsely portray scientists and journalists who investigate vaccine safety as "anti-vaccine." In his statement, Thompson emphasizes his safety concerns do not reflect an "anti-vaccine" mentality.

"I want to be absolutely clear that I believe vaccines have saved and continue to save countless lives," Thompson states. "I would never suggest that any parent avoid vaccinating children of any race. Vaccines prevent serious diseases, and the risks associated with their administration are vastly outweighed by their individual and societal benefits.

"My concern has been the decision to omit relevant findings in a particular study for a particular sub group for a particular vaccine. There have always been recognized risks for vaccination and I believe it is the responsibility of the CDC to properly convey the risks associated with receipt of those vaccines."

Subgroup Susceptibility?

Former National Institutes of Health Director Dr. Bernadine Healy broke ranks with her Institute of Medicine colleagues in 2008 in saying that public health officials have intentionally avoided researching whether subsets of children are "susceptible" to vaccine side effects because they are afraid that the answer will scare the public.

"What we're seeing in the bulk of the population: vaccines are safe," said Healy. "But there may be this susceptible group. The fact that there is concern, that you don't want to know that susceptible group is a real disappointment to me. If you know that susceptible group, you can save those children. If you turn your back on the notion that there is a susceptible group… what can I say?"

"You're saying that public health officials have turned their back on a viable area of research largely because they're afraid of what might be found?" I asked Healy, at the time.

Healy answered, "There is a completely expressed concern that they don't want to pursue a hypothesis because that hypothesis could be damaging to the public health community at large by scaring people. "First of all," Healy said, "I think the public's smarter than that. The public values vaccines. But more importantly, I don't think you should ever turn your back on any scientific hypothesis because you're afraid of what it might show."

To date, the only vaccine that carries an explicit autism warning under "Adverse Reactions" on its label is Tripe-

dia's DTaP (Diphtheria and Tetanus Toxoids and Acellular Pertussis Vaccine Adsorbed) vaccine. The label states that "autism" is included, along with SIDS, encephalopathy (brain damage) among other adverse events "because of the seriousness or frequency of reporting." The label states, "Because these events are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequencies or to establish a causal relationship to components of Tripedia vaccine."

The CDC's MMR vaccine information page cites the following "very rare" severe problems: "deafness, long-term seizures, coma, or lowered consciousness and permanent brain damage."

This week, in response to a query, the CDC stated that it is not currently investigating the relation between vaccines and autism spectrum disorders (ASD). "Further, CDC does not have any planned research addressing vaccines and autism," said a CDC spokesman.

"CDC believes that this topic has been thoroughly studied and no causal links have been found. Current CDC ASD related research focuses on determining how many people have ASD and understanding risk factors and causes for ASD."–CDC spokesman

In his statement, Thompson says that his colleagues and supervisors at the CDC have been entirely professional since his allegations became public. "In fact, I received a performance-based award" after the news came out, he says.

Further responding to Thompson's allegations, the CDC says, "Additional studies and a more recent rigorous review by the Institute of Medicine have found that MMR vaccine does not increase the risk

CDC: “Possibility” that vaccines rarely trigger autism

September 2014

by Sharyl Attkisson

CDC’s immunization safety director says it’s a “possibility” that vaccines rarely trigger autism but “it’s hard to predict who those children might be.” (They’re not even trying.)

A CDC senior epidemiologist stepped forward last week to say that he and his CDC colleagues omitted data that linked MMR vaccine to autism in a 2004 study. The scientist, William Thompson, said “I regret that my coauthors and I omitted statistically significant information.” A coauthor of the questioned study is Dr. Frank DeStefano, Director of the CDC Immunization Safety Office. In a telephone interview last week, DeStefano defended the study and reiterated the commonly accepted position that there’s no “causal” link between vaccines and autism. But he acknowledged the prospect that vaccines might rarely trigger autism.

“I guess, that, that is a possibility,” said DeStefano. “It’s hard to predict who those children might be, but certainly, individual cases can be studied to look at those possibilities.”

It is a significant admission from a leading health official at an agency that has worked for nearly 15 years to dispel the public of any notion of a tie between vaccines and autism. Vaccines are among the most heralded medical inventions of our time. Billions of people have been vaccinated worldwide, countless lives have been saved and debilitating injuries prevented. The possibility that vaccines may also partly be responsible for autism, in individual cases, is not something public health officials are typically eager to address. One such individual case is that of Hannah Poling.

Hannah Poling

Hannah Poling was considered normal, happy and precocious until 19 months of age when she was vaccinated against nine diseases in one doctor’s visit: measles, mumps, rubella, polio, varicella, diphtheria, pertussis, tetanus, and Haemophilus influenzae. Afterward, she developed high fevers, had screaming fits, stopped eating, didn’t respond when spoken to and began showing signs of autism. As vaccination has grown into a multi-billion dollar industry, children have gone from being inoculated against four diseases in 1953 to today’s recommended schedule of shots for 16 diseases requiring 49 doses by age 6. The government and pharmaceutical industry have said evidence shows babies’ systems can easily handle the immune boost.

In federal “vaccine court,” the U.S. government defends injury claims on behalf of vaccine makers In 2002, Hannah’s parents—her father a neurologist, her mother a nurse and attorney—filed a claim in a specially-created federal vaccine court in which the U.S. Department of Justice defends vaccine interests. Hannah was to serve as a test case to help decide the outcome of thousands of vaccine-autism claims. The case was strong. In 2007, contemplating Hannah would win her claim, sources say the vaccine court analyzed what the broader financial impact might be. It found that a flood of similar vaccine-autism claims would quickly deplete the government’s vaccine injury compensation fund, which is supported by a small fee patients pay on each dose of vaccine.

But instead of allowing Hannah’s case to publicly serve as a precedent for other possible victims, the government took another course: it quietly settled the case and sealed the results. Other families with autistic children were never to know. Hannah’s family petitioned the court to be allowed to reveal the findings but the government fought to keep the case sealed—and prevailed. Still, news of Hannah’s case leaked out in 2008—along with the medical explanation for her vaccine-related “autistic encephalopathy [brain damage].” Vaccines prevent many diseases that once routinely killed or harmed. But can vaccines trigger autism in a small subset of vulnerable children? In a court-submitted opinion, neurologist Dr. Andrew Zimmerman, Director of Medical Research at the Kennedy Krieger Institute, stated that he had “personally witnessed [Hannah’s] developmental regression” following “vaccine-induced fever and immune stimulation.”

Zimmerman concluded that Hannah was vulnerable to vaccine injury because she had a metabolic disorder called mitochondrial dysfunction. While vaccines are safe for most children, in Hannah, they triggered a brain injury, according to Zimmerman. Whether vaccines “caused” or “triggered” Hannah’s autism, the result was the same: but for her vaccinations, Zimmerman said, “Hannah may have led a normal full productive life.” Instead, she suffers “significant lifelong disability.”

A second underlying condition that was aggravated by vaccines, resulting in mental retardation and autism, is tuberous sclerosis or “TS,” according to a 1986 vaccine court case. According to the National Institutes of Health, TS affects 1 in every 6,000 newborns. Not all children who developed autism as a result of vaccine injuries, as determined by vaccine court, had identifiable pre-existing conditions. But I asked the CDC’s DeStefano whether it was worth trying to figure out what underlying conditions put kids at risk so they can be tested in advance and, if vulnerable, spared.

“That’s very difficult to do,” DeStefano told me. He said the CDC’s priorities are gaining a better understanding of the pathogenesis, genetics and biology of autism. “And then, I think… it’d be more feasible to try to establish if vaccines in an individual case, say a person with a certain set of genes…if we ever get to that point, then that kind of research might be fruitful.”

Not worthy of study?

But it turns out the CDC has ruled out that sort of research. A CDC spokesman told me that the agency is not “currently investigating the relation between vaccines and autism spectrum disorders (ASD). Further, CDC does not have any planned research addressing vaccines and autism.” As of May, 2010 the government had compensated 1,296 vaccine brain damage (encephalopathy/encephalitis and seizure cases) but was not tracking how many of the brain-injured children specifically ended up with autism.

“CDC believes that this topic has been thoroughly studied and no causal links have been found,” said the spokesman in an email. “Current CDC ASD related research focuses on determining how many people have ASD and understanding risk factors and causes for ASD,” said the CDC. Seven years after Hannah’s case settled, twenty-eight years after the TS case, it’s impossible to know how many similar children, if any, are out there. And the government isn’t trying to find out.

Attkisson: And is, is the pos—the current position that any potential link between vaccines and autism, secondary, any kind at all, has been entirely ruled out 100%?

DeStefano: I re, you know, I re—uh, I think every hypothesis that’s been looked at has been, uh, ruled out.
Attkisson: But, I mean, are you, are you, can I say the CDC’s position is that if anybody thinks there’s anything anymore, it’s a myth? It’s all been disproven?

DeStefano: Wouldn’t say it’s a myth, I’d say, you know, all the evidence, thus far, points to that there’s not a causal association between vaccines and autism.

Attkisson: What about secondary?
DeStefano: Sec—I don’t understand what do you mean “secondary”?
Attkisson: What about not “causal,” but “as a result of” vaccines, as in the Poling case? The medical expert found, you know, as a result of the damages she had from the vaccines, she ended up with autism. And the distinc-

tion was made in the medical expert, ‘well, that’s not ‘causal’, it’s sort of a ‘but for’ but it’s not a ‘causal.’
DeStefano: Yeah, I mean, I mean in that case, you know, she had a, I mean, you know, she had an underlying uh biological illness that uh either vaccination, or it could’ve been an infection that that would trigger some physiological stress in her, uh, seems to have, you know, could’ve, could’ve caused uh, um, manifestations that, characteristics of autism which, you, you know, appears to be what happened in her case.
Attkisson: But I mean doesn’t that, is—isn’t that a “link”? It’s not a “causal” link, but isn’t that a potential link between vaccination and autism if certain children with a “underyling biological illness” can have a “trigger” through vaccination?
DeStefano: [Unintell] as you call it, a secondary link if you wanna call it that way, w– in certain children, I mean ri—I mean, I, maybe that, but, you know, then I guess, that, that is a possibility.
Attkisson: Do you think that’s an important area of study so we could figure out which kids might have that predisposition?
DeStefano: uh, [phone noise] Yeah, I mean, I think um…You know, I think it’s something that, uh, well I mean, you know, in terms of uh… I mean, It’s hard, it’s hard to say, you know, I mean it’s like, um…I mean how how important that is. I mean, it’s a theoretical possibility, I guess the, the Poling case maybe suggested it could happen. Uh, but [unintell] cause it’s hard to predict who those children might be, but certainly, um individual cases, uh, can be studied to try to, uh, to look at those, uh, those possibilities.
Attkisson: Well I would just think—and then, then I’ll let you go in a few minutes unless you have more time—but as a parent, if my kid had whatever Poling had and we could figure that out, that would be one kid you would cull out [from vaccination] versus not worry about other kids if they don’t have that predisposition. But maybe you could identify the ones that would be vulnerable. But I haven’t seen that there’s any—is there an area of study trying to do such a thing within CDC or funded by CDC? Or NIH?
DeStefano: Well, in terms of like, you know, the area at CDC that’s that’s studying autism and possible causal relationships of autism, uh, you know, whatever they may be, uh, is in the Center the National Center for Birth Defects and Developmental Disability, and they, they do monitoring for autism prevalence and they do have, uh, studies trying to go on, you know, going on to, to look at, uh, a number of factors that could be, uh, related to, uh, increasing the risk of autism or causing autism.
Attkisson: I mean I think to sum up, you’re you’re saying what I, what I think is also the case just based on my own research: that while the government has ruled out any known “causal” link between autism and vaccines, it hasn’t ruled out the possibility, and in fact there seems to be at least one case where it’s acknowledged what I called a “secondary” link, meaning not “causal” but uh “triggered.” And the result for the parent, you know, may–to them it may be one and the same. And they may be trying to figure out which kids, you know, might have that predisposition.
DeStefano: Yeah, but you know, that’s very difficult to do. That’s almost circular reasoning, say, you know, kind of, you can’t, I mean, you know, the, the useful thing for parents who are clinically would be able to identify the kids who are gonna have, I mean, this way we’re identifying one certain child after the fact and say, you know, maybe in that one child, it was this or that that happened to him. But uh, it’s very difficult to make a causal link in in just one case.
Attkisson: Well, but isn’t that what you guys are supposed to do, figure it out? That’s a, as you know, autism is such a huge problem, even if a teeny percentage is perhaps triggered by vaccination, I would think that’d be very, very important to, to learn and try to figure out. You guys are the best at it, I’m sure somebody there can do it over time.
DeStefano: Yeah…[unintell] I think…[unintell] have a better understanding of uh of the pathogenesis of autism and the genetics and the biology and then, I think, I mean, and then, and then, with these individual cases, it’d be, you know, more feasible to try to establish if, uh, if, if vaccines in an individual case, say a person with a certain, certain set of genes or something, you know, if we ever get to that point, then that kind of research, uh, might be fruitful, you know.

https://sharylattkisson.com/cdc-possibility-that-vaccines-rarely-trigger-autism/

June 2011

Basics of the Human Immune System Prior to Introduction of Vaccines: Are Vaccines Turning Our Children's Immune Systems Inside Out?

Harold E Buttram, MD and Catherine J Frompovich

There is a universal principle referred to as "atrophy of disuse" which, as far as can be determined, applies to all physiologic processes of the human body. Although a normal full-term infant comes into the world with virtually all of the brain cells (neurons) that it will ever have, the brain continues to grow from increasing numbers of glial (connective tissue) cells and dendrite branching extensions that continue throughout life with mental activity. As an example, the story is told of two sisters who were identical twins and entered a nunnery, one gravitating into administrative work, the other into menial labor. With the passage of years the former remained mentally alert and bright, while the latter lapsed into Alzheimer's disease from brain atrophy.

As a brief review of Part 1, the human newborn comes into the world with temporary protection from residual maternal antibodies. Otherwise the infant's immune system is rudimentary, requiring a series of challenges to become fully functional, which is around three years of age. Although the so-called minor childhood diseases of earlier times were looked upon as nuisances (chickenpox and mumps) or potentially dangerous (measles and rubella), they may have evolved as friends-in-disguise by challenging and therefore uniquely activating and strengthening both epithelial and endothelial tissues, their respective organs, and lymph nodes. Those natural diseases also had the advantage of conferring permanent immunity, which is not necessarily the case with vaccines as attested to with revaccination every few years and higher percentages of infectious disease among those vaccinated.

Concerning the dangers of measles, aside from hygiene and sanitation, this largely involves personal disciplines in terms of diet, nutrition, and other health habits in which restriction/avoidance of sugar plays a prominent role along with abundant dietary sources (fresh fruits and vegetables) containing vitamins C and A. Nutrient deficiency may be an underlying reason that flu epidemics tend to occur over holidays, when people are inclined to overindulge in sweet treats and alcoholic beverages, which metabolize like sugar in the body.

There is an experimental basis for demonstrating sugar's paralyzing effects on the immune system. As demonstrated by Professor Emanuel Cheraskin at the Alabama University Medical School, blood samples were drawn from students before and after drinking a single soft drink (soda). White cells were siphoned from the blood samples and the white cells inoculated with staphylococcus microorganisms. After a period of incubation, the number of staphylococcus phagocytized (engulfed) by the white cells were counted under a microscope. The numbers of engulfed staphylococcus were reduced by more than half following consumption of the soft drink, indicating that the white cells were significantly paralyzed and crippled by that sugar-containing beverage. [1]

Also pertinent was a study conducted in Afghanistan in which 200 children with measles were divided into two groups, one of which received aspirin and Tylenol® to lower fever, the other not receiving aspirin or Tylenol®. The children receiving antipyretics had more prolonged illnesses, more diarrhea, ear infections, respiratory complications such as pneumonia and bronchitis, and higher death rates. [2]

Concerning the chickenpox (varicella) vaccine, articles by Gary Goldman seriously question the advisability of universal varicella vaccination as related to increasing subsequent occurrences of herpes zoster (shingles or zona). [3-4] The differing functions of the Th1 cellular and Th2 humoral immune systems were summarized in a review article by P. Kidd:

"The Th1 cells are hypothesized to lead the attack against intracellular pathogens such as viruses, raise the classic delayed-type to viral and bacterial antigens, and fight cancer cells. The Th2 cells are believed to emphasize protection against extracellular pathogens. On the negative side, the Th1 pathway is often portrayed as being the more aggressive of the two, and when it is overreactive, can generate organ-specific autoimmune disease (e.g. arthritis, multiple sclerosis, type 1 diabetes). The Th2 pathway is seen as underlying allergy and related IgE disease." [5]

Regarding vaccines and their propensity toward fostering allergies, Imani and Kehoe found a previously unrecognized side effect of the MMR vaccine by incubating it with a line of human plasma cells, which resulted in increased expression of allergy-related IgE antibodies accompanied by a corresponding decrease in protective IgG antibodies. Based on these findings, the authors concluded that viral vaccines might be playing a role in the increasing incidence of asthma and other allergic diseases. [6]

Much the same also holds true for a causal relationship between vaccines and the rising incidence of juvenile diabetes. In 1998 John Classen, MD, gave a presentation at a conference held by the American College of Medicine in which he reviewed 32 published articles, five authored by himself, indicating a causal relationship between vaccines and the rising incidence of insulin-dependant diabetes mellitus (IDDM). Nations represented in the papers included New Zealand, Canada, the United Kingdom, Denmark, Finland, Sweden, the USA, and Holland. Single vaccines were used including haemophilus influenza, hepatitis B, pertussis, BCG, and smallpox.

A prototype study was conducted in Finland by Classen and reported in the British Medical Journal. [7] In this study, from all children born in Finland between October 1, 1985 and August 31, 1987, approximately 116,000 were randomized as test subjects to receive four doses of haemophilus vaccine starting at three months of age, or one dose starting at 24 months. Additionally, 125,000 unvaccinated children served as controls. Each group was followed until age 10 years for development of IDDM. The incidence at seven years for those receiving four doses, those receiving one dose, and those receiving none was 261, 237, and 207 respectively with relative risks of 1.2, 1.14, and 1 for those children receiving no vaccine.

In virtually all of the reports from other countries the results were very similar, indicating a slight but consistent increase in IDDM following each of the five single vaccines listed above. Classen interpreted these results as indicating that it was not the type of vaccination that mattered so much as the immunologic impact of vaccination itself. Typically there was a 3 to 5 year delay between vaccines and onset of IDDM.

Quotations by Classen during the 1998 conference included:

"Vaccinating every child against every disease is fundamentally unsound."

"There is a 3.78-fold increased risk of insulin-dependent
diabetes mellitus in children from today's vaccines."

"All autoimmune diseases are increasing in incidence.
General immune (over) stimulation from vaccines is a cause of autoimmunity."

Genetic Exchanges in the World Around Us

Barbara McClintock, the 1983 Nobel Laureate "Corn Lady," was the first to discover genetic mobility in the so-called jumping genes in the 1930s. For over 50 years she pursued solitary research with corn, uncovering some of nature's innermost secrets about life. McClintock studied maize, a form of Indian corn, where distribution of red kernels and yellow kernels is genetically determined. What she first perceived was that some of the genes were moving from one place to another on the cell's chromosomes (the floating threads on which genes are lined like beads on a string). She then saw patterns in the movements, with sharply differing results in the colored kernels, and realized that some genes, once moved into position, switched other genes on or off. It followed that while most genes were workers, others were controllers or managers of genes.

According to an article in World Medicine [8] scientists at the University of Geneva made the startling discovery that biological substances entering directly into the bloodstream may truly become a part of us, even a part of our genetic material. The article stated in part:

"When Japanese bacteriologists discovered that bacteria of one species transferred their own highly specific antibiotic resistance to bacteria of an entirely different species, they seemed to hit on a unique if not startling phenomenon. Dr. Maurice Stroun and Dr. Phillippe Anker, with colleagues in the Plant Physiology Department at the University of Geneva, have now accumulated a wealth of evidence that the transfer of genetic information is not confined to bacteria but also can occur between bacteria and higher plants and animals.

"Dr. Stroun and colleagues did most of their research in plants but have now turned to animals. In their latest experiments they used the isolated auricles of frogs' hearts, [9] from which they dipped RNA extracted from the frog auricles into a bacterial suspension, resulting in a high percentage interlinkage of frog RNA with bacterial DNA."

The article concluded that the implications of this work on "transcession" are enormous and reflect something that may be commonly taking place in human bodies. From the standpoint of future generations, the possibility that vaccines may be bringing about genetic hybridization in our children may represent far and away the greatest hazard of today's childhood vaccine programs.

A Case On Point

During June 2011 a great number of German E.coli infections (3,406) and 39 deaths have occurred with suspicions that organically grown bean sprouts are the source of contamination. The findings have vacillated from yes, it was the sprouts to no, it was not the sprouts to now as of this writing, it IS the sprouts. However, the real issue may be more than bean sprouts, if they truly are the source of contamination and not a scapegoat. It seems the medical profession did not recognize that they were dealing with a rare strain of E.coli, O104:H4.

"What most predominantly differentiates O104 from O157 is its adoption of numerous traits not typically found congregated in one strain: Not only does it produce the noxious Shiga toxin of the virulent enterohemorrhagic strains, it also possesses defensive enteroaggregative traits –a combined mouthful of properties much more difficult to tolerate physically than verbally."

"When people come into a hospital with bloody diarrhea, they would normally assume it's O157 and not give antibiotics to the patients," he said. "In this case, because it wasn't O157, the physicians might have thought it was okay to give antibiotics, not knowing that O104 would produce the Shiga toxin."

"This potential misunderstanding over antibiotics might at least partially explain the high rate of HUS [hemolytic-uremic syndrome] among the ill. Girón [Jorge Girón, Ph.D., E. coli researcher and associate professor of microbiology at the University of Florida's Emerging Pathogens Institute] said this outbreak may necessitate new screening procedures at hospitals to account for O104 alongside O157, ensuring patients don't receive antibiotics that could exacerbate their illness or kill them." [Emphasis added] [11]

The above may be the classic example needed to illustrate the unknowns involved in vaccine pharmacology and morphology, and medicine's inability or unwillingness to address that aspect of vaccinology.

Are Vaccines Sowing the Seeds of Genetic Change?

As reviewed above, the first six months of an infant's life is a period of heightened vulnerability because of the infant's immature and rapidly growing nervous system and highly immature immune system. It is during this time-period that 19 or 20 vaccines are routinely administered, according to officially recommended schedules, irrespective of whether the infant was born prematurely, a condition that apparently predisposes preterm infants to a series of vaccine adverse reactions. [12]

A very revealing study reported in Virus Research tends to support the hypothesis of genetic exchange associated with viral vaccines. In the study of 24 passages of a nuclear polyhedrosis virus through cell cultures, there were both insertions and deletions in the virus, [10] suggesting that the virus freely exchanged genetic material with the tissues in which it was cultured [similar to transcession discussed above].

Considering that today's vaccines have been incubated in cell cultures of aborted fetuses, monkey kidneys, and other animal tissues, this should give any thinking person pause to consider the possible implications involved in manufacturing, injecting, and receiving vaccines.

Dr. Buttram discusses the immune system and the impact that vaccines have upon it in his book, A Commentary on Current Childhood Vaccine Programs, ISBN: 1-891485-30-X), published in 2010 by Philosophical Publishing Co., PO Box 77, Quakertown, PA 18951, phone 215-538-5300.

Catherine J Frompovich is the author of Our Chemical Lives And The Hijacking Of Our DNA available on Amazon.com here.

References:

1. Information presented at a lecture by Dr. Cheraskin in the 1970s.
2. Ahmady, AS et al. The adverse effects of antipyretics in measles. Indian Pediatrics. Jan. 1981; 49-52.
3. Goldman, GS. Universal varicella vaccination: Efficacy trends and effect on herpes zoster. Intern Journ Toxicol. 2005; 24: 205-213.
4. Goldman, GS. The case against universal varicella vaccination. Intern J Toxicol, 2006; 25:313-317.
5. Kidd, P. TH1/TH2 balance: The hypothesis, its limitations and implications in health and disease. Altern Med Rev. 2003; 8:223-246.
6. Imani, E and Kehoe, KE. Infection of human B-lymphocytes with MMR vaccine induces IgE class switching. Journ Clin Immunol. 2001; 100(3):355-361.
7. Classen, JB and Classen, DC. Association between type 1 diabetes and Hib vaccine, causal relation likely, British Med Journ. 1999; 319: 1133.
8. World Medicine (Scientific News Report): Mobility of genetic material between life forms, 1971, Sept. 22nd, London: Clareville House, Oxendon St: 69-72.
9. Anker, P and Stroun, M. Transcription of spontaneously released bacterial deoxyribonucleic acid in frog auricles, Journal of Bacteriology, 1973; 114: 114-120.
10. Kumar, S and Miller, IK. Effects of serial passage of Autographa californica nuclear polyhydrosis virus to cell culture. Virus Research. 1987; 7: 335-349.
11. Food Safety News, 0104:H4 May Change How We Deal With E. coli http://www.foodsafetynews.com/2011/06/e-coli-expert-weighs-in-with-facts-about-o104h4/ Accessed June 16, 2011.
12. Pourcyrous M, Korones SB, Kristopher LA, Bada HS. Primary immunization of premature infants with gestational age <35 weeks: Cardiorespiratory complications and C-reactive protein responses associated with administration of single and multiple separate vaccines simultaneously. J Pediatrics. 2007:151, p. 171.
- See more at: http://www.vaccinationcouncil.org/2011/06/21/risks-damage-basics-of-the-human-immune-system-prior-to-introduction-of-vaccines-are-vaccines-turning-our-childrens-immune-systems-inside-out-part-2/#sthash.SG9xMVCU.dpuf

Government Wipes Recent Vaccine Injury Data From Website

December 30, 2015 • Sharyl Attkisson

In March, the federal government removed the latest vaccine injury court statistics—more than a year's worth of data—from one of its publicly reported charts. It was an abrupt departure from the normal practice of updating the figures monthly.

Wiping the latest data means the "adjudication categories by alleged vaccine" chart on a government website no longer reflects the recent, sharp rise in court victories for plaintiffs who claimed their children were seriously injured or killed by one or more vaccines. Since January of 2014, the number of flu vaccine cases conceded by the government is more than double the previous eight years combined. The adjudication chart only reflects half of the current number.

Concessions Won by Flu Shot Victims since 2006
Chart shows (through 2013): 42
Actual number (through April 2015): 88

Total Flu Shot Victims Compensated Since 2006
Chart shows (through 2013): 1091
Actual number (through April 2015): 1271

Also on the rise is the number of vaccine injury cases the government has 'conceded:' up 55% in a little over one year. As a result of the recent website changes, neither of these trends is reflected on the current 'adjudication' chart." Since its inception in 2013, the "adjudication categories by alleged vaccine" chart included monthly, updated totals.

But shortly after publishing the March 2015 chart, the government removed the 2015 and 2014 data, reverting back to outdated statistics from 2013. The chart appears on the government vaccine court website, which falls under Health Resources and Services Administration, an agency of the Department of Health and Human Services (HHS). In the unusual vaccine court, the government acts on behalf of pharmaceutical companies rather than the public, defending vaccine makers against alleged victims. Money damages are not paid by vaccine companies, but through fees collected from patients on every dose of vaccine.

Older Data Doesn't Reflect Uptick in Awards to Vaccine Victims

HRSA says vaccine makers had no influence over the decision to revert to older data. The agency said it did so to synch up with a statistic the Centers for Disease Control (CDC) provides for the same chart that is only current through 2013: the number of vaccine doses distributed in US. "An internal decision was made to ensure that all internal data was consistent…and to update [the chart] only when all relevant data was available," said HRSA in a statement.

Court Decisions Won By Vaccine Victims Since 2006
Chart Shows (through 2013): 159
Actual Number (through April 2015): 165

Concessions Won By Vaccine Victims Since 2006
Chart Shows (through 2013): 127
Actual Number (through April 2015): 198

Vaccine Victims Paid After Settlements Since 2006
Chart Shows (through 2013): 1388
Actual Number (through April 2015): 1488

Only about one injury case for every million doses of vaccines is compensated in vaccine court. Adverse events occur more frequently, according to vaccine warning labels, but rarely end up in the little-known vaccine court. Still, vaccine court statistics can be useful in reflecting trends. Another recent change made vaccine injury data harder to find. The "adjudication categories by alleged vaccine" chart used to be the first item that showed up on the statistics page, but that has been replaced by language stating vaccines are safe and effective.

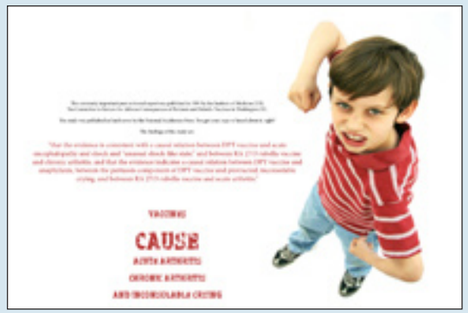
"Being awarded compensation for your claim does not necessarily mean that the vaccine caused the alleged injury," adds the government to the statement where the adjudication chart used to be. Readers are directed to click a link to view the actual vaccine injury statistics. But clicking it only leads back to the statement that vaccines are safe and effective. To find the statistics, instead of clicking the link, readers must scroll down past it. According to the government, from 2006 to 2013, over 2.2 billion doses of vaccines were distributed in the U.S. For every 1 million doses, 1 alleged victim was compensated in vaccine court. Since 1998, over 15,916 claims have been filed in vaccine court. 4,121 were compensated, 9,904 were dismissed. The total amount paid to victims is approximately $3.1 billion.

https://sharylattkisson.com/govt-wipes-recent-vaccine-injury-data-from-website/

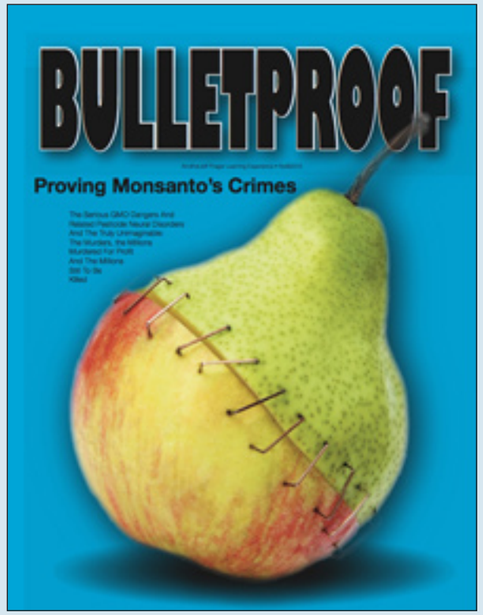
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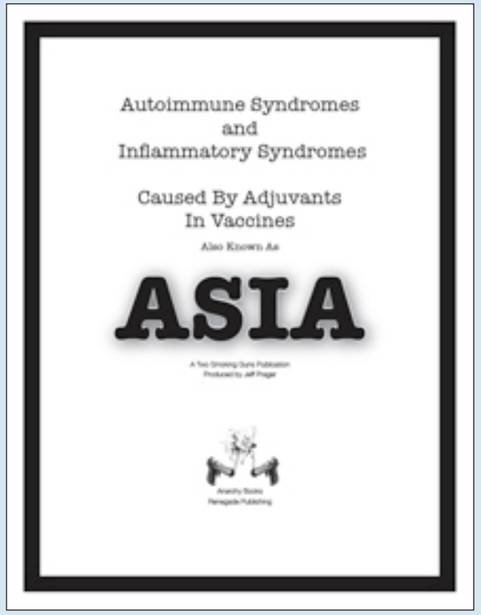
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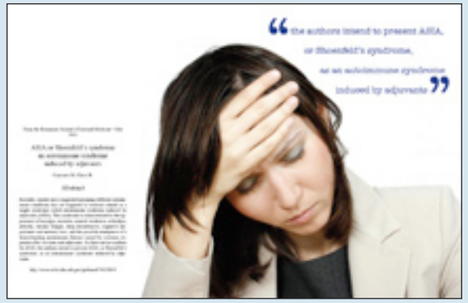






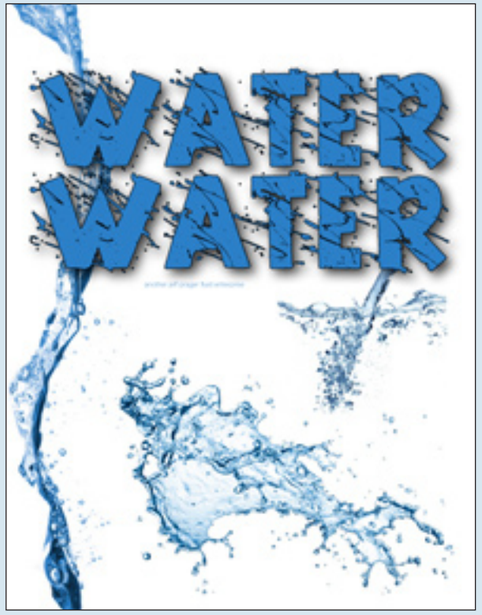
Bulletproof • An Expose On Glyphosate

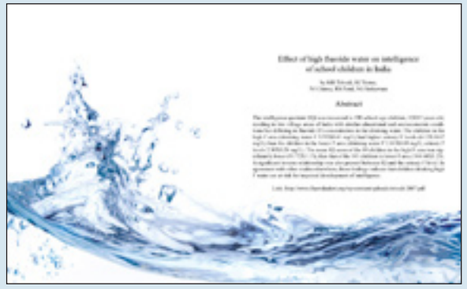






ASIA • Autoimmune And Inflammatory Disorders Caused By Vaccines







Water Water • Peer Review And Fluoridated Drinking Water

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The End

COVID VACCINE PEER REVIEW

An Examination Of Vaccines
In Published Peer Review

With A Focus On All CoV-2 Injectible Biologics
And A Brief History Of Known And Recognized
Vaccine-Related Adverse Events
1990 - 2022



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"Dissent is crucial for the advancement of science. Disagreement is at the heart of peer review and is important for uncovering unjustified assumptions, flawed methodologies and problematic reasoning."

I. de Melo-Martín and K. Intemann
Division of Medical Ethics
Department of Public Health
Weill Cornell Medical College, New York, USA

"This book is just a small sample of the tens of thousands of peer reviewed reports that are much the same as these, absolutely frightening.

It's also a stark and purposeful reminder of injuries not yet recorded in the peer review, injuries that may never be properly documented, vaccine injuries often suffered in silence, unrecognized, and alone."

Jeff Prager
January 29th, 2022

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INTENT

The publisher(s) and writer(s) warrants that the information presented in this report is an accurate reflection of information presented in published, peer reviewed journals gleaned from public news sites and US government web sites on the internet. The intent of this report is to 1) provide an honest explanation for the CoV-2 vaccine adverse events that incorporates currently public information not included in official government reports, not included in any mainstream media sources whether internet, video or written formats and 2) focus public attention on circumstances that strongly suggest there has been wrong doing by private individuals, public officials and national and international organizations involved in the dissemination of propaganda leading to the misuse of government resources, and 3) provide a foundation of research for future investigation. Information presented in this report documents that the federal institutions responsible for investigating these events are currently involved in efforts to suppress the facts. Hence, this information is being made public in the hope that unknown officials with appropriate level of authority can re-institute the appropriate investigation, or that private investigative resources can further substantiate the claims made herein.

TABLE OF CONTENTS

CHAPTER 1 · PAGE 10

Here is a list of 1024 hyper-linked peer reviewed, published reports from a wide variety of medical disciplines encompassing several thousand authors with tens of thousands of references and citations. These reports describe the real-world damage seen from the CoV-2 injection program. All hyperlinks were checked and functional at the time of publication, 1-30-2022.

CHAPTER 2 · PAGE 100

What I'll refer to as the lost, forgotten and discarded peer review, in particular from the CDC and the NIH. The reports that are sometimes difficult to locate and the reports we never actually read in the first place. The research community has known vaccines cause damage for decades and the peer reviewed reports they write, in this case, are frank, plain and easy to understand. Vaccines cause significant harm and that harm is ubiquitous. You won't find this peer review on your local news channel.

CHAPTER 3 · PAGE 142

Institutional Corruption of Pharmaceuticals and the Myth of Safe and Effective Drugs by Professor Donald W. Light, Ph.D., Rowan University, School of Osteopathic Medicine, Harvard University - Edmond J. Safra Center for Ethics and Dr. Joel Lexchin, M.Sc., M.D., York University and Dr. Jonathan J. Darrow, J.D., M.B.A., LL.M., S.J.D., Harvard Medical School.

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Dr. Stephanie Seneff, Dr. Peter McCullough, Dr. Sucharit Bhakdi, Dr. Arne Burkhardt, and more.



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INTRODUCTION

Most of the ingredients in previous vaccines, those pre-COVID—including aluminum, mercury, formaldehyde, B2 glycoprotein, Triton X-100®, Polysorbate or Tween 80®, 60® and 20®, 2-Phenoxyethanol, etc.—are neurotoxins, toxic to cells, cell structure and neurons. Vaccines are designed such that "tissue damage" is a necessary component of antibody creation to acquire some level of assumed immunity. Tissue damage, cell death or apoptosis are required aspects of vaccination success. The key is to cause tissue damage without damaging the person herself. After 100 years of vaccination science it's my opinion that we are still as yet unable to achieve that goal to perfection and I'd suggest the vast genetic differences between us all is a driving factor. A one-size-fits-all injection is akin to making the entire population of the United States eat peanuts and stand back to see what happens. Therefore, vaccine damage is ubiquitous. The peer review will prove that so.

There are low-responders and non-responders, a topic rarely discussed in the mainstream media. Well, never discussed. Within every country-population cohort this group—people that will respond to vaccination with low or zero recognizable titers and whose immune system simply will not "take" to the vaccine—make up a normal and expected percentage of the population. Non- and low-responders can be responsible for outbreaks of disease just as fully vaccinated individuals can acquire and spread the illnesses they were vaccinated for. Vaccination is never, ever 100% and comes with no guarantees of protection or immunity to disease nor guarantees against serious harm or death. It's not that vaccines don't work, they do, for a certain segment of society. For the 100s of 1000s of people that are vaccine damaged and whose voices are never heard, whose faces are never seen, whose family is economically destroyed, whose futures are plagued with seemingly insurmountable odds at every corner, injectible biologics for the prevention of various viral or bacterial challenges fails the risk-benefit analysis. Albeit far too late.

It wasn't arbitrary that, pre-COVID, what was referred to on the CDC web site and in their own peer reviewed reports as "vaccine failure" (as you'll see) has morphed into "breakthrough infections". I have CDC peer reviewed reports that discuss what's called "Primary and Secondary Vaccine Failure" and all of a sudden the twice vaccinated can still get COVID and pass it on to others and it's called a "Breakthrough Infection" when the vaccinated get sick. Like the virus broke through a biological defense system when the terms "Vaccine Failure" are, in all honesty, the appropriate terms to use in these cases. We're seeing Primary Vaccine Failure.

Historically, the innate immune system was at the forefront of disease defense and it mobilized epithelial barriers (referring to the skin and the thin tissue covering the body's surface and lining the alimentary canal and other hollow structures of the ears, eyes, nose and throat), special lymphocytes called " natural killer (NK)" cells, plasma proteins and other immune system components. Vaccination bypasses the innate immune system and directly affects only the humoral immune system (referring to antibodies in body fluids as distinct from cells).

Decades of bypassing the innate immune system along with removal of common and tolerable childhood "challenge" diseases—mumps, chicken pox, measles, etc.—has caused a reversal in the way our bodies fight viral and bacterial infection. Evolutions first line of defense and the faster, stronger primary system, the innate immune system, has been relegated to second place with vaccination causing the slower acting humoral immune system to occupy the first line of defense. The result of repeated vaccination to perturb the human immune system into developing antibodies to less than 2 dozen different tolerable childhood ailments—antibodies which have never been proven to be markers of immunity—has manifest as 100 or more human disorders after little more than 100 years of vaccination. The epidemic of disease we can now see surrounding us is staggering as you'll see in the highly respected peer reviewed reports collected here. Make sure you read chapters 3 through 5.

CHAPTER ONE

CoV-2 VACCINE ADVERSE EVENTS

1,024
HYPERLINKED
PEER REVIEWED REPORTS

Journal of Stroke and Cerebrovascular Diseases
June 23, 2021

Vaccine-Induced Immune Thrombotic Thrombocytopenia with Disseminated Intravascular Coagulation and Death following the ChAdOx1 nCoV-19 Vaccine

Dr. Yasser Aladdin, MD, FRCPC (abc)
Dr. Hussein Algahtani, MD, FRCPC, MMed (abc)
Dr. Bader Shirah, MD (bc)

a. King Abdulaziz Medical City, Jeddah, Saudi Arabia
b. King Saud bin Abdulaziz University for Health Sciences, Jeddah, Saudi Arabia
c. King Abdullah International Medical Research Center, Jeddah, Saudi Arabia

Abstract

Coronavirus is a novel human pathogen causing fulminant respiratory syndrome (COVID-19). Although COVID-19 is primarily a disease of the lungs with florid respiratory manifestations, there are increasing reports of cardiovascular, musculoskeletal, gastrointestinal, and thromboembolic complications. Developing an effective and reliable vaccine was emergently pursued to control the catastrophic spread of the global pandemic. We report a fatal case of vaccine-induced immune thrombotic thrombocytopenia (VITT) after receiving the first dose of the ChAdOx1 nCoV-19 vaccine. We attribute this fatal thrombotic condition to the vaccine due to the remarkable temporal relationship. The proposed mechanism of VITT is production of rogue antibodies against platelet factor-4 resulting in massive platelet aggregation. Healthcare providers should be aware of the possibility of such fatal complication, and the vaccine recipients should be warned about the symptoms of VITT.

https://www.sciencedirect.com/science/article/pii/S1052305721003414

"Healthcare providers should be aware
of the possibility of such fatal complication,
and the vaccine recipients should be warned
about the symptoms of VITT
(Vaccine-Induced Immune Thrombotic Thrombocytopenia).

The Lancet
September 25, 2021

Cerebral venous thrombosis after vaccination against COVID-19 in the UK: a multicentre cohort study

Richard J Perry, PhD, Arina Tamborska, MBChB, Bhagteshwar Singh, MRCP
Brian Craven, MBBCh, Richard Marigold, FRCP, Peter Arthur-Farraj, PhD, et al.

A new syndrome of vaccine-induced immune thrombotic thrombocytopenia (VITT) has emerged as a rare side-effect of vaccination against COVID-19. Cerebral venous thrombosis is the most common manifestation of this syndrome but, to our knowledge, has not previously been described in detail. We aimed to document the features of post-vaccination cerebral venous thrombosis with and without VITT and to assess whether VITT is associated with poorer outcomes.

https://www.thelancet.com/journals/lancet/article/PIIS0140-6736(21)01608-1/fulltext

"Cerebral venous thrombosis
is more severe in the context of VITT."
(Vaccine-Induced Immune Thrombotic Thrombocytopenia).

Tidsskr Nor Laegeforen
April 30, 2021

Tor Halvor Bjørnstad-Tuveng, Anders Rudjord, Peder Anker

Fatal cerebral haemorrhage after COVID-19 vaccine

Background: New vaccines against COVID-19 are being rolled out globally. AstraZeneca's vaccine ChAdOx1 nCoV-19 was not known to cause vaccine-induced immune thrombotic thrombocytopenia (VITT) at the time of this case.

Case presentation: The patient was a previously healthy woman in her thirties with headaches that developed one week after vaccination with ChAdOx1 nCoV-19. Three days later, her condition deteriorated rapidly, and she presented to the emergency department with slurred speech, uncoordinated movements and reduced consciousness. Symptoms progressed to left-sided hemiparesis and her level of consciousness deteriorated. Computed tomography (CT) of the head showed a large right-sided haemorrhage and incipient herniation. She was found to have severe thrombocytopenia 37 x 109/l, (ref 145 - 390 x 109/l). In spite of efforts to reduce intracranial pressure, the patient died the following day. Post mortem examination revealed antibodies to PF4, and fresh small thrombi were found in the transverse sinus, frontal lobe and pulmonary artery.

https://pubmed.ncbi.nlm.nih.gov/33928772/

Severe thrombocytopenia and antibodies to PF4 make a diagnosis of vaccine-induced immune thrombotic thrombocytopenia (VITT) likely.

American Heart Journal Plus: Cardiology Research and Practice
Volume 8, August 2021

William W.King, Matthew R.Petersen
Ralph M.Matar, Jeffery B.Budweg, LydaCuervo Pardo, John W.Petersen

Myocarditis following mRNA vaccination against SARS-CoV-2, a case series

mRNA COVID-19 vaccines have emerged as a new form of vaccination that has proven to be highly safe and effective against COVID-19 vaccination. Rare adverse events including myocarditis have been reported in the literature.

Data were gathered from the electronic medical record of four patients personally treated by the authors.

Four patients, ages 20 to 30, presented with myocarditis characterized by chest pain, elevations in troponin-I and C-reactive protein, and negative viral serologies two to four days following mRNA vaccine administration. One had a cardiac MRI showing delayed gadolinium enhancement in a subpericardial pattern. All experienced symptom resolution by the following day, and the two who have returned for follow-up had normal troponin-I and CRP values.

https://www.sciencedirect.com/science/article/pii/S2666602221000409

Along with previously reported instances, these cases raise suspicion for a possible link between mRNA vaccines and myocarditis.

Journal of Vascular Surgery: Venous and Lymphatic Disorders
Volume 10, Issue 1, January 2022, Pages 14-17

Elizabeth A. Andraska MD, MS, Rohan Kulkarni, MD,
Mirnal Chaudhary, MD, Ulka Sachdev, MD

Three cases of acute venous thromboembolism in females after vaccination for coronavirus disease 2019

Since December 2020, four vaccines for SARS-CoV-2 (severe acute respiratory syndrome coronavirus 2) have been developed, and three have been approved for immediate use in the United States. Two are mRNA vaccines, and one uses a viral vector mechanism. Thrombotic complications have been reported after vaccine administration, which were primarily cerebral sinus thromboses after administration of the viral vector vaccines. To the best of our knowledge, we are the first to report venous thrombotic complications within days of administration of the mRNA-1273 (Moderna) vaccine. We present a series of three women who developed venous thromboembolism after RNA-1273 vaccination at a single healthcare system.

https://www.sciencedirect.com/science/article/pii/S2213333X21003929

Recent cases of cerebral venous sinus thrombosis in women after receiving the Ad26.COV2.S (Janssen Pharmaceuticals, Johnson & Johnson, Beerse, Belgium) vaccine have been reported,4 which caused the U.S. Food and Drug Administration to recommend a pause in its use in the United States on April 13, 2021.

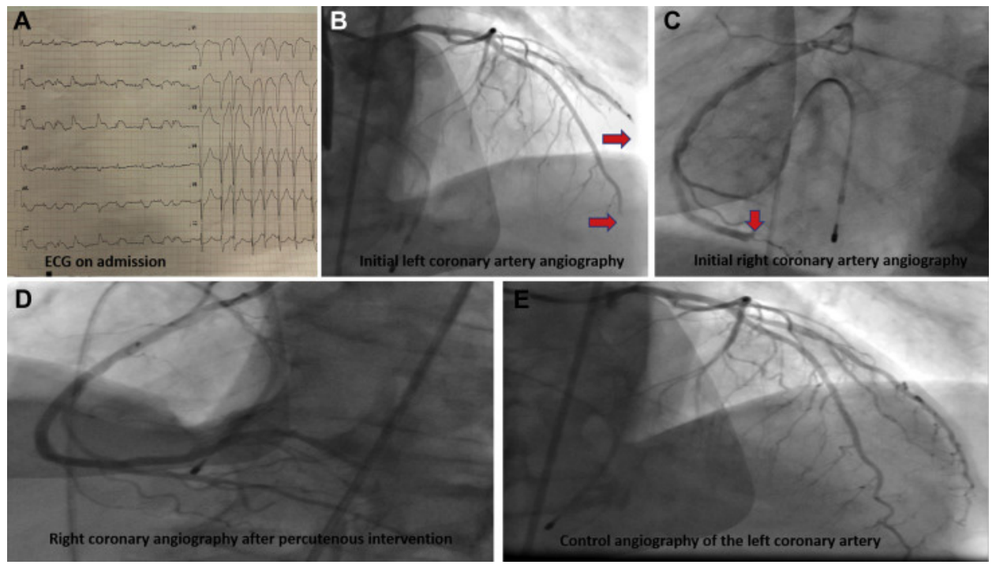
JACC: Cardiovascular Interventions
Volume 14, Issue 9, 10 May 2021, Pages e103-e104

Mateusz Tajstra, MD, PhD, Jerzy Jaroszewicz, MD, PhD, Mariusz GąsiorMD, PhD

Acute Coronary Tree Thrombosis After Vaccination for COVID-19

Although the 3 authorized vaccines for COVID-19 appear to be very safe (1, 2, 3), the vaccines are quite new and dedicated for a new disease, which calls for even very rare events to be shared and discussed broadly with the medical community. Therefore, we would like to present a clinical case of a serious adverse event, possibly linked to 1 of the vaccines for COVID-19.

https://www.sciencedirect.com/science/article/pii/S1936879821003988



Therefore, the presented case of triple coronary artery thrombosis in a patient recently vaccinated against COVID-19 may provide a causative link between those facts.

JAMA • June 2021

Isaac See 1 , John R Su 1 , Allison Lale 1 , Emily Jane Woo 2 , Alice Y Guh 1 , Tom T Shimabukuro 1 , Michael B Streiff 3 , Agam K Rao 1 , Allison P Wheeler 4 , Suzanne F Beavers 1 , Anna P Durbin 3 , Kathryn Edwards 4 , Elaine Miller 1 , Theresa A Harrington 1 , Adamma Mba-Jonas 2 , Narayan Nair 2 , Duong T Nguyen 1 , Kawsar R Talaat 3 , Victor C Urrutia 3 , Shannon C Walker 4 , C Buddy Creech 4 , Thomas A Clark 1 , Frank DeStefano 1 , Karen R Broder 1

US Case Reports of Cerebral Venous Sinus Thrombosis With Thrombocytopenia After Ad26.COV2.S Vaccination, March 2 to April 21, 2021

A mechanism similar to autoimmune heparin-induced thrombocytopenia (HIT) has been proposed. In the US, the Ad26.COV2.S COVID-19 vaccine (Janssen/Johnson & Johnson), which uses a human adenoviral vector, received Emergency Use Authorization (EUA) on February 27, 2021. By April 12, 2021, approximately 7 million Ad26.COV2.S vaccine doses had been given in the US, and 6 cases of CVST with thrombocytopenia had been identified among the recipients, resulting in a temporary national pause in vaccination with this product on April 13, 2021.

https://pubmed.ncbi.nlm.nih.gov/33929487/

The initial 12 US cases of CVST with thrombocytopenia after Ad26.COV2.S vaccination represent serious events.

This case series may inform clinical guidance as Ad26.COV2.S vaccination resumes in the US as well as investigations into the potential relationship between Ad26.COV2.S vaccine and CVST with thrombocytopenia.

The Lancet
Gastroenterology and Hepatology
June 8, 2021

Osman Öcal, MD
Stephanie-Susanne Stecher, MD
Prof Moritz Wildgruber, MD

Portal vein thrombosis associated with ChAdOx1 nCov-19 vaccination

A 41-year-old man with an unremarkable medical history presented to the emergency department with a headache that woke him and persisted despite painkillers. He had no neurological symptoms. The initial evaluation revealed severe thrombocytopenia (64 000 per µL) and increased D-dimer (42 028 µg/L). Cranial CT identified no findings of haematoma or ischaemia, and there was no sign of dural venous thrombosis on CT angiography. Thorax CT showed peripheral pulmonary emboli in the right lower lobe. There were no clinical signs of COVID-19, and upper abdominal organs were normal. The patient had received the first dose of ChAdOx1 nCov-19 vaccination (AstraZeneca) 11 days previously. Due to suspicion of COVID-19 vaccine-induced immune thrombotic thrombocytopenia (VITT), a modified heparin-induced platelet activation (HIPA) test was sent, and low-dose anticoagulation with apixaban was initiated. The headaches stopped, and no neurological symptoms developed. 4 days later, abdomen CT was obtained due to sudden severe abdominal pain, which revealed massive thrombosis of the entire portal venous system with no residual enhancement in the portal vein, splenic vein, and superior mesenteric vein.

https://www.thelancet.com/journals/langas/article/PIIS2468-1253(21)00197-7/fulltext

Early diagnosis of VITT is essential to initiate early treatment, as porto-splenic-mesenteric thrombosis can lead to venous congestion of the gut, splenic rupture, and even liver failure.

Blood Transfusion
July 2021

Paolo Gresele 1 , Marco Marietta 2 , Walter Ageno 3 , Rossella Marcucci 4 ,
Laura Contino 5 , Marco P Donadini 6 , Laura Russo 7 , Giovanni L Tiscia 8 ,
Gualtiero Palareti 9 , Armando Tripodi 10 , Pier Mannuccio Mannucci 10 , Valerio De Stefano 11

Management of cerebral and splanchnic vein thrombosis associated with thrombocytopenia in subjects previously vaccinated with Vaxzevria (AstraZeneca):

A position statement from the Italian Society for the Study of Haemostasis and Thrombosis (SISET)

https://pubmed.ncbi.nlm.nih.gov/33871350/

Any new event should be immediately reported to the National Pharmacovigilance Authority specifying the exact localisation of the thrombotic event and the degree and temporal evolution of the thrombocytopenia;

These patients should be hospitalised in high-intensity intensive care units and undergo rapid assessment for the presence of thrombosis at sites other than that leading to hospitalisation (e.g. by total body angio-computed tomography scan).

Journal of the Neurological Sciences
Volume 428, September 15, 2021

Maryam Sharifian-Dorche, Mohammad Bahmanyar,
Amirhossein Sharifian-Dorche, Pegah Mohamma, MasoodNomovi, Ashkan Mowla

Vaccine-induced immune thrombotic thrombocytopenia and cerebral venous sinus thrombosis post COVID-19 vaccination; a systematic review

The common reported adverse effects of COVID-19 vaccination consist of the injection site's local reaction followed by several non-specific flu-like symptoms. However, rare cases of vaccine-induced immune thrombotic thrombocytopenia (VITT) and cerebral venous sinus thrombosis (CVST) after viral vector vaccines (ChAdOx1 nCoV-19 vaccine, Ad26.COV2 vaccine) have been reported. Herein we systemically reviewed the reported cases of CVST and VITT following the COVID-19 vaccination.

https://www.sciencedirect.com/science/article/pii/S0022510X21003014

Health care providers should be familiar with the clinical presentations, pathophysiology, diagnostic criteria, and management consideration of this rare but severe and potentially fatal complication of the COVID-19 vaccination. Early diagnosis and quick initiation of the treatment may help to provide patients with a more favorable neurological outcome.

The American Journal of Emergency Medicine
Volume 49, November 2021, Pages 58-61

Brit Long, M.D.
Rachel Bridwell, M.D.
Michael GottliebM.D.

Thrombosis with thrombocytopenia syndrome associated with COVID-19 vaccines

Current vaccines for the Coronavirus Disease of 2019 (COVID-19) have demonstrated efficacy with low risk of adverse events. However, recent reports of thrombosis with thrombocytopenia syndrome (TTS) associated with adenovirus vector vaccines have raised concern.

https://www.sciencedirect.com/science/article/pii/S0735675721004381

With increasing vaccine distribution, it is essential for emergency clinicians to be aware of the evaluation and management of this condition.

Progress in Cardiovascular Diseases
Volume 67, July–August 2021, Pages 105-107

Aashish Gupta
Partha Sardar
Michael E.Cash
Richard V.Milani
Carl J.Lavie

Covid-19 vaccine- induced thrombosis and thrombocytopenia- a commentary on an important and practical clinical dilemma

On February 27, 2021, the United States (US) Food and Drug Administration (FDA) issued an emergency use authorization (EUA) of coronavirus disease 2019 (COVID-19) vaccine manufactured by Johnson and Johnson's vaccine division Janssen (Beerse, Belgium) for use in individuals 18 years of age or older.1 This was the 3rd vaccine to receive EUA for prevention of COVID-19 caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) in the US following COVID-19 vaccines from Moderna (Moderna TX, Inc., Massachusetts, US) and Pfizer-BioNTech (New York, US; Rhineland-Palatinate, Germany). As of April 12, 2021 6.8 million doses of Janssen's COVID-19 vaccine have been administered in the US.2 The Janssen's COVID-19 vaccine is a recombinant vaccine that uses replication-incompetent human Adenovirus 26 (Ad26) as a vector to express the SARS-CoV-2 Spike (S) protein. Vector adenoviruses are able to accommodate large genetic payloads and can be modified so they do not initiate an infection. Vector vaccines have been studied and utilized most recently against the Ebola virus. These cases were all associated with thrombocytopenia and were seen in women aged 18–48 years occurring 6–13 days after vaccination.2 Vaccine induced Thrombosis and Thrombocytopenia (VITT) have not been reported as a side effect of Ebola vaccines, however, scale of vaccinations has been significantly lower.3

https://www.sciencedirect.com/science/article/pii/S0033062021000505

On April 13, 2021, a joint statement issued by FDA and Centers for Disease Control and Prevention (CDC) confirmed 6 cases of cerebral venous thrombosis (CVT) reported in the US and halted further use of Janssen's COVID-19 vaccines.

European Journal of Internal Medicine
Volume 89, July 2021, Pages 22-24

MarcoCattaneo

Thrombosis with Thrombocytopenia Syndrome associated with viral vector COVID-19 vaccines

On March 11 2021, the European Medical Agency highlighted two relevant issues, after the decision by the Danish Health Authority to temporarily suspend its vaccination campaign with Vaxzevria (the COVID-19 vaccine by AstraZeneca) following the reports of thromboembolic events (TE) associated with the administration of the vaccine: 1) lack of evidence of a cause/effect relationship between the vaccine and TE; 2) the number of reported TE (30 in around 5,000,000 vaccinated people) was no higher than that expected [1]. However, the real essence of the problem emerged about a week later: it was not the number of TE that was of concern, but, rather, their unusual nature: the affected patients were all young (<50 years old) and previously healthy, they displayed widespread thrombi, predominantly in unusual sites, and also had thrombocytopenia [2]. These data suggested that a new syndrome had emerged, which is termed "Thrombosis with Thrombocytopenia Syndrome (TTS)". I think that the two alternative definitions of the syndrome, "vaccine-induced prothrombotic immune thrombocytopenia (VIPIT)" and "vaccine-induced immune thrombotic thrombocytopenia (VITT)", should be dismissed for two reasons: 1) the cause-effect relationship with vaccination has not yet been unequivocally established; 2) the general reference to "vaccine" is not justified, as the syndrome has been observed only in association with 2 particular COVID-19 vaccines.

https://www.sciencedirect.com/science/article/pii/S0953620521001904

About 250 cases of TTS after Vaxzevria vaccination have been recorded as of the first days of April 2021.

5.3.6 CUMULATIVE ANALYSIS OF POST-AUTHORIZATION ADVERSE EVENT REPORTS OF PF-07302048 (BNT162B2) RECEIVED THROUGH 28-FEB-2021



090177e196ea1800\Approved\Approved On: 30-Apr-2021 09:26 (GMT)

Report Prepared by:

Worldwide Safety

Pfizer

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FDA-CBER-2021-5683-0000054

https://www.academia.edu/62695286/PFIZERS_APPENDIX_1_EXPLOSIVE_LIST_OF_ADVERSE_EVENTS_OF_SPECIAL_INTEREST

A small selection of the tens of thousands of peer reviewed reports detailing, discussing and warning of CoV-2 vaccine-related adverse events—early adverse events—with the knowledge that long-term adverse events are unknown and won't be known for a decade or more to come.

1. Cerebral venous thrombosis after COVID-19 vaccination in the UK: a multicentre cohort study:
https://www.thelancet.com/journals/lancet/article/PIIS0140-6736(21)01608-1/

2. Vaccine-induced immune thrombotic thrombocytopenia with disseminated intravascular coagulation and death after ChAdOx1 nCoV-19 vaccination:
https://www.sciencedirect.com/science/article/pii/S1052305721003414

3. Fatal cerebral hemorrhage after COVID-19 vaccine:
https://pubmed.ncbi.nlm.nih.gov/33928772/

4. Myocarditis after mRNA vaccination against SARS-CoV-2, a case series:
https://www.sciencedirect.com/science/article/pii/S2666602221000409

5. Three cases of acute venous thromboembolism in women after vaccination against COVID-19:
https://www.sciencedirect.com/science/article/pii/S2213333X21003929

6. Acute thrombosis of the coronary tree after vaccination against COVID-19:
https://www.sciencedirect.com/science/article/abs/pii/S1936879821003988

7. US case reports of cerebral venous sinus thrombosis with thrombocytopenia after vaccination with Ad26. COV2.S (against covid-19), March 2 to April 21, 2020:
https://pubmed.ncbi.nlm.nih.gov/33929487/

8. Portal vein thrombosis associated with ChAdOx1 nCov-19 vaccine:
https://www.thelancet.com/journals/langas/article/PIIS2468-1253(21)00197-7/

9. Management of cerebral and splanchnic vein thrombosis associated with thrombocytopenia in subjects previously vaccinated with Vaxzevria (AstraZeneca): position statement of the Italian Society for the Study of Hemostasis and Thrombosis (SISET):
https://pubmed.ncbi.nlm.nih.gov/33871350/

10. Vaccine-induced immune immune thrombotic thrombocytopenia and cerebral venous sinus thrombosis after vaccination with COVID-19; a systematic review:
https://www.sciencedirect.com/science/article/pii/S0022510X21003014

11. Thrombosis with thrombocytopenia syndrome associated with COVID-19 vaccines:
https://www.sciencedirect.com/science/article/abs/pii/S0735675721004381

12. Covid-19 vaccine-induced thrombosis and thrombocytopenia: a commentary on an important and practical clinical dilemma:
https://www.sciencedirect.com/science/article/abs/pii/S0033062021000505

13. Thrombosis with thrombocytopenia syndrome associated with COVID-19 viral vector vaccines:
https://www.sciencedirect.com/science/article/abs/pii/S0953620521001904

14. COVID-19 vaccine-induced immune-immune thrombotic thrombocytopenia: an emerging cause of splanchnic vein thrombosis:
https://www.sciencedirect.com/science/article/pii/S1665268121000557

15. The roles of platelets in COVID-19-associated coagulopathy and vaccine-induced immune thrombotic immune thrombocytopenia (covid):
https://www.sciencedirect.com/science/article/pii/S1050173821000967

16. Roots of autoimmunity of thrombotic events after COVID-19 vaccination:
https://www.sciencedirect.com/science/article/abs/pii/S1568997221002160

17. Cerebral venous sinus thrombosis after vaccination: the United Kingdom experience:
https://www.thelancet.com/journals/lancet/article/PIIS0140-6736(21)01788-8/fulltext

18. Thrombotic immune thrombocytopenia induced by SARS-CoV-2 vaccine:
https://www.nejm.org/doi/full/10.1056/nejme2106315

19. Myocarditis after immunization with COVID-19 mRNA vaccines in members of the US military. This article reports that in "23 male patients, including 22 previously healthy military members, myocarditis was identified within 4 days after receipt of the vaccine":
https://jamanetwork.com/journals/jamacardiology/fullarticle/2781601

20. Thrombosis and thrombocytopenia after vaccination with ChAdOx1 nCoV-19:
https://www.nejm.org/doi/full/10.1056/NEJMoa2104882?query=recirc_curatedRelated_article

21. Association of myocarditis with the BNT162b2 messenger RNA COVID-19 vaccine in a case series of children:
https://pubmed.ncbi.nlm.nih.gov/34374740/

22. Thrombotic thrombocytopenia after vaccination with ChAdOx1 nCov-19:
https://www.nejm.org/doi/full/10.1056/NEJMoa2104840?query=recirc_curatedRelated_article

23. Post-mortem findings in vaccine-induced thrombotic thrombocytopenia (covid-19):
https://haematologica.org/article/view/haematol.2021.279075

24. hrombocytopenia, including immune thrombocytopenia after receiving COVID-19 mRNA vaccines reported to the Vaccine Adverse Event Reporting System (VAERS):
https://www.sciencedirect.com/science/article/pii/S0264410X21005247

25. Acute symptomatic myocarditis in seven adolescents after Pfizer-BioNTech COVID-19 vaccination:
https://pediatrics.aappublications.org/content/early/2021/06/04/peds.2021-052478

26. Aphasia seven days after the second dose of an mRNA-based SARS-CoV-2 vaccine. Brain MRI revealed an intracerebral hemorrhage (ICBH) in the left temporal lobe in a 52-year-old man.
https://www.sciencedirect.com/science/article/pii/S2589238X21000292#f0005

27. Comparison of vaccine-induced thrombotic episodes between ChAdOx1 nCoV-19 and Ad26.COV.2.S vaccines:
https://www.sciencedirect.com/science/article/abs/pii/S0896841121000895

28. Hypothesis behind the very rare cases of thrombosis with thrombocytopenia syndrome after SARS-CoV-2 vaccination:
https://www.sciencedirect.com/science/article/abs/pii/S0049384821003315

29. Blood clots and bleeding episodes after BNT162b2 and ChAdOx1 nCoV-19 vaccination: analysis of European data:
https://www.sciencedirect.com/science/article/pii/S0896841121000937

30. Cerebral venous thrombosis after BNT162b2 mRNA SARS-CoV-2 vaccine:
https://www.sciencedirect.com/science/article/abs/pii/S1052305721003098

31. rimary adrenal insufficiency associated with thrombotic immune thrombocytopenia induced by the Oxford-AstraZeneca ChAdOx1 nCoV-19 vaccine (VITT):
https://www.sciencedirect.com/science/article/pii/S0953620521002363

32. Myocarditis and pericarditis after vaccination with COVID-19 mRNA: practical considerations for care providers:
https://www.sciencedirect.com/science/article/pii/S0828282X21006243

33. "Portal vein thrombosis occurring after the first dose of SARS-CoV-2 mRNA vaccine in a patient with antiphospholipid syndrome":
https://www.sciencedirect.com/science/article/pii/S2666572721000389

34. Early results of bivalirudin treatment for thrombotic thrombocytopenia and cerebral venous sinus thrombosis after vaccination with Ad26.COV2.S:
https://www.sciencedirect.com/science/article/pii/S0196064421003425

35. Myocarditis, pericarditis and cardiomyopathy after COVID-19 vaccination:
https://www.sciencedirect.com/science/article/pii/S1443950621011562

36. Mechanisms of immunothrombosis in vaccine-induced thrombotic thrombocytopenia (VITT) compared to natural SARS-CoV-2 infection:
https://www.sciencedirect.com/science/article/abs/pii/S0896841121000706

37. Prothrombotic immune thrombocytopenia after COVID-19 vaccination:
https://www.sciencedirect.com/science/article/pii/S0006497121009411

38. Vaccine-induced thrombotic thrombocytopenia: the dark chapter of a success story:
https://www.sciencedirect.com/science/article/pii/S2589936821000256

39. Cerebral venous sinus thrombosis negative for anti-PF4 antibody without thrombocytopenia after immunization with COVID-19 vaccine in a non-comorbid elderly Indian male treated with conventional heparin-warfarin based anticoagulation:
https://www.sciencedirect.com/science/article/pii/S1871402121002046

40. Thrombosis after COVID-19 vaccination: possible link to ACE pathways:
https://www.sciencedirect.com/science/article/pii/S0049384821004369

41. Cerebral venous sinus thrombosis in the U.S. population after SARS-CoV-2 vaccination with adenovirus and after COVID-19: https://www.sciencedirect.com/science/article/pii/S0735109721051949

42. A rare case of a middle-aged Asian male with cerebral venous thrombosis after AstraZeneca COVID-19 vaccination:
https://www.sciencedirect.com/science/article/pii/S0735675721005714

43. Cerebral venous sinus thrombosis and thrombocytopenia after COVID-19 vaccination: report of two cases in the United Kingdom:
https://www.sciencedirect.com/science/article/abs/pii/S088915912100163X

44. Immune thrombocytopenic purpura after vaccination with COVID-19 vaccine (ChAdOx1 nCov-19):
https://www.sciencedirect.com/science/article/abs/pii/S0006497121013963

45. Antiphospholipid antibodies and risk of thrombophilia after COVID-19 vaccination: the straw that breaks the camel's back?:
https://docs.google.com/document/d/1XzajasO8VMMnC3CdxSBKks1o7kiOLXFQ

46. Vaccine-induced thrombotic thrombocytopenia, a rare but severe case of friendly fire in the battle against the COVID-19 pandemic: What pathogenesis?:
https://www.sciencedirect.com/science/article/pii/S0953620521002314

47. Diagnostic-therapeutic recommendations of the ad-hoc FACME expert working group on the management of cerebral venous thrombosis related to COVID-19 vaccination:
https://www.sciencedirect.com/science/article/pii/S0213485321000839

48. Thrombocytopenia and intracranial venous sinus thrombosis after exposure to the "AstraZeneca COVID-19 vaccine":
https://pubmed.ncbi.nlm.nih.gov/33918932/

49. Thrombocytopenia following Pfizer and Moderna SARS-CoV-2 vaccination:
https://pubmed.ncbi.nlm.nih.gov/33606296/

50. Severe and refractory immune thrombocytopenia occurring after SARS-CoV-2 vaccination:
https://pubmed.ncbi.nlm.nih.gov/33854395/

51. Purpuric rash and thrombocytopenia after mRNA-1273 (Modern) COVID-19 vaccine:
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7996471/

52. COVID-19 vaccination: information on the occurrence of arterial and venous thrombosis using data from VigiBase:
https://pubmed.ncbi.nlm.nih.gov/33863748/

53. Cerebral venous thrombosis associated with the covid-19 vaccine in Germany:
https://onlinelibrary.wiley.com/doi/10.1002/ana.26172

54. Cerebral venous thrombosis following BNT162b2 mRNA vaccination of BNT162b2 against SARS-CoV-2: a black swan event:
https://pubmed.ncbi.nlm.nih.gov/34133027/

55. The importance of recognizing cerebral venous thrombosis following anti-COVID-19 vaccination:
https://pubmed.ncbi.nlm.nih.gov/34001390/

56. Thrombosis with thrombocytopenia after messenger RNA vaccine -1273:
https://pubmed.ncbi.nlm.nih.gov/34181446/

57. Blood clots and bleeding after BNT162b2 and ChAdOx1 nCoV-19 vaccination: an analysis of European data:
https://pubmed.ncbi.nlm.nih.gov/34174723/

58. First dose of ChAdOx1 and BNT162b2 COVID-19 vaccines and thrombocytopenic, thromboembolic, and hemorrhagic events in Scotland:
https://www.nature.com/articles/s41591-021-01408-4

59. Exacerbation of immune thrombocytopenia after COVID-19 vaccination:
https://pubmed.ncbi.nlm.nih.gov/34075578/

60. First report of a de novo iTTP episode associated with a COVID-19 mRNA-based anti-COVID-19 vaccine:
https://pubmed.ncbi.nlm.nih.gov/34105244/

61. PF4 immunoassays in vaccine-induced thrombotic thrombocytopenia:
https://www.nejm.org/doi/full/10.1056/NEJMc2106383

62. Antibody epitopes in vaccine-induced immune immune thrombotic thrombocytopenia:
https://www.nature.com/articles/s41586-021-03744-4

63. Myocarditis with COVID-19 mRNA vaccines:
https://www.ahajournals.org/doi/pdf/10.1161/CIRCULATIONAHA.121.056135

64. Myocarditis and pericarditis after COVID-19 vaccination:
https://jamanetwork.com/journals/jama/fullarticle/2782900

65. Myocarditis temporally associated with COVID-19 vaccination:
https://www.ahajournals.org/doi/pdf/10.1161/CIRCULATIONAHA.121.055891

66. COVID-19 Vaccination Associated with Myocarditis in Adolescents:
https://pediatrics.aappublications.org/content/pediatrics/early/2021/08/12/peds.2021-053427.full.pdf

67. Acute myocarditis after administration of BNT162b2 vaccine against COVID-19:
https://pubmed.ncbi.nlm.nih.gov/33994339/

68. Temporal association between COVID-19 vaccine Ad26.COV2.S and acute myocarditis: case report and review of the literature:
https://www.sciencedirect.com/science/article/pii/S1553838921005789

69. COVID-19 vaccine-induced myocarditis: a case report with review of the literature:
https://www.sciencedirect.com/science/article/pii/S1871402121002253

70. Potential association between COVID-19 vaccine and myocarditis: clinical and CMR findings:
https://www.sciencedirect.com/science/article/pii/S1936878X2100485X

71. Recurrence of acute myocarditis temporally associated with receipt of coronavirus mRNA disease vaccine 2019 (COVID-19) in a male adolescent:
https://www.sciencedirect.com/science/article/pii/S002234762100617X

72. Fulminant myocarditis and systemic hyper inflammation temporally associated with BNT162b2 COVID-19 mRNA vaccination in two patients:
https://www.sciencedirect.com/science/article/pii/S0167527321012286

73. Acute myocarditis after administration of BNT162b2 vaccine:
https://www.sciencedirect.com/science/article/pii/S2214250921001530

74. Lymphohistocytic myocarditis after vaccination with COVID-19 Ad26.COV2.S viral vector:
https://www.sciencedirect.com/science/article/pii/S2352906721001573

75. Myocarditis following vaccination with BNT162b2 in a healthy male:
https://www.sciencedirect.com/science/article/pii/S0735675721005362

76. Acute myocarditis after Comirnaty (Pfizer) vaccination in a healthy male with previous SARS-CoV-2 infection:
https://www.sciencedirect.com/science/article/pii/S1930043321005549

77. Myopericarditis after Pfizer mRNA COVID-19 vaccination in adolescents:
https://www.sciencedirect.com/science/article/pii/S002234762100665X

78. Pericarditis after administration of BNT162b2 mRNA COVID-19 mRNA vaccine:
https://www.sciencedirect.com/science/article/pii/S1885585721002218

79. Acute myocarditis after vaccination with SARS-CoV-2 mRNA-1273 mRNA:
https://www.sciencedirect.com/science/article/pii/S2589790X21001931

80. Temporal relationship between the second dose of BNT162b2 mRNA Covid-19 vaccine and cardiac involvement in a patient with previous SARS-COV-2 infection:
https://www.sciencedirect.com/science/article/pii/S2352906721000622

81. Myopericarditis after vaccination with COVID-19 mRNA in adolescents 12 to 18 years of age:
https://www.sciencedirect.com/science/article/pii/S0022347621007368

82. Acute myocarditis after SARS-CoV-2 vaccination in a 24-year-old man:
https://www.sciencedirect.com/science/article/pii/S0870255121003243

83. Important information on myopericarditis after vaccination with Pfizer COVID-19 mRNA in adolescents:
https://www.sciencedirect.com/science/article/pii/S0022347621007496

84. A series of patients with myocarditis after vaccination against SARS-CoV-2 with mRNA-1279 and BNT162b2:
https://www.sciencedirect.com/science/article/pii/S1936878X21004861

85. Takotsubo cardiomyopathy after vaccination with mRNA COVID-19:
https://www.sciencedirect.com/science/article/pii/S1443950621011331

86. COVID-19 mRNA vaccination and myocarditis:
https://pubmed.ncbi.nlm.nih.gov/34268277/

87. COVID-19 vaccine and myocarditis:
https://pubmed.ncbi.nlm.nih.gov/34399967/

88. Epidemiology and clinical features of myocarditis/pericarditis before the introduction of COVID-19 mRNA vaccine in Korean children: a multicenter study
https://search.bvsalud.org/global-literature-on-novel-coronavirus-2019-ncov/resourc e/en/covidwho-1360706

89. COVID-19 vaccines and myocarditis:
https://pubmed.ncbi.nlm.nih.gov/34246566/

90. Myocarditis and other cardiovascular complications of COVID-19 mRNA-based COVID-19 vaccines
https://www.cureus.com/articles/61030-myocarditis-and-other-cardiovascular-complications-of-the-mr-na-based-covid-19-vaccines
https://www.cureus.com/articles/61030-myocarditis-and-other-cardiovascular-complications-of-the-mrna-based-covid-19-vaccines

91. Myocarditis, pericarditis, and cardiomyopathy after COVID-19 vaccination:
https://pubmed.ncbi.nlm.nih.gov/34340927/

92. Myocarditis with covid-19 mRNA vaccines:
https://www.ahajournals.org/doi/10.1161/CIRCULATIONAHA.121.056135

93. Association of myocarditis with COVID-19 mRNA vaccine in children:
https://media.jamanetwork.com/news-item/association-of-myocarditis-with-mrna-co vid-19-vaccine-in-children/

94. Association of myocarditis with COVID-19 messenger RNA vaccine BNT162b2 in a case series of children:
https://jamanetwork.com/journals/jamacardiology/fullarticle/2783052

95. Myocarditis after immunization with COVID-19 mRNA vaccines in members of the U.S. military:
https://jamanetwork.com/journals/jamacardiology/fullarticle/2781601%5C

96. Myocarditis occurring after immunization with COVID-19 mRNA-based COVID-19 vaccines:
https://jamanetwork.com/journals/jamacardiology/fullarticle/2781600

97. Myocarditis following immunization with Covid-19 mRNA:
https://www.nejm.org/doi/full/10.1056/NEJMc2109975

98. Patients with acute myocarditis after vaccination withCOVID-19 mRNA:
https://jamanetwork.com/journals/jamacardiology/fullarticle/2781602

99. Myocarditis associated with vaccination with COVID-19 mRNA:
https://pubs.rsna.org/doi/10.1148/radiol.2021211430

100. Symptomatic Acute Myocarditis in 7 Adolescents after Pfizer-BioNTech COVID-19 Vaccination:
https://pediatrics.aappublications.org/content/148/3/e2021052478

101. Cardiovascular magnetic resonance imaging findings in young adult patients with acute myocarditis after COVID-19 mRNA vaccination: a case series:
https://jcmr-online.biomedcentral.com/articles/10.1186/s12968-021-00795-4

102. Clinical Guidance for Young People with Myocarditis and Pericarditis after Vaccination with COVID-19 mRNA:
https://www.cps.ca/en/documents/position/clinical-guidance-for-youth-with-myocarditis-and-pericarditis

103. Cardiac imaging of acute myocarditis after vaccination with COVID-19 mRNA:
https://pubmed.ncbi.nlm.nih.gov/34402228/

104. Case report: acute myocarditis after second dose of mRNA-1273 SARS-CoV-2 mRNA vaccine:
https://academic.oup.com/ehjcr/article/5/8/ytab319/6339567

105. Myocarditis / pericarditis associated with COVID-19 vaccine:
https://science.gc.ca/eic/site/063.nsf/eng/h_98291.html

106. Transient cardiac injury in adolescents receiving the BNT162b2 mRNA COVID-19 vaccine:
https://journals.lww.com/pidj/Abstract/9000/Transient_Cardiac_Injury_in_Adolesce nts_Receiving.95800.aspx

107. Perimyocarditis in adolescents after Pfizer-BioNTech COVID-19 vaccine:
https://academic.oup.com/jpids/advance-article/doi/10.1093/jpids/piab060/6329543

108. The new COVID-19 mRNA vaccine platform and myocarditis: clues to the possible underlying mechanism:
https://pubmed.ncbi.nlm.nih.gov/34312010/

109. Acute myocardial injury after COVID-19 vaccination: a case report and review of current evidence from the Vaccine Adverse Event Reporting System database:
https://pubmed.ncbi.nlm.nih.gov/34219532/

110. Be alert to the risk of adverse cardiovascular events after COVID-19 vaccination:
https://www.xiahepublishing.com/m/2472-0712/ERHM-2021-00033

111. Myocarditis associated with COVID-19 vaccination: echocardiographic, cardiac tomography, and magnetic resonance imaging findings:
https://www.ahajournals.org/doi/10.1161/CIRCIMAGING.121.013236

112. In-depth evaluation of a case of presumed myocarditis after the second dose of COVID-19 mRNA vaccine:
https://www.ahajournals.org/doi/10.1161/CIRCULATIONAHA.121.056038

113. Occurrence of acute infarct-like myocarditis after COVID-19 vaccination: just an accidental coincidence or rather a vaccination-associated autoimmune myocarditis?:
https://pubmed.ncbi.nlm.nih.gov/34333695/

114. Recurrence of acute myocarditis temporally associated with receipt of coronavirus mRNA disease vaccine 2019 (COVID-19) in a male adolescent:
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8216855/

115. Myocarditis after SARS-CoV-2 vaccination: a vaccine-induced reaction?:
https://pubmed.ncbi.nlm.nih.gov/34118375/

116. Self-limited myocarditis presenting with chest pain and ST-segment elevation in adolescents after vaccination with the BNT162b2 mRNA vaccine:
https://pubmed.ncbi.nlm.nih.gov/34180390/

117. Myopericarditis in a previously healthy adolescent male after COVID-19 vaccination: Case report:
https://pubmed.ncbi.nlm.nih.gov/34133825/

118. Biopsy-proven lymphocytic myocarditis after first COVID-19 mRNA vaccination in a 40-year-old man: case report:
https://pubmed.ncbi.nlm.nih.gov/34487236/

119. Insights from a murine model of COVID-19 mRNA vaccine-induced myopericarditis: could accidental intravenous injection of a vaccine induce myopericarditis
https://academic.oup.com/cid/advance-article/doi/10.1093/cid/ciab741/6359059

120. Unusual presentation of acute perimyocarditis after modern SARS-COV-2 mRNA-1237 vaccination:
https://pubmed.ncbi.nlm.nih.gov/34447639/

121. Perimyocarditis after the first dose of mRNA-1273 SARS-CoV-2 (Modern) mRNA-1273 vaccine in a young healthy male: case report:
https://bmccardiovascdisord.biomedcentral.com/articles/10.1186/s12872-021-02183

122. Acute myocarditis after the second dose of SARS-CoV-2 vaccine: serendipity or causal relationship:
https://pubmed.ncbi.nlm.nih.gov/34236331/

123. Rhabdomyolysis and fasciitis induced by the COVID-19 mRNA vaccine:
https://pubmed.ncbi.nlm.nih.gov/34435250/

124. COVID-19 vaccine-induced rhabdomyolysis: case report with literature review:
https://pubmed.ncbi.nlm.nih.gov/34186348/

125. GM1 ganglioside antibody and COVID-19-related Guillain Barre syndrome: case report, systemic review, and implications for vaccine development:
https://www.sciencedirect.com/science/article/pii/S2666354621000065

126. Guillain-Barré syndrome after AstraZeneca COVID-19 vaccination: causal or casual association:
https://www.sciencedirect.com/science/article/pii/S0303846721004169

127. Sensory Guillain-Barré syndrome after ChAdOx1 nCov-19 vaccine: report of two cases and review of the literature:
https://www.sciencedirect.com/science/article/pii/S0165572821002186

128. Guillain-Barré syndrome after the first dose of SARS-CoV-2 vaccine: a temporary occurrence, not a causal association:
https://www.sciencedirect.com/science/article/pii/S2214250921000998

129. Guillain-Barré syndrome presenting as facial diplegia after vaccination with COVID-19: a case report:
https://www.sciencedirect.com/science/article/pii/S0736467921006442

130. Guillain-Barré syndrome after the first injection of ChAdOx1 nCoV-19 vaccine: first report:
https://www.sciencedirect.com/science/article/pii/S0035378721005853

131. SARS-CoV-2 vaccines are not safe for those with Guillain-Barre syndrome following vaccination:
https://www.sciencedirect.com/science/article/pii/S2049080121005343

132. Acute hyperactive encephalopathy following COVID-19 vaccination with dramatic response to methylprednisolone: a case report:
https://www.sciencedirect.com/science/article/pii/S2049080121007536

133. Facial nerve palsy following administration of COVID-19 mRNA vaccines: analysis of self-report database:
https://www.sciencedirect.com/science/article/pii/S1201971221007049

134. Neurological symptoms and neuroimaging alterations related to COVID-19 vaccine: cause or coincidence:
https://www.sciencedirect.com/science/article/pii/S0899707121003557

135. New-onset refractory status epilepticus after ChAdOx1 nCoV-19 vaccination:
https://www.sciencedirect.com/science/article/pii/S0165572821001569

136. Acute myelitis and ChAdOx1 nCoV-19 vaccine: coincidental or causal association:
https://www.sciencedirect.com/science/article/pii/S0165572821002137

137. Bell's palsy and SARS-CoV-2 vaccines: an unfolding story:
https://www.sciencedirect.com/science/article/pii/S1473309921002735

138. Bell's palsy after the second dose of the Pfizer COVID-19 vaccine in a patient with a history of recurrent Bell's palsy:
https://www.sciencedirect.com/science/article/pii/S266635462100020X

139. Acute-onset central serous retinopathy after immunization with COVID-19 mRNA vaccine:.
https://www.sciencedirect.com/science/article/pii/S2451993621001456

140. Bell's palsy after COVID-19 vaccination: case report:
https://www.sciencedirect.com/science/article/pii/S217358082100122X

141. An academic hospital experience assessing the risk of COVID-19 mRNA vaccine using patient's allergy history:
https://www.sciencedirect.com/science/article/pii/S2213219821007972

142. COVID-19 vaccine-induced axillary and pectoral lymphadenopathy in PET:
https://www.sciencedirect.com/science/article/pii/S1930043321002612

143. ANCA-associated vasculitis after Pfizer-BioNTech COVID-19 vaccine:
https://www.sciencedirect.com/science/article/pii/S0272638621007423

144. Late cutaneous reactions after administration of COVID-19 mRNA vaccines:
https://www.sciencedirect.com/science/article/pii/S2213219821007996

145. COVID-19 vaccine-induced rhabdomyolysis: case report with review of the literature:
https://www.sciencedirect.com/science/article/pii/S1871402121001880

146. Clinical and pathologic correlates of skin reactions to COVID-19 vaccine, including V-REPP: a registry-based study:
https://www.sciencedirect.com/science/article/pii/S0190962221024427

147. Thrombosis with thrombocytopenia syndrome associated with COVID-19 vaccines:.
https://www.sciencedirect.com/science/article/abs/pii/S0735675721004381

148. COVID-19 vaccine-associated anaphylaxis: a statement from the Anaphylaxis Committee of the World Allergy Organization:.
https://www.sciencedirect.com/science/article/pii/S1939455121000119

149. Cerebral venous sinus thrombosis negative for anti-PF4 antibody without thrombocytopenia after immunization with COVID-19 vaccine in an elderly, non-comorbid Indian male treated with conventional heparin-warfarin-based anticoagulation:.
https://www.sciencedirect.com/science/article/pii/S1871402121002046

150. Acute myocarditis after administration of BNT162b2 vaccine against COVID-19:.
https://www.sciencedirect.com/science/article/abs/pii/S188558572100133X

151. Blood clots and bleeding after BNT162b2 and ChAdOx1 nCoV-19 vaccine: an analysis of European data:.
https://www.sciencedirect.com/science/article/pii/S0896841121000937

152. immune thrombocytopenia associated with Pfizer-BioNTech's COVID-19 BNT162b2 mRNA vaccine:.
https://www.sciencedirect.com/science/article/pii/S2214250921002018

153. Bullous drug eruption after the second dose of COVID-19 mRNA-1273 (Moderna) vaccine: Case report:
https://www.sciencedirect.com/science/article/pii/S1876034121001878

154. COVID-19 RNA-based vaccines and the risk of prion disease:
https://scivisionpub.com/pdfs/covid19rna-based-vaccines-and-the-risk-of-prion-dis ease-1503.pdf

155. This study notes that 115 pregnant women lost their babies, out of 827 who participated in a study on the safety of covid-19 vaccines:
https://www.nejm.org/doi/full/10.1056/NEJMoa2104983

156. Process-related impurities in the ChAdOx1 nCov-19 vaccine:
https://www.researchsquare.com/article/rs-477964/v1

157. COVID-19 mRNA vaccine causing CNS inflammation: a case series:
https://link.springer.com/article/10.1007/s00415-021-10780-7

158. Allergic reactions, including anaphylaxis, after receiving the first dose of the Pfizer-BioNTech COVID-19 vaccine:
https://pubmed.ncbi.nlm.nih.gov/33475702/

159. Allergic reactions to the first COVID-19 vaccine: a potential role of polyethylene glycol:
https://pubmed.ncbi.nlm.nih.gov/33320974/

160. Pfizer Vaccine Raises Allergy Concerns:
https://pubmed.ncbi.nlm.nih.gov/33384356/

161. Allergic reactions, including anaphylaxis, after receiving the first dose of Pfizer-BioNTech COVID-19 vaccine – United States, December 14-23, 2020:
https://pubmed.ncbi.nlm.nih.gov/33444297/

162. Allergic reactions, including anaphylaxis, after receiving first dose of Modern COVID-19 vaccine – United States, December 21, 2020-January 10, 2021:
https://pubmed.ncbi.nlm.nih.gov/33507892/

163. Reports of anaphylaxis after coronavirus disease vaccination 2019, South Korea, February 26-April 30, 2021:
https://pubmed.ncbi.nlm.nih.gov/34414880/

164. Reports of anaphylaxis after receiving COVID-19 mRNA vaccines in the U.S.-Dec 14, 2020-Jan 18, 2021:
https://pubmed.ncbi.nlm.nih.gov/33576785/

165. Immunization practices and risk of anaphylaxis: a current, comprehensive update of COVID-19 vaccination data:
https://pubmed.ncbi.nlm.nih.gov/34269740/

166. Relationship between pre-existing allergies and anaphylactic reactions following administration of COVID-19 mRNA vaccine:
https://pubmed.ncbi.nlm.nih.gov/34215453/

167. Anaphylaxis Associated with COVID-19 mRNA Vaccines: Approach to Allergy Research:
https://pubmed.ncbi.nlm.nih.gov/33932618/

168. Severe Allergic Reactions after COVID-19 Vaccination with the Pfizer / BioNTech Vaccine in Great Britain and the USA: Position Statement of the German Allergy Societies: German Medical Association of Allergologists (AeDA), German Society for Allergology and Clinical Immunology (DGAKI) and Society for Pediatric Allergology and Environmental Medicine (GPA):
https://pubmed.ncbi.nlm.nih.gov/33643776/

169. Allergic reactions and anaphylaxis to LNP-based COVID-19 vaccines:
https://pubmed.ncbi.nlm.nih.gov/33571463/

170. Reported orofacial adverse effects from COVID-19 vaccines: the known and the unknown:
https://pubmed.ncbi.nlm.nih.gov/33527524/

171. Cutaneous adverse effects of available COVID-19 vaccines:
https://pubmed.ncbi.nlm.nih.gov/34518015/

172. Cumulative adverse event report of anaphylaxis following injections of COVID-19 mRNA vaccine (Pfizer-BioNTech) in Japan: the first month report:
https://pubmed.ncbi.nlm.nih.gov/34347278/

173. COVID-19 vaccines increase the risk of anaphylaxis:
https://pubmed.ncbi.nlm.nih.gov/33685103/

174. Biphasic anaphylaxis after exposure to the first dose of the Pfizer-BioNTech COVID-19 mRNA vaccine COVID-19:
https://pubmed.ncbi.nlm.nih.gov/34050949/

175. Allergenic components of the mRNA-1273 vaccine for COVID-19: possible involvement of polyethylene glycol and IgG-mediated complement activation:
https://pubmed.ncbi.nlm.nih.gov/33657648/

176. Polyethylene glycol (PEG) is a cause of anaphylaxis to Pfizer / BioNTech mRNA COVID-19 vaccine:
https://pubmed.ncbi.nlm.nih.gov/33825239/

177. Acute allergic reactions to COVID-19 mRNA vaccines:
https://pubmed.ncbi.nlm.nih.gov/33683290/

178. Polyethylene glycole allergy of the SARS CoV2 vaccine recipient: case report of a young adult recipient and management of future exposure to SARS-CoV2:
https://pubmed.ncbi.nlm.nih.gov/33919151/

179. Elevated rates of anaphylaxis after vaccination with Pfizer BNT162b2 mRNA vaccine against COVID-19 in Japanese healthcare workers; a secondary analysis of initial post-approval safety data:
https://pubmed.ncbi.nlm.nih.gov/34128049/

180. Allergic reactions and adverse events associated with administration of mRNA-based vaccines. A health system experience:
https://pubmed.ncbi.nlm.nih.gov/34474708/

181. Allergic reactions to COVID-19 vaccines: statement of the Belgian Society of Allergy and Clinical Immunology (BelSACI):
https://www.tandfonline.com/doi/abs/10.1080/17843286.2021.1909447

182. .IgE-mediated allergy to polyethylene glycol (PEG) as a cause of anaphylaxis to COVID-19 mRNA vaccines:
https://pubmed.ncbi.nlm.nih.gov/34318537/

183. Allergic reactions after COVID-19 vaccination: putting the risk in perspective:
https://pubmed.ncbi.nlm.nih.gov/34463751/

184. Anaphylactic reactions to COVID-19 mRNA vaccines: a call for further studies:
https://pubmed.ncbi.nlm.nih.gov/33846043/188

185. Risk of severe allergic reactions to COVID-19 vaccines among patients with allergic skin disease: practical recommendations. An ETFAD position statement with external experts:
https://pubmed.ncbi.nlm.nih.gov/33752263/

186. COVID-19 vaccine and death: causality algorithm according to the WHO eligibility diagnosis:
https://pubmed.ncbi.nlm.nih.gov/34073536/

187. Fatal brain hemorrhage after COVID-19 vaccine:
https://pubmed.ncbi.nlm.nih.gov/33928772/

188. A case series of skin reactions to COVID-19 vaccine in the Department of Dermatology at Loma Linda University:
https://pubmed.ncbi.nlm.nih.gov/34423106/

189. Skin reactions reported after Moderna and Pfizer's COVID-19 vaccination: a study based on a registry of 414 cases:
https://pubmed.ncbi.nlm.nih.gov/33838206/

190. Clinical and pathologic correlates of skin reactions to COVID-19 vaccine, including V-REPP: a registry-based study:
https://pubmed.ncbi.nlm.nih.gov/34517079/

191. Skin reactions after vaccination against SARS-COV-2: a nationwide Spanish cross-sectional study of 405 cases:
https://pubmed.ncbi.nlm.nih.gov/34254291/

192. Varicella zoster virus and herpes simplex virus reactivation after vaccination with COVID-19: review of 40 cases in an international dermatologic registry:
https://pubmed.ncbi.nlm.nih.gov/34487581/

193. Immune thrombosis and thrombocytopenia (VITT) associated with the COVID-19 vaccine: diagnostic and therapeutic recommendations for a new syndrome:
https://pubmed.ncbi.nlm.nih.gov/33987882/

194. Laboratory testing for suspicion of COVID-19 vaccine-induced thrombotic (immune) thrombocytopenia:
https://pubmed.ncbi.nlm.nih.gov/34138513/

195. Intracerebral hemorrhage due to thrombosis with thrombocytopenia syndrome after COVID-19 vaccination: the first fatal case in Korea:
https://pubmed.ncbi.nlm.nih.gov/34402235/

196. Risk of thrombocytopenia and thromboembolism after covid-19 vaccination and positive SARS-CoV-2 tests: self-controlled case series study:
https://pubmed.ncbi.nlm.nih.gov/34446426/

197. Vaccine-induced immune thrombotic thrombocytopenia and cerebral venous sinus thrombosis after covid-19 vaccination; a systematic review:
https://pubmed.ncbi.nlm.nih.gov/34365148/

198. Nerve and muscle adverse events after vaccination with COVID-19: a systematic review and meta-analysis of clinical trials:
https://pubmed.ncbi.nlm.nih.gov/34452064/

199. A rare case of cerebral venous thrombosis and disseminated intravascular coagulation temporally associated with administration of COVID-19 vaccine:
https://pubmed.ncbi.nlm.nih.gov/33917902/

200. Primary adrenal insufficiency associated with thrombotic immune thrombocytopenia induced by Oxford-AstraZeneca ChAdOx1 nCoV-19 vaccine (VITT):
https://pubmed.ncbi.nlm.nih.gov/34256983/

201. Acute cerebral venous thrombosis and pulmonary artery embolism associated with the COVID-19 vaccine:
https://pubmed.ncbi.nlm.nih.gov/34247246/

202. Thromboaspiration infusion and fibrinolysis for portomesenteric thrombosis after administration of AstraZeneca COVID-19 vaccine:
https://pubmed.ncbi.nlm.nih.gov/34132839/

203. 59-year-old woman with extensive deep venous thrombosis and pulmonary thromboembolism 7 days after a first dose of Pfizer-BioNTech BNT162b2 mRNA vaccine COVID-19:
https://pubmed.ncbi.nlm.nih.gov/34117206/

204. Cerebral venous thrombosis and vaccine-induced thrombocytopenia.a. Oxford-AstraZeneca COVID-19: a missed opportunity for a rapid return on experience:
https://pubmed.ncbi.nlm.nih.gov/34033927/

205. Myocarditis and other cardiovascular complications of mRNA-based COVID-19 vaccines:
https://pubmed.ncbi.nlm.nih.gov/34277198/

206. ericarditis after administration of COVID-19 mRNA BNT162b2 vaccine:
https://pubmed.ncbi.nlm.nih.gov/34364831/

207. Unusual presentation of acute pericarditis after vaccination against SARS-COV-2 mRNA-1237 Modern:
https://pubmed.ncbi.nlm.nih.gov/34447639/

208. Case report: acute myocarditis after second dose of SARS-CoV-2 mRNA-1273 vaccine mRNA-1273:
https://pubmed.ncbi.nlm.nih.gov/34514306/

209. Immune-mediated disease outbreaks or recent-onset disease in 27 subjects after mRNA/DNA vaccination against SARS-CoV-2:
https://pubmed.ncbi.nlm.nih.gov/33946748/

210. Insights from a murine model of myopericarditis induced by COVID-19 mRNA vaccine: could accidental intravenous injection of a vaccine induce myopericarditis:
https://pubmed.ncbi.nlm.nih.gov/34453510/

211. Immune thrombocytopenia in a 22-year-old post Covid-19 vaccine:
https://pubmed.ncbi.nlm.nih.gov/33476455/

212. propylthiouracil-induced neutrophil anti-cytoplasmic antibody-associated vasculitis after COVID-19 vaccination:
https://pubmed.ncbi.nlm.nih.gov/34451967/

213. Secondary immune thrombocytopenia (ITP) associated with ChAdOx1 Covid-19 vaccine: case report:
https://pubmed.ncbi.nlm.nih.gov/34377889/

214. Thrombosis with thrombocytopenia syndrome (TTS) following AstraZeneca ChAdOx1 nCoV-19 (AZD1222) COVID-19 vaccination: risk-benefit analysis for persons <60 years in Australia:
https://pubmed.ncbi.nlm.nih.gov/34272095/

215. COVID-19 vaccination association and facial nerve palsy: A case-control study:
https://pubmed.ncbi.nlm.nih.gov/34165512/

216. The association between COVID-19 vaccination and Bell's palsy:
https://pubmed.ncbi.nlm.nih.gov/34411533/

217. Bell's palsy after COVID-19 vaccination:
https://pubmed.ncbi.nlm.nih.gov/33611630/

218. Acute transverse myelitis (ATM): clinical review of 43 patients with COVID-19-associated ATM and 3 serious adverse events of post-vaccination ATM with ChAdOx1 nCoV-19 vaccine (AZD1222):
https://pubmed.ncbi.nlm.nih.gov/33981305/

219. Bell's palsy after 24 hours of mRNA-1273 SARS-CoV-2 mRNA-1273 vaccine:
https://pubmed.ncbi.nlm.nih.gov/34336436/

220. Sequential contralateral facial nerve palsy after first and second doses of COVID-19 vaccine:
https://pubmed.ncbi.nlm.nih.gov/34281950/

221. Transverse myelitis induced by SARS-CoV-2 vaccination:
https://pubmed.ncbi.nlm.nih.gov/34458035/

222. Peripheral facial nerve palsy after vaccination with BNT162b2 (COVID-19):
https://pubmed.ncbi.nlm.nih.gov/33734623/

223. Acute abducens nerve palsy after COVID-19 vaccination:
https://pubmed.ncbi.nlm.nih.gov/34044114/

224. Facial nerve palsy after administration of COVID-19 mRNA vaccines: analysis of self-report database:
https://pubmed.ncbi.nlm.nih.gov/34492394/

225. Transient oculomotor paralysis after administration of RNA-1273 messenger vaccine for SARS-CoV-2 diplopia after COVID-19 vaccine:
https://pubmed.ncbi.nlm.nih.gov/34369471/

226. Bell's palsy after Ad26.COV2.S COVID-19 vaccination:
https://pubmed.ncbi.nlm.nih.gov/34014316/

227. Bell's palsy after COVID-19 vaccination: case report:
https://pubmed.ncbi.nlm.nih.gov/34330676/

228. A case of acute demyelinating polyradiculoneuropathy with bilateral facial palsy following ChAdOx1 nCoV-19 vaccination:
https://pubmed.ncbi.nlm.nih.gov/34272622/

229. Guillian Barré syndrome after vaccination with mRNA-1273 against COVID-19:
https://pubmed.ncbi.nlm.nih.gov/34477091/

230. Acute facial paralysis as a possible complication of SARS-CoV-2 vaccination:
https://pubmed.ncbi.nlm.nih.gov/33975372/

231. Bell's palsy after COVID-19 vaccination with high antibody response in CSF:
https://pubmed.ncbi.nlm.nih.gov/34322761/

232. Parsonage-Turner syndrome associated with SARS-CoV-2 or SARS-CoV-2 vaccination. Comment on: "Neuralgic amyotrophy and COVID-19 infection: 2 cases of accessory spinal nerve palsy" by Coll et al. Articular Spine 2021; 88: 10519:
https://pubmed.ncbi.nlm.nih.gov/34139321/

233. Bell's palsy after a single dose of vaccine mRNA. SARS-CoV-2: case report:
https://pubmed.ncbi.nlm.nih.gov/34032902/

234. Autoimmune hepatitis developing after coronavirus disease vaccine 2019 (COVID-19): causality or victim?:
https://pubmed.ncbi.nlm.nih.gov/33862041/

235. Autoimmune hepatitis triggered by vaccination against SARS-CoV-2:
https://pubmed.ncbi.nlm.nih.gov/34332438/

236. Acute autoimmune-like hepatitis with atypical antimitochondrial antibody after vaccination with COVID-19 mRNA: a new clinical entity:
https://pubmed.ncbi.nlm.nih.gov/34293683/

237. Autoimmune hepatitis after COVID vaccine:
https://pubmed.ncbi.nlm.nih.gov/34225251/

238. A novel case of bifacial diplegia variant of Guillain-Barré syndrome after vaccination with Janssen COVID-19:
https://pubmed.ncbi.nlm.nih.gov/34449715/

239. Comparison of vaccine-induced thrombotic events between ChAdOx1 nCoV-19 and Ad26.COV.2.S vaccines:
https://pubmed.ncbi.nlm.nih.gov/34139631/

240. Bilateral superior ophthalmic vein thrombosis, ischemic stroke and immune thrombocytopenia after vaccination with ChAdOx1 nCoV-19:
https://pubmed.ncbi.nlm.nih.gov/33864750/

241. Diagnosis and treatment of cerebral venous sinus thrombosis with vaccine-induced immune-immune thrombotic thrombocytopenia:
https://pubmed.ncbi.nlm.nih.gov/33914590/

242. Venous sinus thrombosis after vaccination with ChAdOx1 nCov-19:
https://pubmed.ncbi.nlm.nih.gov/34420802/

243. Cerebral venous sinus thrombosis following vaccination against SARS-CoV-2: an analysis of cases reported to the European Medicines Agency:
https://pubmed.ncbi.nlm.nih.gov/34293217/

244. Risk of thrombocytopenia and thromboembolism after covid-19 vaccination and positive SARS-CoV-2 tests: self-controlled case series study:
https://pubmed.ncbi.nlm.nih.gov/34446426/

245. Blood clots and bleeding after BNT162b2 and ChAdOx1 nCoV-19 vaccination: an analysis of European data:
https://pubmed.ncbi.nlm.nih.gov/34174723/

246. Arterial events, venous thromboembolism, thrombocytopenia and bleeding after vaccination with Oxford-AstraZeneca ChAdOx1-S in Denmark and Norway: population-based cohort study:
https://pubmed.ncbi.nlm.nih.gov/33952445/

247. First dose of ChAdOx1 and BNT162b2 COVID-19 vaccines and thrombocytopenic, thromboembolic and hemorrhagic events in Scotland:
https://pubmed.ncbi.nlm.nih.gov/34108714/

248. Cerebral venous thrombosis associated with COVID-19 vaccine in Germany:
https://pubmed.ncbi.nlm.nih.gov/34288044/

249. Malignant cerebral infarction after vaccination with ChAdOx1 nCov-19: a catastrophic variant of vaccine-induced immune-mediated thrombotic thrombocytopenia:
https://pubmed.ncbi.nlm.nih.gov/34341358/

250. celiac artery and splenic artery thrombosis complicated by splenic infarction 7 days after the first dose of Oxford vaccine, causal relationship or coincidence:
https://pubmed.ncbi.nlm.nih.gov/34261633/

251. Primary adrenal insufficiency associated with Oxford-AstraZeneca ChAdOx1 nCoV-19 (VITT) vaccine-induced immune thrombotic thrombocytopenia:
https://pubmed.ncbi.nlm.nih.gov/34256983/

252. Thrombocytopenia after COVID-19 vaccination:
https://pubmed.ncbi.nlm.nih.gov/34332437/

253. Cerebral venous sinus thrombosis associated with thrombocytopenia after COVID-19 vaccination:
https://pubmed.ncbi.nlm.nih.gov/33845870/

254. Thrombosis with thrombocytopenia syndrome after COVID-19 immunization:
https://pubmed.ncbi.nlm.nih.gov/34236343/

255. Acute myocardial infarction within 24 hours after COVID-19 vaccination:
https://pubmed.ncbi.nlm.nih.gov/34364657/

256. Bilateral acute macular neuroretinopathy after SARS-CoV-2 vaccination:
https://pubmed.ncbi.nlm.nih.gov/34287612/

257. central venous sinus thrombosis with subarachnoid hemorrhage after COVID-19 mRNA vaccination: are these reports merely coincidental:
https://pubmed.ncbi.nlm.nih.gov/34478433/

258. Intracerebral hemorrhage due to thrombosis with thrombocytopenia syndrome after COVID-19 vaccination: the first fatal case in Korea:
https://pubmed.ncbi.nlm.nih.gov/34402235/

259. Cerebral venous sinus thrombosis negative for anti-PF4 antibody without thrombocytopenia after immunization with COVID-19 vaccine in a non-comorbid elderly Indian male treated with conventional heparin-warfarin-based anticoagulation:
https://pubmed.ncbi.nlm.nih.gov/34186376/

260. Cerebral venous sinus thrombosis 2 weeks after first dose of SARS-CoV-2 mRNA vaccine:
https://pubmed.ncbi.nlm.nih.gov/34101024/

261. A case of multiple thrombocytopenia and thrombosis following vaccination with ChAdOx1 nCoV-19 against SARS-CoV-2:
https://pubmed.ncbi.nlm.nih.gov/34137813/

262. Vaccine-induced thrombotic thrombocytopenia: the elusive link between thrombosis and adenovirus-based SARS-CoV-2 vaccines:
https://pubmed.ncbi.nlm.nih.gov/34191218/

263. Acute ischemic stroke revealing immune thrombotic thrombocytopenia induced by ChAdOx1 nCov-19 vaccine: impact on recanalization strategy:
https://pubmed.ncbi.nlm.nih.gov/34175640/

264. New-onset refractory status epilepticus after ChAdOx1 nCoV-19 vaccine:
https://pubmed.ncbi.nlm.nih.gov/34153802/

265. Thrombosis with thrombocytopenia syndrome associated with COVID-19 viral vector vaccines:
https://pubmed.ncbi.nlm.nih.gov/34092488/

266. Pulmonary embolism, transient ischemic attack, and thrombocytopenia after Johnson & Johnson COVID-19 vaccine:
https://pubmed.ncbi.nlm.nih.gov/34261635/

267. Thromboaspiration infusion and fibrinolysis for portomesenteric thrombosis after administration of the AstraZeneca COVID-19 vaccine:
https://pubmed.ncbi.nlm.nih.gov/34132839/

268. Spontaneous HIT syndrome: knee replacement, infection, and parallels with vaccine-induced immune thrombotic thrombocytopenia:
https://pubmed.ncbi.nlm.nih.gov/34144250/

269. Deep venous thrombosis (DVT) occurring shortly after second dose of SARS-CoV-2 mRNA vaccine:
https://pubmed.ncbi.nlm.nih.gov/33687691/

270. Procoagulant antibody-mediated procoagulant platelets in immune thrombotic thrombocytopenia associated with SARS-CoV-2 vaccination:
https://pubmed.ncbi.nlm.nih.gov/34011137/

271. Vaccine-induced immune thrombotic thrombocytopenia causing a severe form of cerebral venous thrombosis with high mortality rate: a case series:
https://pubmed.ncbi.nlm.nih.gov/34393988/

272. Procoagulant microparticles: a possible link between vaccine-induced immune thrombocytopenia (VITT) and cerebral sinus venous thrombosis:
https://pubmed.ncbi.nlm.nih.gov/34129181/

273. Atypical thrombosis associated with the vaccine VaxZevria® (AstraZeneca): data from the French network of regional pharmacovigilance centers:
https://pubmed.ncbi.nlm.nih.gov/34083026/

274. Acute cerebral venous thrombosis and pulmonary artery embolism associated with the COVID-19 vaccine:
https://pubmed.ncbi.nlm.nih.gov/34247246/

275. Vaccine-induced thrombosis and thrombocytopenia with bilateral adrenal haemorrhage:
https://pubmed.ncbi.nlm.nih.gov/34235757/

276. Palmar digital vein thrombosis after Oxford-AstraZeneca COVID-19 vaccination:
https://pubmed.ncbi.nlm.nih.gov/34473841/

277. Cutaneous thrombosis associated with cutaneous necrosis following Oxford-AstraZeneca COVID-19 vaccination:
https://pubmed.ncbi.nlm.nih.gov/34189756/

278. Cerebral venous thrombosis following COVID-19 vaccination:
https://pubmed.ncbi.nlm.nih.gov/34045111/

279. Lipschütz ulcers after AstraZeneca COVID-19 vaccination:
https://pubmed.ncbi.nlm.nih.gov/34366434/

280. Amyotrophic Neuralgia secondary to Vaxzevri vaccine (AstraZeneca) COVID-19:
https://pubmed.ncbi.nlm.nih.gov/34330677/

281. Thrombosis with thrombocytopenia after Messenger vaccine RNA-1273:
https://pubmed.ncbi.nlm.nih.gov/34181446/

282. Intracerebral hemorrhage twelve days after vaccination with ChAdOx1 nCoV-19:
https://pubmed.ncbi.nlm.nih.gov/34477089/

283. Thrombotic thrombocytopenia after vaccination with COVID-19: in search of the underlying mechanism:
https://pubmed.ncbi.nlm.nih.gov/34071883/

284. Coronavirus (COVID-19) Vaccine-induced immune thrombotic thrombocytopenia (VITT):
https://pubmed.ncbi.nlm.nih.gov/34033367/

285. Comparison of adverse drug reactions among four COVID-19 vaccines in Europe using the EudraVigilance database: Thrombosis in unusual sites:
https://pubmed.ncbi.nlm.nih.gov/34375510/

286. Immunoglobulin adjuvant for vaccine-induced immune thrombotic thrombocytopenia:
https://pubmed.ncbi.nlm.nih.gov/34107198/

287. Severe vaccine-induced thrombotic thrombocytopenia following vaccination with COVID-19: an autopsy case report and review of the literature:
https://pubmed.ncbi.nlm.nih.gov/34355379/

288. A case of acute pulmonary embolism after immunization with SARS-CoV-2 mRNA:
https://pubmed.ncbi.nlm.nih.gov/34452028/

289. Neurosurgical considerations regarding decompressive craniectomy for intracerebral hemorrhage after SARS-CoV-2 vaccination in vaccine-induced thrombotic thrombocytopenia-VITT:
https://pubmed.ncbi.nlm.nih.gov/34202817/

290. Thrombosis and SARS-CoV-2 vaccines: vaccine-induced immune thrombotic thrombocytopenia:
https://pubmed.ncbi.nlm.nih.gov/34237213/

291. Acquired thrombotic thrombocytopenic thrombocytopenic purpura: a rare disease associated with the BNT162b2 vaccine:
https://pubmed.ncbi.nlm.nih.gov/34105247/

292. Immune complexes, innate immunity and NETosis in ChAdOx1 vaccine-induced thrombocytopenia:
https://pubmed.ncbi.nlm.nih.gov/34405870/

293. Sensory Guillain-Barré syndrome following ChAdOx1 nCov-19 vaccine: report of two cases and review of the literature:
https://pubmed.ncbi.nlm.nih.gov/34416410/

294. Vogt-Koyanagi-Harada syndrome after COVID-19 and ChAdOx1 nCoV-19 (AZD1222) vaccination:
https://pubmed.ncbi.nlm.nih.gov/34462013/

295. Reactivation of Vogt-Koyanagi-Harada disease under control for more than 6 years, after anti-SARS-CoV-2 vaccination:
https://pubmed.ncbi.nlm.nih.gov/34224024/

296. Post-vaccinal encephalitis after ChAdOx1 nCov-19:
https://pubmed.ncbi.nlm.nih.gov/34324214/

297. Neurological symptoms and neuroimaging alterations related to COVID-19 vaccine: cause or coincidence?:
https://pubmed.ncbi.nlm.nih.gov/34507266/

298. Fatal systemic capillary leak syndrome after SARS-COV-2 vaccination in a patient with multiple myeloma:
https://pubmed.ncbi.nlm.nih.gov/34459725/

299. Polyarthralgia and myalgia syndrome after vaccination with ChAdOx1 nCOV-19:
https://pubmed.ncbi.nlm.nih.gov/34463066/

300. Three cases of subacute thyroiditis after SARS-CoV-2 vaccination: post-vaccination ASIA syndrome:
https://pubmed.ncbi.nlm.nih.gov/34043800/

301. Facial diplegia: a rare and atypical variant of Guillain-Barré syndrome and the Ad26.COV2.S vaccine:
https://pubmed.ncbi.nlm.nih.gov/34447646/

302. Association between ChAdOx1 nCoV-19 vaccination and bleeding episodes: large population-based cohort study:
https://pubmed.ncbi.nlm.nih.gov/34479760/

303. fulminant myocarditis and systemic hyperinflammation temporally associated with BNT162b2 COVID-19 mRNA vaccination in two patients:
https://pubmed.ncbi.nlm.nih.gov/34416319/

304. Adverse effects reported after COVID-19 vaccination in a tertiary care hospital, centered on cerebral venous sinus thrombosis (CVST):
https://pubmed.ncbi.nlm.nih.gov/34092166/

305. Induction and exacerbation of subacute cutaneous lupus erythematosus erythematosus after mRNA- or adenoviral vector-based SARS-CoV-2 vaccination:
https://pubmed.ncbi.nlm.nih.gov/34291477/

306. Petechiae and peeling of fingers after immunization with BTN162b2 messenger RNA (mRNA)-based COVID-19 vaccine:
https://pubmed.ncbi.nlm.nih.gov/34513435/

307. Hepatitis C virus reactivation after COVID-19 vaccination: a case report:
https://pubmed.ncbi.nlm.nih.gov/34512037/

308. Bilateral immune-mediated keratolysis after immunization with SARS-CoV-2 recombinant viral vector vaccine:
https://pubmed.ncbi.nlm.nih.gov/34483273/

309. Immune-mediated thrombocytopenic purpura after Pfizer-BioNTech COVID-19 vaccine in an elderly woman:
https://pubmed.ncbi.nlm.nih.gov/34513446/

310. Platelet activation and modulation in thrombosis with thrombocytopenia syndrome associated with the ChAdO × 1 nCov-19 vaccine:
https://pubmed.ncbi.nlm.nih.gov/34474550/

311. Reactive arthritis after COVID-19 vaccination:
https://pubmed.ncbi.nlm.nih.gov/34033732/

312. Two cases of Graves' disease after SARS-CoV-2 vaccination: an autoimmune / inflammatory syndrome induced by adjuvants:
https://pubmed.ncbi.nlm.nih.gov/33858208/

313. Acute relapse and impaired immunization after COVID-19 vaccination in a patient with multiple sclerosis treated with rituximab:
https://pubmed.ncbi.nlm.nih.gov/34015240/

314. Widespread fixed bullous drug eruption after vaccination with ChAdOx1 nCoV-19:
https://pubmed.ncbi.nlm.nih.gov/34482558/

315. COVID-19 mRNA vaccine causing CNS inflammation: a case series:
https://pubmed.ncbi.nlm.nih.gov/34480607/

316. Thymic hyperplasia after Covid-19 mRNA-based vaccination with Covid-19:
https://pubmed.ncbi.nlm.nih.gov/34462647/

317. Acute disseminated encephalomyelitis following vaccination against SARS-CoV-2:
https://pubmed.ncbi.nlm.nih.gov/34325334/

318. Tolosa-Hunt syndrome occurring after COVID-19 vaccination:
https://pubmed.ncbi.nlm.nih.gov/34513398/

319. Systemic capillary extravasation syndrome following vaccination with ChAdOx1 nCOV-19 (Oxford-Astra-Zeneca):
https://pubmed.ncbi.nlm.nih.gov/34362727/

320. Immune-mediated thrombocytopenia associated with Ad26.COV2.S vaccine (Janssen; Johnson & Johnson):
https://pubmed.ncbi.nlm.nih.gov/34469919/

321. Transient thrombocytopenia with glycoprotein-specific platelet autoantibodies after vaccination with Ad26.COV2.S: case report:
https://pubmed.ncbi.nlm.nih.gov/34516272/

322. Acute hyperactive encephalopathy following COVID-19 vaccination with dramatic response to methylprednisolone: case report:
https://pubmed.ncbi.nlm.nih.gov/34512961/

323. Transient cardiac injury in adolescents receiving the BNT162b2 mRNA COVID-19 vaccine:
https://pubmed.ncbi.nlm.nih.gov/34077949/

324. Autoimmune hepatitis developing after ChAdOx1 nCoV-19 vaccine (Oxford-AstraZeneca):
https://pubmed.ncbi.nlm.nih.gov/34171435/

325. Severe relapse of multiple sclerosis after COVID-19 vaccination: a case report:
https://pubmed.ncbi.nlm.nih.gov/34447349/

326. Lymphohistocytic myocarditis after vaccination with the COVID-19 viral vector Ad26.COV2.S:
https://pubmed.ncbi.nlm.nih.gov/34514078/

327. Hemophagocytic lymphohistiocytosis after vaccination with ChAdOx1 nCov-19:
https://pubmed.ncbi.nlm.nih.gov/34406660/

328. IgA vasculitis in adult patient after vaccination with ChadOx1 nCoV-19:
https://pubmed.ncbi.nlm.nih.gov/34509658/

329. A case of leukocytoclastic vasculitis after vaccination with a SARS-CoV2 vaccine: case report:
https://pubmed.ncbi.nlm.nih.gov/34196469/

330. Onset / outbreak of psoriasis after Corona virus ChAdOx1 nCoV-19 vaccine (Oxford-AstraZeneca / Covishield): report of two cases:
https://pubmed.ncbi.nlm.nih.gov/34350668/

331. Hailey-Hailey disease exacerbation after SARS-CoV-2 vaccination:
https://pubmed.ncbi.nlm.nih.gov/34436620/

332. Supraclavicular lymphadenopathy after COVID-19 vaccination in Korea: serial follow-up by ultrasonography:
https://pubmed.ncbi.nlm.nih.gov/34116295/

333. COVID-19 vaccine, immune thrombotic thrombocytopenia, jaundice, hyperviscosity: concern in cases with underlying hepatic problems:
https://pubmed.ncbi.nlm.nih.gov/34509271/

334. Report of the International Cerebral Venous Thrombosis Consortium on cerebral venous thrombosis after SARS-CoV-2 vaccination:
https://pubmed.ncbi.nlm.nih.gov/34462996/

335. Immune thrombocytopenia after vaccination during the COVID-19 pandemic:
https://pubmed.ncbi.nlm.nih.gov/34435486/

336. COVID-19: lessons from the Norwegian tragedy should be taken into account in planning for vaccine launch in less developed/developing countries:
https://pubmed.ncbi.nlm.nih.gov/34435142/

337. Rituximab-induced acute lympholysis and pancytopenia following vaccination with COVID-19:
https://pubmed.ncbi.nlm.nih.gov/34429981/

338. Exacerbation of plaque psoriasis after COVID-19 inactivated mRNA and BNT162b2 vaccines: report of two cases:
https://pubmed.ncbi.nlm.nih.gov/34427024/

339. Vaccine-induced interstitial lung disease: a rare reaction to COVID-19 vaccine:
https://pubmed.ncbi.nlm.nih.gov/34510014/

340. Vesiculobullous cutaneous reactions induced by COVID-19 mRNA vaccine: report of four cases and review of the literature:
https://pubmed.ncbi.nlm.nih.gov/34236711/

341. Vaccine-induced thrombocytopenia with severe headache:
https://pubmed.ncbi.nlm.nih.gov/34525282/

342. Acute perimyocarditis after the first dose of COVID-19 mRNA vaccine:
https://pubmed.ncbi.nlm.nih.gov/34515024/

343. Rhabdomyolysis and fasciitis induced by COVID-19 mRNA vaccine:
https://pubmed.ncbi.nlm.nih.gov/34435250/

344. Rare cutaneous adverse effects of COVID-19 vaccines: a case series and review of the literature:
https://pubmed.ncbi.nlm.nih.gov/34363637/

345. Immune thrombocytopenia associated with the Pfizer-BioNTech COVID-19 mRNA vaccine BNT162b2:
https://www.sciencedirect.com/science/article/pii/S2214250921002018

346. Secondary immune thrombocytopenia putatively attributable to COVID-19 vaccination:
https://casereports.bmj.com/content/14/5/e242220.abstract

347. Immune thrombocytopenia following Pfizer-BioNTech BNT162b2 mRNA COVID-19 vaccine:
https://pubmed.ncbi.nlm.nih.gov/34155844/

348. Newly diagnosed idiopathic thrombocytopenia after COVID-19 vaccine administration:
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8176657/

349. Idiopathic thrombocytopenic purpura and the Modern Covid-19 vaccine:
https://www.annemergmed.com/article/S0196-0644(21)00122-0/fulltext

350. Thrombocytopenia after Pfizer and Moderna SARS vaccination – CoV -2:
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8014568/

351. Immune thrombocytopenic purpura and acute liver injury after COVID-19 vaccination:
https://casereports.bmj.com/content/14/7/e242678

352. Collection of complement-mediated and autoimmune-mediated hematologic conditions after SARS-CoV-2 vaccination:
https://ashpublications.org/bloodadvances/article/5/13/2794/476324/Autoimmune-and-complement-mediated-hematologic

353. Petechial rash associated with CoronaVac vaccination: first report of cutaneous side effects before phase 3 results:
https://ejhp.bmj.com/content/early/2021/05/23/ejhpharm-2021-002794

354. COVID-19 vaccines induce severe hemolysis in paroxysmal nocturnal hemoglobinuria:
https://ashpublications.org/blood/article/137/26/3670/475905/COVID-19-vaccines-induce-severe-hemolysis-in

355. Cerebral venous thrombosis associated with COVID-19 vaccine in Germany:
https://pubmed.ncbi.nlm.nih.gov/34288044/

356. Cerebral venous sinus thrombosis after COVID-19 vaccination : Neurological and radiological management:
https://pubmed.ncbi.nlm.nih.gov/34327553/

357. Cerebral venous thrombosis and thrombocytopenia after COVID-19 vaccination:
https://pubmed.ncbi.nlm.nih.gov/33878469/

358. Cerebral venous sinus thrombosis and thrombocytopenia after COVID-19 vaccination: report of two cases in the United Kingdom:
https://pubmed.ncbi.nlm.nih.gov/33857630/

359. Cerebral venous thrombosis induced by SARS-CoV-2 vaccine:
https://pubmed.ncbi.nlm.nih.gov/34090750/

360. Carotid artery immune thrombosis induced by adenovirus-vectored COVID-19 vaccine: case report:
https://pubmed.ncbi.nlm.nih.gov/34312301/

361. Cerebral venous sinus thrombosis associated with vaccine-induced thrombotic thrombocytopenia:
https://pubmed.ncbi.nlm.nih.gov/34333995/

362. The roles of platelets in COVID-19-associated coagulopathy and vaccine-induced immune-immune thrombotic thrombocytopenia:
https://pubmed.ncbi.nlm.nih.gov/34455073/

363. Cerebral venous thrombosis after the BNT162b2 mRNA SARS-CoV-2 vaccine:
https://pubmed.ncbi.nlm.nih.gov/34111775/

364. Cerebral venous thrombosis after COVID-19 vaccination:
https://pubmed.ncbi.nlm.nih.gov/34045111/

365. Lethal cerebral venous sinus thrombosis after COVID-19 vaccination:
https://pubmed.ncbi.nlm.nih.gov/33983464/

366. Cerebral venous sinus thrombosis in the U.S. population, After SARS-CoV-2 vaccination with adenovirus and after COVID-19:
https://pubmed.ncbi.nlm.nih.gov/34116145/

367. Cerebral venous thrombosis after COVID-19 vaccination: is the risk of thrombosis increased by intravascular administration of the vaccine:
https://pubmed.ncbi.nlm.nih.gov/34286453/

368. Central venous sinus thrombosis with subarachnoid hemorrhage after COVID-19 mRNA vaccination: are these reports merely coincidental:
https://pubmed.ncbi.nlm.nih.gov/34478433/

369. Cerebral venous sinus thrombosis after ChAdOx1 nCov-19 vaccination with a misleading first brain MRI:
https://pubmed.ncbi.nlm.nih.gov/34244448/

370. Early results of bivalirudin treatment for thrombotic thrombocytopenia and cerebral venous sinus thrombosis after vaccination with Ad26.COV2.S:
https://pubmed.ncbi.nlm.nih.gov/34226070/

371. Cerebral venous sinus thrombosis associated with post-vaccination thrombocytopenia by COVID-19:
https://pubmed.ncbi.nlm.nih.gov/33845870/

372. Cerebral venous sinus thrombosis 2 weeks after the first dose of SARS-CoV-2 mRNA vaccine:
https://pubmed.ncbi.nlm.nih.gov/34101024/

373. Vaccine-induced immune thrombotic thrombocytopenia causing a severe form of cerebral venous thrombosis with a high mortality rate: a case series:
https://pubmed.ncbi.nlm.nih.gov/34393988/

374. Adenovirus interactions with platelets and coagulation and vaccine-associated autoimmune thrombocytopenia thrombosis syndrome:
https://pubmed.ncbi.nlm.nih.gov/34407607/

375. Headache attributed to COVID-19 (SARS-CoV-2 coronavirus) vaccination with the ChAdOx1 nCoV-19 (AZD1222) vaccine: a multicenter observational cohort study:
https://pubmed.ncbi.nlm.nih.gov/34313952/

376. Adverse effects reported after COVID-19 vaccination in a tertiary care hospital, focus on cerebral venous sinus thrombosis (CVST):
https://pubmed.ncbi.nlm.nih.gov/34092166/

377. Cerebral venous sinus thrombosis following vaccination against SARS-CoV-2: an analysis of cases reported to the European Medicines Agency:
https://pubmed.ncbi.nlm.nih.gov/34293217/

378. A rare case of a middle-age Asian male with cerebral venous thrombosis after COVID-19 AstraZeneca vaccination:
https://pubmed.ncbi.nlm.nih.gov/34274191/

379. Cerebral venous sinus thrombosis negative for anti-PF4 antibody without thrombocytopenia after immunization with COVID-19 vaccine in a non-comorbid elderly Indian male treated with conventional heparin-warfarin-based anticoagulation:
https://pubmed.ncbi.nlm.nih.gov/34186376/

380. Arterial events, venous thromboembolism, thrombocytopenia and bleeding after vaccination with Oxford-AstraZeneca ChAdOx1-S in Denmark and Norway: population-based cohort study:
https://pubmed.ncbi.nlm.nih.gov/33952445/

381. Procoagulant microparticles: a possible link between vaccine-induced immune thrombocytopenia (VITT) and cerebral sinus venous thrombosis:
https://pubmed.ncbi.nlm.nih.gov/34129181/

382. S. case reports of cerebral venous sinus thrombosis with thrombocytopenia after vaccination with Ad26. COV2.S, March 2-April 21, 2021:
https://pubmed.ncbi.nlm.nih.gov/33929487/

383. Malignant cerebral infarction after vaccination with ChAdOx1 nCov-19: a catastrophic variant of vaccine-induced immune-mediated thrombotic thrombocytopenia:
https://pubmed.ncbi.nlm.nih.gov/34341358/

384. Acute ischemic stroke revealing immune thrombotic thrombocytopenia induced by ChAdOx1 nCov-19 vaccine: impact on recanalization strategy:
https://pubmed.ncbi.nlm.nih.gov/34175640/

385. Vaccine-induced immune thrombotic immune thrombocytopenia (VITT): a new clinicopathologic entity with heterogeneous clinical presentations:
https://pubmed.ncbi.nlm.nih.gov/34159588/

386. Imaging and hematologic findings in thrombosis and thrombocytopenia after vaccination with ChAdOx1 nCoV-19 (AstraZeneca):
https://pubmed.ncbi.nlm.nih.gov/34402666/

387. Autoimmunity roots of thrombotic events after vaccination with COVID-19:
https://pubmed.ncbi.nlm.nih.gov/34508917/

388. Cerebral venous sinus thrombosis after vaccination: the UK experience:
https://pubmed.ncbi.nlm.nih.gov/34370974/

389. Massive cerebral venous thrombosis and venous basin infarction as late complications of COVID-19: a case report:
https://pubmed.ncbi.nlm.nih.gov/34373991/

390. Australian and New Zealand approach to the diagnosis and treatment of vaccine-induced immune thrombosis and immune thrombocytopenia:
https://pubmed.ncbi.nlm.nih.gov/34490632/

391. An observational study to identify the prevalence of thrombocytopenia and anti-PF4 / polyanion antibodies in Norwegian health care workers after COVID-19 vaccination:
https://pubmed.ncbi.nlm.nih.gov/33909350/

392. Acute transverse myelitis (ATM): clinical review of 43 patients with COVID-19-associated ATM and 3 serious adverse events of post-vaccination ATM with ChAdOx1 nCoV-19 (AZD1222) vaccine:
https://pubmed.ncbi.nlm.nih.gov/33981305/

393. A case of acute demyelinating polyradiculoneuropathy with bilateral facial palsy after ChAdOx1 nCoV-19 vaccine:.
https://pubmed.ncbi.nlm.nih.gov/34272622/

394. Thrombocytopenia with acute ischemic stroke and hemorrhage in a patient recently vaccinated with an adenoviral vector-based COVID-19 vaccine:.
https://pubmed.ncbi.nlm.nih.gov/33877737/

395. Predicted and observed incidence of thromboembolic events among Koreans vaccinated with the ChAdOx1 nCoV-19 vaccine:
https://pubmed.ncbi.nlm.nih.gov/34254476/

396. First dose of ChAdOx1 and BNT162b2 COVID-19 vaccines and thrombocytopenic, thromboembolic, and hemorrhagic events in Scotland:
https://pubmed.ncbi.nlm.nih.gov/34108714/

397. ChAdOx1 nCoV-19 vaccine-associated thrombocytopenia: three cases of immune thrombocytopenia after 107,720 doses of ChAdOx1 vaccination in Thailand:
https://pubmed.ncbi.nlm.nih.gov/34483267/

398. Pulmonary embolism, transient ischemic attack, and thrombocytopenia after Johnson & Johnson COVID-19 vaccine:
https://pubmed.ncbi.nlm.nih.gov/34261635/

399. Neurosurgical considerations with respect to decompressive craniectomy for intracerebral hemorrhage after SARS-CoV-2 vaccination in vaccine-induced thrombotic thrombocytopenia-VITT:
https://pubmed.ncbi.nlm.nih.gov/34202817/

400. Large hemorrhagic stroke after vaccination against ChAdOx1 nCoV-19: a case report:
https://pubmed.ncbi.nlm.nih.gov/34273119/

401. Polyarthralgia and myalgia syndrome after vaccination with ChAdOx1 nCOV-19:
https://pubmed.ncbi.nlm.nih.gov/34463066/

402. A rare case of thrombosis and thrombocytopenia of the superior ophthalmic vein after ChAdOx1 nCoV-19 vaccination against SARS-CoV-2:
https://pubmed.ncbi.nlm.nih.gov/34276917/

403. Thrombosis and severe acute respiratory syndrome Coronavirus 2 vaccines: vaccine-induced immune thrombotic thrombocytopenia:
https://pubmed.ncbi.nlm.nih.gov/34237213/

404. Renal vein thrombosis and pulmonary embolism secondary to vaccine-induced thrombotic immune thrombocytopenia (VITT):
https://pubmed.ncbi.nlm.nih.gov/34268278/

405. Limb ischemia and pulmonary artery thrombosis after ChAdOx1 nCoV-19 vaccine (Oxford-AstraZeneca): a case of vaccine-induced immune thrombotic thrombocytopenia:
https://pubmed.ncbi.nlm.nih.gov/33990339/

406. Association between ChAdOx1 nCoV-19 vaccination and bleeding episodes: large population-based cohort study:
https://pubmed.ncbi.nlm.nih.gov/34479760/

407. Secondary thrombocytopenia after SARS-CoV-2 vaccination: case report of haemorrhage and hematoma after minor oral surgery:
https://pubmed.ncbi.nlm.nih.gov/34314875/

408. Venous thromboembolism and mild thrombocytopenia after vaccination with ChAdOx1 nCoV-19:
https://pubmed.ncbi.nlm.nih.gov/34384129/

409. Fatal exacerbation of ChadOx1-nCoV-19-induced thrombotic thrombocytopenia syndrome after successful initial therapy with intravenous immunoglobulins: a rationale for monitoring immunoglobulin G levels:
https://pubmed.ncbi.nlm.nih.gov/34382387/

410. A case of ANCA-associated vasculitis after AZD1222 (Oxford-AstraZeneca) SARS-CoV-2 vaccination: victim or causality?:
https://pubmed.ncbi.nlm.nih.gov/34416184/

411. Intracerebral hemorrhage associated with vaccine-induced thrombotic thrombocytopenia after ChAdOx1 nCOVID-19 vaccination in a pregnant woman:
https://pubmed.ncbi.nlm.nih.gov/34261297/

412. Massive cerebral venous thrombosis due to vaccine-induced immune thrombotic thrombocytopenia:
https://pubmed.ncbi.nlm.nih.gov/34261296/

413. Nephrotic syndrome after ChAdOx1 nCoV-19 vaccine against SARScoV-2:
https://pubmed.ncbi.nlm.nih.gov/34250318/

414. A case of vaccine-induced immune-immune thrombotic thrombocytopenia with massive arteriovenous thrombosis:
https://pubmed.ncbi.nlm.nih.gov/34059191/

415. Cutaneous thrombosis associated with cutaneous necrosis following Oxford-AstraZeneca COVID-19 vaccination:
https://pubmed.ncbi.nlm.nih.gov/34189756/

416. Thrombocytopenia in an adolescent with sickle cell anemia after COVID-19 vaccination:
https://pubmed.ncbi.nlm.nih.gov/34331506/

417. Vaccine-induced thrombocytopenia with severe headache:
https://pubmed.ncbi.nlm.nih.gov/34525282/

418. Myocarditis associated with SARS-CoV-2 mRNA vaccination in children aged 12 to 17 years: stratified analysis of a national database:
https://www.medrxiv.org/content/10.1101/2021.08.30.21262866v1

419. COVID-19 mRNA vaccination and development of CMR-confirmed myopericarditis:
https://www.medrxiv.org/content/10.1101/2021.09.13.21262182v1.full?s=09

420. Severe autoimmune hemolytic anemia after receipt of SARS-CoV-2 mRNA vaccine:
https://onlinelibrary.wiley.com/doi/10.1111/trf.16672

421. Intravenous injection of coronavirus disease 2019 (COVID-19) mRNA vaccine can induce acute myopericarditis in a mouse model:
https://t.co/j0IEM8cMXI

422. A report of myocarditis adverse events in the U.S. Vaccine Adverse Event Reporting System. (VAERS) in association with COVID-19 injectable biologics:
https://pubmed.ncbi.nlm.nih.gov/34601006/

423. This study concludes that: "The vaccine was associated with an excess risk of myocarditis (1 to 5 events per 100,000 persons). The risk of this potentially serious adverse event and of many other serious adverse events increased substantially after SARS-CoV-2 infection":
https://www.nejm.org/doi/full/10.1056/NEJMoa2110475

424. Bilateral uveitis after inoculation with COVID-19 vaccine: a case report:
https://www.sciencedirect.com/science/article/pii/S1201971221007797

425. Myocarditis associated with SARS-CoV-2 mRNA vaccination in children aged 12 to 17 years: stratified analysis of a national database:
https://www.medrxiv.org/content/10.1101/2021.08.30.21262866v1

426. Immune-mediated hepatitis with the Moderna vaccine is no longer a coincidence but confirmed:
https://www.sciencedirect.com/science/article/pii/S0168827821020936

427. Extensive investigations revealed consistent pathophysiologic alterations after vaccination with COVID-19 vaccines:
https://www.nature.com/articles/s41421-021-00329-3

428. Lobar hemorrhage with ventricular rupture shortly after the first dose of an mRNA-based SARS-CoV-2 vaccine:
https://www.ncbi.nlm.nih.gov/labs/pmc/articles/PMC8553377/

429. Mrna COVID vaccines dramatically increase endothelial inflammatory markers and risk of Acute Coronary Syndrome as measured by PULS cardiac testing: a caution:
https://www.ahajournals.org/doi/10.1161/circ.144.suppl_1.10712

430. ChAdOx1 interacts with CAR and PF4 with implications for thrombosis with thrombocytopenia syndrome:
https://www.science.org/doi/10.1126/sciadv.abl8213

431. Lethal vaccine-induced immune thrombotic immune thrombocytopenia (VITT) following announcement 26.COV2.S: first documented case outside the U.S.:
https://pubmed.ncbi.nlm.nih.gov/34626338/

432. A prothrombotic thrombocytopenic disorder resembling heparin-induced thrombocytopenia after coronavirus-19 vaccination:
https://europepmc.org/article/PPR/PPR304469435

433. VITT (vaccine-induced immune thrombotic thrombocytopenia) after vaccination with ChAdOx1 nCoV-19:
https://pubmed.ncbi.nlm.nih.gov/34731555/

434. Vaccine-induced immune thrombotic thrombocytopenia (VITT): a new clinicopathologic entity with heterogeneous clinical presentations:
https://pubmed.ncbi.nlm.nih.gov/34159588/

435. Treatment of acute ischemic stroke associated with ChAdOx1 nCoV-19 vaccine-induced immune thrombotic thrombocytopenia:
https://pubmed.ncbi.nlm.nih.gov/34461442/

436. Spectrum of neurological complications after COVID-19 vaccination:
https://pubmed.ncbi.nlm.nih.gov/34719776/

437. Cerebral venous sinus thrombosis after vaccination: the UK experience:
https://pubmed.ncbi.nlm.nih.gov/34370974/

438. Cerebral venous vein/venous sinus thrombosis w/thrombocytopenia syndrome after Covid-19 vaccination:
https://pubmed.ncbi.nlm.nih.gov/34373413/

439. Portal vein thrombosis due to vaccine-induced immune thrombotic immune thrombocytopenia (VITT) after Covid vaccination with ChAdOx1 nCoV-19:
https://pubmed.ncbi.nlm.nih.gov/34598301/

440. Hematuria, a generalized petechial rash and headaches after Oxford AstraZeneca ChAdOx1 nCoV-19 vaccination:
https://pubmed.ncbi.nlm.nih.gov/34620638/

441. Myocardial infarction and azygos vein thrombosis after vaccination with ChAdOx1 nCoV-19 in a hemodialysis patient:
https://pubmed.ncbi.nlm.nih.gov/34650896/

442. Takotsubo (stress) cardiomyopathy after vaccination with ChAdOx1 nCoV-19:
https://pubmed.ncbi.nlm.nih.gov/34625447/

443. Humoral response induced by Prime-Boost vaccination with ChAdOx1 nCoV-19 and BNT162b2 mRNA vaccines in a patient with multiple sclerosis treated with teriflunomide:
https://pubmed.ncbi.nlm.nih.gov/34696248/

444. Guillain-Barré syndrome after ChAdOx1 nCoV-19 COVID-19 vaccination: a case series:
https://pubmed.ncbi.nlm.nih.gov/34548920/

445. Refractory vaccine-induced immune thrombotic thrombocytopenia (VITT) treated with delayed therapeutic plasma exchange (TPE):
https://pubmed.ncbi.nlm.nih.gov/34672380/

446. Rare case of COVID-19 vaccine-associated intracranial hemorrhage with venous sinus thrombosis:
https://pubmed.ncbi.nlm.nih.gov/34556531/

447. Delayed headache after COVID-19 vaccination: a warning sign for vaccine-induced cerebral venous thrombosis:
https://pubmed.ncbi.nlm.nih.gov/34535076/

448. Clinical features of vaccine-induced thrombocytopenia and immune thrombosis:
https://pubmed.ncbi.nlm.nih.gov/34379914/

449. Predictors of mortality in thrombotic thrombocytopenia after adenoviral COVID-19 vaccination: the FAPIC score:
https://pubmed.ncbi.nlm.nih.gov/34545400/

450. Ischemic stroke as a presenting feature of immune thrombotic thrombocytopenia induced by ChAdOx1-nCoV-19 vaccination:
https://pubmed.ncbi.nlm.nih.gov/34035134/

451. In-hospital observational study of neurological disorders in patients recently vaccinated with COVID-19 mRNA vaccines:
https://pubmed.ncbi.nlm.nih.gov/34688190/

452. Endovascular treatment for vaccine-induced cerebral venous sinus thrombosis and thrombocytopenia after vaccination with ChAdOx1 nCoV-19: report of three cases:
https://pubmed.ncbi.nlm.nih.gov/34782400/

453. Cardiovascular, neurological, and pulmonary events after vaccination with BNT162b2, ChAdOx1 nCoV-19, and Ad26.COV2.S vaccines: an analysis of European data:
https://pubmed.ncbi.nlm.nih.gov/34710832/

454. Cerebral venous thrombosis developing after vaccination. COVID-19: VITT, VATT, TTS and more:
https://pubmed.ncbi.nlm.nih.gov/34695859/

455. Cerebral venous thrombosis and myeloproliferative neoplasms: a three-center study of 74 consecutive cases:
https://pubmed.ncbi.nlm.nih.gov/34453762/

456. Possible triggers of thrombocytopenia and/or hemorrhage by BNT162b2 vaccine, Pfizer-BioNTech:
https://pubmed.ncbi.nlm.nih.gov/34660652/

457. Multiple sites of arterial thrombosis in a 35-year-old patient after vaccination with ChAdOx1 (AstraZeneca), which required emergency femoral and carotid surgical thrombectomy:
https://pubmed.ncbi.nlm.nih.gov/34644642/

458. Case series of vaccine-induced thrombotic thrombocytopenia in a London teaching hospital:
https://pubmed.ncbi.nlm.nih.gov/34694650/

459. Neuro-ophthalmic complications with thrombocytopenia and thrombosis induced by ChAdOx1 nCoV-19 vaccine:
https://pubmed.ncbi.nlm.nih.gov/34726934/

460. Thrombotic events after COVID-19 vaccination in over 50 years of age: results of a population-based study in Italy:
https://pubmed.ncbi.nlm.nih.gov/34835237/

461. Intracerebral hemorrhage associated with vaccine-induced thrombotic thrombocytopenia after ChAdOx1 nCOVID-19 vaccination in a pregnant woman:
https://pubmed.ncbi.nlm.nih.gov/34261297/

462. Age- and sex-specific incidence of cerebral venous sinus thrombosis associated with Ad26.COV2.S COVID-19 vaccination:
https://pubmed.ncbi.nlm.nih.gov/34724036/

463. Genital necrosis with cutaneous thrombosis following vaccination with COVID-19 mRNA:
https://pubmed.ncbi.nlm.nih.gov/34839563/

464. Cerebral venous sinus thrombosis after mRNA-based COVID-19 vaccination:
https://pubmed.ncbi.nlm.nih.gov/34783932/

465. COVID-19 vaccine-induced immune thrombosis with thrombocytopenia thrombosis (VITT) and shades of gray in thrombus formation:
https://pubmed.ncbi.nlm.nih.gov/34624910/

466. Inflammatory myositis after vaccination with ChAdOx1:
https://pubmed.ncbi.nlm.nih.gov/34585145/

467. Acute ST-segment elevation myocardial infarction secondary to vaccine-induced immune thrombosis with thrombocytopenia (VITT):
https://pubmed.ncbi.nlm.nih.gov/34580132/

468. A rare case of COVID-19 vaccine-induced thrombotic thrombocytopenia (VITT) affecting the venos-planchnic and pulmonary arterial circulation from a UK district general hospital:
https://pubmed.ncbi.nlm.nih.gov/34535492/

469. COVID-19 vaccine-induced thrombotic thrombocytopenia: a case series:
https://pubmed.ncbi.nlm.nih.gov/34527501/

470. Thrombosis w/thrombocytopenia syndrome after vaccination w/AstraZeneca ChAdOx1 nCoV-19 (AZD1222) Covid-19: a risk-benefit analysis for persons <60% years in Australia:
https://pubmed.ncbi.nlm.nih.gov/34272095/

471. Immune thrombocytopenia after immunization with Vaxzevria ChadOx1-S vaccine (AstraZeneca), Victoria, Australia:
https://pubmed.ncbi.nlm.nih.gov/34756770/

472. Characteristics and outcomes of patients with cerebral venous sinus thrombosis in thrombotic immune thrombocytopenia induced by SARS-CoV-2 vaccine:
https://jamanetwork.com/journals/jamaneurology/fullarticle/2784622

473. Case study of thrombosis and thrombocytopenia syndrome after administration of the AstraZeneca COVID-19 vaccine:
https://pubmed.ncbi.nlm.nih.gov/34781321/

474. Thrombosis with Thrombocytopenia Syndrome Associated with COVID-19 Vaccines:
https://pubmed.ncbi.nlm.nih.gov/34062319/

475. Cerebral venous sinus thrombosis following vaccination with ChAdOx1: the first case of definite thrombosis with thrombocytopenia syndrome in India:
https://pubmed.ncbi.nlm.nih.gov/34706921/

476. COVID-19 vaccine-associated thrombosis with thrombocytopenia syndrome (TTS): systematic review and post hoc analysis:
https://pubmed.ncbi.nlm.nih.gov/34698582/

477. Case report of immune thrombocytopenia after vaccination with ChAdOx1 nCoV-19:
https://pubmed.ncbi.nlm.nih.gov/34751013/

478. Acute transverse myelitis after COVID-19 vaccination:
https://pubmed.ncbi.nlm.nih.gov/34684047/

479. Concerns for adverse effects of thrombocytopenia and thrombosis after adenovirus-vectored COVID-19 vaccination:
https://pubmed.ncbi.nlm.nih.gov/34541935/

480. Major hemorrhagic stroke after ChAdOx1 nCoV-19 vaccination: a case report:
https://pubmed.ncbi.nlm.nih.gov/34273119/

481. Cerebral venous sinus thrombosis after COVID-19 vaccination: neurologic and radiologic management:
https://pubmed.ncbi.nlm.nih.gov/34327553/

482. Thrombocytopenia with acute ischemic stroke and hemorrhage in a patient recently vaccinated with an adenoviral vector-based COVID-19 vaccine:
https://pubmed.ncbi.nlm.nih.gov/33877737/

483. Intracerebral hemorrhage and thrombocytopenia after AstraZeneca COVID-19 vaccine: clinical and diagnostic challenges of vaccine-induced thrombotic thrombocytopenia:
https://pubmed.ncbi.nlm.nih.gov/34646685/

484. Minimal change disease with severe acute kidney injury after Oxford-AstraZeneca COVID-19 vaccine: case report:
https://pubmed.ncbi.nlm.nih.gov/34242687/

485. Case report: cerebral sinus vein thrombosis in two patients with AstraZeneca SARS-CoV-2 vaccine:
https://pubmed.ncbi.nlm.nih.gov/34609603/

486. Case report: Pityriasis rosea-like rash after vaccination with COVID-19:
https://pubmed.ncbi.nlm.nih.gov/34557507/

487. Extensive longitudinal transverse myelitis after ChAdOx1 nCOV-19 vaccine: case report:
https://pubmed.ncbi.nlm.nih.gov/34641797/

488. Acute eosinophilic pneumonia associated with anti-COVID-19 vaccine AZD1222:
https://pubmed.ncbi.nlm.nih.gov/34812326/

489. Thrombocytopenia, including immune thrombocytopenia after receiving COVID-19 mRNA vaccines reported to the Vaccine Adverse Event Reporting System (VAERS):
https://pubmed.ncbi.nlm.nih.gov/34006408/

490. A case of ANCA-associated vasculitis after AZD1222 (Oxford-AstraZeneca) SARS-CoV-2 vaccination: victim or causality?:
https://pubmed.ncbi.nlm.nih.gov/34416184/

491. Vaccine-induced immune thrombosis and thrombocytopenia syndrome after adenovirus-vectored severe acute respiratory syndrome coronavirus 2 vaccination: a new hypothesis on mechanisms and implications for future vaccine development:
https://pubmed.ncbi.nlm.nih.gov/34664303/

492. Thrombosis in peripheral artery disease and thrombotic thrombocytopenia following adenoviral COVID-19 vaccination:
https://pubmed.ncbi.nlm.nih.gov/34649281/

493. Newly diagnosed immune thrombocytopenia in a pregnant patient after coronavirus disease 2019 vaccination:
https://pubmed.ncbi.nlm.nih.gov/34420249/

494. Cerebral venous sinus thrombosis and thrombotic events after vector-based COVID-19 vaccines: systematic review and meta-analysis:
https://pubmed.ncbi.nlm.nih.gov/34610990/

495. Sweet's syndrome after Oxford-AstraZeneca COVID-19 vaccine (AZD1222) in an elderly woman:
https://pubmed.ncbi.nlm.nih.gov/34590397/

496. Sudden sensorineural hearing loss after COVID-19 vaccination:
https://pubmed.ncbi.nlm.nih.gov/34670143/

497. Prevalence of serious adverse events among health care professionals after receiving the first dose of ChAdOx1 nCoV-19 coronavirus vaccine (Covishield) in Togo, March 2021:
https://pubmed.ncbi.nlm.nih.gov/34819146/

498. Acute hemichorea-hemibalismus after COVID-19 (AZD1222) vaccination:
https://pubmed.ncbi.nlm.nih.gov/34581453/

499. Recurrence of alopecia areata after covid-19 vaccination: a report of three cases in Italy:
https://pubmed.ncbi.nlm.nih.gov/34741583/

500. Shingles-like skin lesion after vaccination with AstraZeneca for COVID-19: a case report:
https://pubmed.ncbi.nlm.nih.gov/34631069/

501. Thrombosis after COVID-19 vaccination: possible link to ACE pathways:
https://pubmed.ncbi.nlm.nih.gov/34479129/

502. Thrombocytopenia in an adolescent with sickle cell anemia after COVID-19 vaccination:
https://pubmed.ncbi.nlm.nih.gov/34331506/

503. Leukocytoclastic vasculitis as a cutaneous manifestation of ChAdOx1 corona virus vaccine nCoV-19 (recombinant):
https://pubmed.ncbi.nlm.nih.gov/34546608/

504. Abdominal pain and bilateral adrenal hemorrhage from immune thrombotic thrombocytopenia induced by COVID-19 vaccine:
https://pubmed.ncbi.nlm.nih.gov/34546343/

505. Longitudinally extensive cervical myelitis after vaccination with inactivated virus based COVID-19 vaccine:
https://pubmed.ncbi.nlm.nih.gov/34849183/

506. Induction of cutaneous leukocytoclastic vasculitis after ChAdOx1 nCoV-19 vaccine:
https://pubmed.ncbi.nlm.nih.gov/34853744/

507. A case of toxic epidermal necrolysis after vaccination with ChAdOx1 nCoV-19 (AZD1222):
https://pubmed.ncbi.nlm.nih.gov/34751429/

508. Ocular adverse events following COVID-19 vaccination: https://pubmed.ncbi.nlm.nih.gov/34559576/
509. Depression after ChAdOx1-S / nCoV-19 vaccination:
https://pubmed.ncbi.nlm.nih.gov/34608345/

510. Venous thromboembolism and mild thrombocytopenia after ChAdOx1 nCoV-19 vaccination:
https://pubmed.ncbi.nlm.nih.gov/34384129/

511. Recurrent ANCA-associated vasculitis after Oxford AstraZeneca ChAdOx1-S COVID-19 vaccination: a case series of two patients:
https://pubmed.ncbi.nlm.nih.gov/34755433/

512. Major artery thrombosis and vaccination against ChAdOx1 nCov-19:
https://pubmed.ncbi.nlm.nih.gov/34839830/

513. Rare case of contralateral supraclavicular lymphadenopathy after vaccination with COVID-19: computed tomography and ultrasound findings:
https://pubmed.ncbi.nlm.nih.gov/34667486/

514. Cutaneous lymphocytic vasculitis after administration of the second dose of AZD1222 (Oxford-AstraZeneca) Severe acute respiratory syndrome Coronavirus 2 vaccine: chance or causality:
https://pubmed.ncbi.nlm.nih.gov/34726187/

515. Pancreas allograft rejection after ChAdOx1 nCoV-19 vaccine:
https://pubmed.ncbi.nlm.nih.gov/34781027/

516. Understanding the risk of thrombosis with thrombocytopenia syndrome following Ad26.COV2.S vaccination:
https://pubmed.ncbi.nlm.nih.gov/34595694/

517. Cutaneous adverse reactions of 35,229 doses of COVID-19 Sinovac and AstraZeneca vaccine COVID-19: a prospective cohort study in health care workers:
https://pubmed.ncbi.nlm.nih.gov/34661934/

518. Comments on thrombosis after vaccination: spike protein leader sequence could be responsible for thrombosis and antibody-mediated thrombocytopenia:
https://pubmed.ncbi.nlm.nih.gov/34788138

519. Eosinophilic dermatosis after AstraZeneca COVID-19 vaccination:
https://pubmed.ncbi.nlm.nih.gov/34753210/

520. Severe immune thrombocytopenia following COVID-19 vaccination: report of four cases and review of the literature:
https://pubmed.ncbi.nlm.nih.gov/34653943/

521. Relapse of immune thrombocytopenia after COVID-19 vaccination:
https://pubmed.ncbi.nlm.nih.gov/34591991/

522. Thrombosis in pre- and post-vaccination phase of COVID-19;
https://pubmed.ncbi.nlm.nih.gov/34650382/

523. A look at the role of postmortem immunohistochemistry in understanding the inflammatory pathophysiology of COVID-19 disease and vaccine-related thrombotic adverse events: a narrative review:
https://pubmed.ncbi.nlm.nih.gov/34769454/

524. COVID-19 vaccine in patients with hypercoagulability disorders: a clinical perspective:
https://pubmed.ncbi.nlm.nih.gov/34786893/

525. Vaccine-associated thrombocytopenia and thrombosis: venous endotheliopathy leading to combined venous micro-macrothrombosis:
https://pubmed.ncbi.nlm.nih.gov/34833382/

526. Thrombosis and thrombocytopenia syndrome causing isolated symptomatic carotid occlusion after COVID-19 Ad26.COV2.S vaccine (Janssen):
https://pubmed.ncbi.nlm.nih.gov/34670287/

527. An unusual presentation of acute deep vein thrombosis after Modern COVID-19 vaccine: case report:
https://pubmed.ncbi.nlm.nih.gov/34790811/

528. Immediate high-dose intravenous immunoglobulins followed by direct treatment with thrombin inhibitors is crucial for survival in vaccine-induced immune thrombotic thrombocytopenia Sars-Covid-19-vector adenoviral VITT with venous thrombosis of the cerebral sinus and portal vein:
https://pubmed.ncbi.nlm.nih.gov/34023956/

529. Thrombosis formation after COVID-19 vaccination immunologic aspects: review article:
https://pubmed.ncbi.nlm.nih.gov/34629931/

530. Imaging and hematologic findings in thrombosis and thrombocytopenia after vaccination with ChAdOx1 nCoV-19 (AstraZeneca):
https://pubmed.ncbi.nlm.nih.gov/34402666/

531. Spectrum of neuroimaging findings in post-CoVID-19 vaccination: a case series and review of the literature:
https://pubmed.ncbi.nlm.nih.gov/34842783/

532. Cerebral venous sinus thrombosis, pulmonary embolism, and thrombocytopenia after COVID-19 vaccination in a Taiwanese man: a case report and review of the literature:
https://pubmed.ncbi.nlm.nih.gov/34630307/

533. Fatal cerebral venous sinus thrombosis after COVID-19 vaccination:
https://pubmed.ncbi.nlm.nih.gov/33983464/

534. Autoimmune roots of thrombotic events after COVID-19 vaccination:
https://pubmed.ncbi.nlm.nih.gov/34508917/

535. New portal vein thrombosis in cirrhosis: is thrombophilia exacerbated by vaccine or COVID-19:
https://www.jcehepatology.com/article/S0973-6883(21)00545-4/fulltext

536. Images of immune thrombotic thrombocytopenia induced by Oxford / AstraZeneca® COVID-19 vaccine:
https://pubmed.ncbi.nlm.nih.gov/33962903/

537. Cerebral venous sinus thrombosis after vaccination with COVID-19 mRNA of BNT162b2:
https://pubmed.ncbi.nlm.nih.gov/34796065/

538. Increased risk of urticaria/angioedema after BNT162b2 mRNA COVID-19 vaccination in health care workers taking ACE inhibitors:
https://pubmed.ncbi.nlm.nih.gov/34579248/

539. A case of unusual mild clinical presentation of COVID-19 vaccine-induced immune thrombotic thrombocytopenia with splanchnic vein thrombosis:
https://pubmed.ncbi.nlm.nih.gov/34843991/

540. Cerebral venous sinus thrombosis following vaccination with Pfizer-BioNTech COVID-19 (BNT162b2):
https://pubmed.ncbi.nlm.nih.gov/34595867/

541. A case of idiopathic thrombocytopenic purpura after a booster dose of COVID-19 BNT162b2 vaccine (Pfizer-Biontech):
https://pubmed.ncbi.nlm.nih.gov/34820240/

542. Vaccine-induced immune thrombotic immune thrombocytopenia (VITT): targeting pathologic mechanisms with Bruton's tyrosine kinase inhibitors:
https://pubmed.ncbi.nlm.nih.gov/33851389/

543. Thrombotic thrombocytopenic purpura after vaccination with Ad26.COV2-S:
https://pubmed.ncbi.nlm.nih.gov/33980419/

544. Thromboembolic events in younger females exposed to Pfizer-BioNTech or Moderna COVID-19 vaccines:
https://pubmed.ncbi.nlm.nih.gov/34264151/

545. Potential risk of thrombotic events after COVID-19 vaccination with Oxford-AstraZeneca in women receiving estrogen:
https://pubmed.ncbi.nlm.nih.gov/34734086/

546. Thrombosis after adenovirus-vectored COVID-19 vaccination: a concern for underlying disease:
https://pubmed.ncbi.nlm.nih.gov/34755555/

547. Adenovirus interactions with platelets and coagulation and vaccine-induced immune thrombotic thrombocytopenia syndrome:
https://pubmed.ncbi.nlm.nih.gov/34407607/

548. Thrombotic thrombocytopenic purpura: a new threat after COVID bnt162b2 vaccine:
https://pubmed.ncbi.nlm.nih.gov/34264514/

549. Unusual site of deep vein thrombosis after vaccination against coronavirus mRNA-2019 coronavirus disease (COVID-19):
https://pubmed.ncbi.nlm.nih.gov/34840204/

550. Neurological side effects of SARS-CoV-2 vaccines:
https://pubmed.ncbi.nlm.nih.gov/34750810/

551. Coagulopathies after SARS-CoV-2 vaccination may derive from a combined effect of SARS-CoV-2 spike protein and adenovirus vector-activated signaling pathways:
https://pubmed.ncbi.nlm.nih.gov/34639132/

552. Isolated pulmonary embolism after COVID vaccination: 2 case reports and a review of acute pulmonary embolism complications and follow-up:
https://pubmed.ncbi.nlm.nih.gov/34804412/

553. Central retinal vein occlusion after vaccination with SARS-CoV-2 mRNA: case report:
https://pubmed.ncbi.nlm.nih.gov/34571653/

554. Complicated case report of long-term vaccine-induced thrombotic immune thrombocytopenia A:
https://pubmed.ncbi.nlm.nih.gov/34835275/

555. Deep venous thrombosis after vaccination with Ad26.COV2.S in adult males:
https://pubmed.ncbi.nlm.nih.gov/34659839/

556. Neurological autoimmune diseases after SARS-CoV-2 vaccination: a case series:
https://pubmed.ncbi.nlm.nih.gov/34668274/

557. Severe autoimmune hemolytic autoimmune anemia after receiving SARS-CoV-2 mRNA vaccine:
https://pubmed.ncbi.nlm.nih.gov/34549821/

558. Occurrence of COVID-19 variants among recipients of ChAdOx1 nCoV-19 vaccine (recombinant):
https://pubmed.ncbi.nlm.nih.gov/34528522/

559. Prevalence of thrombocytopenia, anti-platelet factor 4 antibodies, and elevated D-dimer in Thais after vaccination with ChAdOx1 nCoV-19:
https://pubmed.ncbi.nlm.nih.gov/34568726/

560. Epidemiology of acute myocarditis/pericarditis in Hong Kong adolescents after co-vaccination:
https://academic.oup.com/cid/advance-article-abstract/doi/10.1093/cid/ciab989/644 5179

561. Myocarditis after 2019 coronavirus disease mRNA vaccine: a case series and determination of incidence rate:
https://academic.oup.com/cid/advance-article/doi/10.1093/cid/ciab926/6420408

562. Myocarditis and pericarditis after COVID-19 vaccination: inequalities in age and vaccine types:
https://www.mdpi.com/2075-4426/11/11/1106

563. Epidemiology and clinical features of myocarditis/pericarditis before the introduction of COVID-19 mRNA vaccine in Korean children: a multicenter study:
https://pubmed.ncbi.nlm.nih.gov/34402230/

564. Shedding light on post-vaccination myocarditis and pericarditis in COVID-19 and non-COVID-19 vaccine recipients:
https://pubmed.ncbi.nlm.nih.gov/34696294/

565. Myocarditis Following mRNA COVID-19 Vaccine:
https://journals.lww.com/pec-online/Abstract/2021/11000/Myocarditis_Following_mRNA_COVID_19_Vaccine.9.aspx

566. Myocarditis following BNT162b2 mRNA Covid-19 mRNA vaccine in Israel:
https://pubmed.ncbi.nlm.nih.gov/34614328/

567. Myocarditis, pericarditis, and cardiomyopathy following COVID-19 vaccination:
https://www.heartlungcirc.org/article/S1443-9506(21)01156-2/fulltext

568. Myocarditis and other cardiovascular complications of COVID-19 mRNA-based COVID-19 vaccines:
https://pubmed.ncbi.nlm.nih.gov/34277198/

569. Possible Association Between COVID-19 Vaccine and Myocarditis: Clinical and CMR Findings:
https://pubmed.ncbi.nlm.nih.gov/34246586/

570. Hypersensitivity Myocarditis and COVID-19 Vaccines:
https://pubmed.ncbi.nlm.nih.gov/34856634/

571. Severe myocarditis associated with COVID-19 vaccine: zebra or unicorn?:
https://www.internationaljournalofcardiology.com/article/S0167-5273(21)01477-7/fulltext

572. Acute myocardial infarction and myocarditis after COVID-19 vaccination:
https://www.ncbi.nlm.nih.gov/labs/pmc/articles/PMC8522388/

573. Myocarditis after Covid-19 vaccination in a large healthcare organization:
https://www.nejm.org/doi/10.1056/NEJMoa2110737

574. Association of myocarditis with COVID-19 messenger RNA BNT162b2 vaccine in a case series of children:
https://jamanetwork.com/journals/jamacardiology/fullarticle/2783052

575. Clinical suspicion of myocarditis temporally related to COVID-19 vaccination in adolescents and young adults:
https://www.ahajournals.org/doi/abs/10.1161/CIRCULATIONAHA.121.056583?url_ver=Z39.88-2003&rfr_id=ori:rid:crossref.org&rfr_dat=cr_pub%20%200pubmed

576. STEMI mimicry: focal myocarditis in an adolescent patient after COVID-19 mRNA vaccination:.
https://pubmed.ncbi.nlm.nih.gov/34756746/

577. Myocarditis and pericarditis in association with COVID-19 mRNA vaccination: cases from a regional pharmacovigilance center:
https://www.ncbi.nlm.nih.gov/labs/pmc/articles/PMC8587334/

578. Myocarditis after COVID-19 mRNA vaccines:
https://pubmed.ncbi.nlm.nih.gov/34546329/

579. Patients with acute myocarditis after COVID-19 mRNA vaccination:.
https://jamanetwork.com/journals/jamacardiology/fullarticle/2781602

580. Myocarditis after COVID-19 vaccination: a case series:
https://www.sciencedirect.com/science/article/pii/S0264410X21011725?via%3Dihub

581. Myocarditis associated with COVID-19 vaccination in adolescents:
https://publications.aap.org/pediatrics/article/148/5/e2021053427/181357

582. Myocarditis findings on cardiac magnetic resonance imaging after vaccination with COVID-19 mRNA in adolescents:.
https://pubmed.ncbi.nlm.nih.gov/34704459/

583. Myocarditis after COVID-19 vaccination: magnetic resonance imaging study:
https://academic.oup.com/ehjcimaging/advance-article/doi/10.1093/ehjci/jeab230/6421640

584. Acute myocarditis after administration of the second dose of BNT162b2 COVID-19 vaccine:
https://www.ncbi.nlm.nih.gov/labs/pmc/articles/PMC8599115/

585. Myocarditis after COVID-19 vaccination:
https://www.sciencedirect.com/science/article/pii/S2352906721001603

586. Case report: probable myocarditis after Covid-19 mRNA vaccine in a patient with arrhythmogenic left ventricular cardiomyopathy:
https://pubmed.ncbi.nlm.nih.gov/34712717/

587. Acute myocarditis after administration of BNT162b2 vaccine against COVID-19:
https://www.revespcardiol.org/en-linkresolver-acute-myocarditis-after-administration-bnt162b2-S188558572100133X

588. Myocarditis associated with COVID-19 mRNA vaccination:
https://pubs.rsna.org/doi/10.1148/radiol.2021211430

589. Acute myocarditis after COVID-19 vaccination: a case report:
https://www.sciencedirect.com/science/article/pii/S0248866321007098

590. Acute myopericarditis after COVID-19 vaccination in adolescents:.
https://pubmed.ncbi.nlm.nih.gov/34589238/

591. Perimyocarditis in adolescents after Pfizer-BioNTech COVID-19 vaccination:
https://academic.oup.com/jpids/article/10/10/962/6329543

592. Acute myocarditis associated with anti-COVID-19 vaccination:
https://ecevr.org/DOIx.php?id=10.7774/cevr.2021.10.2.196

593. Myocarditis associated with COVID-19 vaccination: echocardiographic, cardiac CT, and MRI findings:.
https://pubmed.ncbi.nlm.nih.gov/34428917/

594. Acute symptomatic myocarditis in 7 adolescents after Pfizer-BioNTech COVID-19 vaccination:.
https://pubmed.ncbi.nlm.nih.gov/34088762/

595. Myocarditis and pericarditis in adolescents after first and second doses of COVID-19 mRNA vaccines:.
https://academic.oup.com/ehjqcco/advance-article/doi/10.1093/ehjqcco/qcab090/6442104

596. COVID 19 vaccine for adolescents. Concern for myocarditis and pericarditis:
https://www.mdpi.com/2036-7503/13/3/61

597. Cardiac imaging of acute myocarditis after vaccination with COVID-19 mRNA:
https://pubmed.ncbi.nlm.nih.gov/34402228/

598. Myocarditis temporally associated with COVID-19 vaccination:
https://pubmed.ncbi.nlm.nih.gov/34133885/

599. Acute myocardial injury after COVID-19 vaccination: a case report and review of current evidence from the vaccine adverse event reporting system database:
https://pubmed.ncbi.nlm.nih.gov/34219532/

600. Acute myocarditis associated with COVID-19 vaccination: report of a case:
https://www.ncbi.nlm.nih.gov/labs/pmc/articles/PMC8639400/

601. Myocarditis following vaccination with COVID-19 messenger RNA: a Japanese case series:
https://pubmed.ncbi.nlm.nih.gov/34840235/

602. Myocarditis in the setting of a recent COVID-19 vaccination:
https://pubmed.ncbi.nlm.nih.gov/34712497/

603. Acute myocarditis after a second dose of COVID-19 mRNA vaccine: report of two cases:
https://www.clinicalimaging.org/article/S0899-7071(21)00265-5/fulltext

604. Prevalence of thrombocytopenia, antiplatelet factor 4 antibodies, and elevated D-dimer in Thais after vaccination with ChAdOx1 nCoV-19:
https://pubmed.ncbi.nlm.nih.gov/34568726/

605. Epidemiology of acute myocarditis/pericarditis in Hong Kong adolescents after co-vaccination:
https://academic.oup.com/cid/advance-article-abstract/doi/10.1093/cid/ciab989/6445179

606. Myocarditis after 2019 coronavirus disease mRNA vaccine: a case series and incidence rate determination:
https://academic.oup.com/cid/advance-article/doi/10.1093/cid/ciab926/6420408

607. Myocarditis and pericarditis after COVID-19 vaccination: inequalities in age and vaccine types:
https://www.mdpi.com/2075-4426/11/11/1106

608. Epidemiology and clinical features of myocarditis/pericarditis before the introduction of COVID-19 mRNA vaccine in Korean children: a multicenter study:
https://pubmed.ncbi.nlm.nih.gov/34402230/

609. Shedding light on post-vaccination myocarditis and pericarditis in COVID-19 and non-COVID-19 vaccine recipients:
https://pubmed.ncbi.nlm.nih.gov/34696294/

610. Diffuse prothrombotic syndrome after administration of ChAdOx1 nCoV-19 vaccine: case report:
https://pubmed.ncbi.nlm.nih.gov/34615534/

611. Three cases of acute venous thromboembolism in women after coronavirus 2019 vaccination:
https://pubmed.ncbi.nlm.nih.gov/34352418/

612. Clinical and biological features of cerebral venous sinus thrombosis after vaccination w/ChAdOx1 nCov-19;
https://jnnp.bmj.com/content/early/2021/09/29/jnnp-2021-327340

613. COV2-S vaccination may reveal hereditary thrombophilia: massive cerebral venous sinus thrombosis in a young man with normal platelet count:
https://pubmed.ncbi.nlm.nih.gov/34632750/

614. Post-mortem findings in vaccine-induced thrombotic thrombocytopenia:
https://haematologica.org/article/view/haematol.2021.279075

615. COVID-19 vaccine-induced thrombosis:
https://pubmed.ncbi.nlm.nih.gov/34802488/

616. Inflammation and platelet activation after COVID-19 vaccines: possible mechanisms behind vaccine-induced immune thrombocytopenia and thrombosis:
https://pubmed.ncbi.nlm.nih.gov/34887867/

617. Anaphylactoid reaction and coronary thrombosis related to COVID-19 mRNA vaccine:
https://pubmed.ncbi.nlm.nih.gov/34863404/

618. Vaccine-induced cerebral venous thrombosis and thrombocytopenia. Oxford-AstraZeneca COVID-19: a missed opportunity for rapid return on experience:
https://www.sciencedirect.com/science/article/pii/S235255682100093X

619. Occurrence of splenic infarction due to arterial thrombosis after vaccination with COVID-19:
https://pubmed.ncbi.nlm.nih.gov/34876440/

620. Deep venous thrombosis more than two weeks after COVID-19 vaccination:
https://pubmed.ncbi.nlm.nih.gov/33928773/

621. Case report: Take a second look: Cerebral venous thrombosis related to Covid-19 vaccination and thrombotic thrombocytopenia syndrome:
https://pubmed.ncbi.nlm.nih.gov/34880826/

622. Information on ChAdOx1 nCoV-19 vaccine-induced immune-mediated thrombotic thrombocytopenia:
https://pubmed.ncbi.nlm.nih.gov/34587242/

623. Change in blood viscosity after COVID-19 vaccination: estimation for persons with underlying metabolic syndrome:
https://pubmed.ncbi.nlm.nih.gov/34868465/

624. Management of a patient with a rare congenital limb malformation syndrome after SARS-CoV-2 vaccine-induced thrombosis and thrombocytopenia (VITT):
https://pubmed.ncbi.nlm.nih.gov/34097311/

625. Bilateral thalamic stroke: a case of COVID-19 (VITT) vaccine-induced immune thrombotic thrombocytopenia or a coincidence due to underlying risk factors:
https://pubmed.ncbi.nlm.nih.gov/34820232/

626. Thrombocytopenia and splanchnic thrombosis after vaccination with Ad26.COV2.S successfully treated with transjugular intrahepatic intrahepatic portosystemic shunt and thrombectomy:
https://onlinelibrary.wiley.com/doi/10.1002/ajh.26258

627. Incidence of acute ischemic stroke after coronavirus vaccination in Indonesia: case series:
https://pubmed.ncbi.nlm.nih.gov/34579636/

628. Successful treatment of vaccine-induced immune immune thrombotic thrombocytopenia in a 26-year-old female patient:
https://pubmed.ncbi.nlm.nih.gov/34614491/

629. Case report: vaccine-induced immune immune thrombotic thrombocytopenia in a patient with pancreatic cancer after vaccination with messenger RNA-1273:
https://pubmed.ncbi.nlm.nih.gov/34790684/

630. Idiopathic idiopathic external jugular vein thrombophlebitis after coronavirus disease vaccination (COVID-19):
https://pubmed.ncbi.nlm.nih.gov/33624509/

631. Squamous cell carcinoma of the lung with hemoptysis following vaccination with tozinameran (BNT162b2, Pfizer-BioNTech):
https://pubmed.ncbi.nlm.nih.gov/34612003/

632. Vaccine-induced thrombotic thrombocytopenia after Ad26.COV2.S vaccination in a man presenting as acute venous thromboembolism:
https://pubmed.ncbi.nlm.nih.gov/34096082/

633. Myocarditis associated with COVID-19 vaccination in three adolescent boys:
https://pubmed.ncbi.nlm.nih.gov/34851078/

634. Cardiovascular magnetic resonance findings in young adult patients with acute myocarditis after COVID-19 mRNA vaccination: a case series:
https://pubmed.ncbi.nlm.nih.gov/34496880/

635. Perimyocarditis after vaccination with COVID-19:
https://pubmed.ncbi.nlm.nih.gov/34866957/

636. Epidemiology of acute myocarditis/pericarditis in Hong Kong adolescents after co-vaccination:
https://pubmed.ncbi.nlm.nih.gov/34849657/

637. Myocarditis-induced sudden death after BNT162b2 COVID-19 mRNA vaccination in Korea: case report focusing on histopathological findings:
https://pubmed.ncbi.nlm.nih.gov/34664804/

638. Acute myocarditis after vaccination with COVID-19 mRNA in adults aged 18 years or older:
https://pubmed.ncbi.nlm.nih.gov/34605853/

639. Recurrence of acute myocarditis temporally associated with receipt of the 2019 coronavirus mRNA disease vaccine (COVID-19) in an adolescent male:
https://pubmed.ncbi.nlm.nih.gov/34166671/

640. Young male with myocarditis after mRNA-1273 coronavirus disease-2019 (COVID-19) mRNA vaccination:
https://pubmed.ncbi.nlm.nih.gov/34744118/

641. Acute myocarditis after SARS-CoV-2 vaccination in a 24-year-old male:
https://pubmed.ncbi.nlm.nih.gov/34334935/

642. Ga-DOTATOC digital PET images of inflammatory cell infiltrates in myocarditis after vaccination with COVID-19:
https://pubmed.ncbi.nlm.nih.gov/34746968/

643. Occurrence of acute infarct-like myocarditis after vaccination with COVID-19: just an accidental coincidence or rather a vaccination-associated autoimmune myocarditis?":
https://pubmed.ncbi.nlm.nih.gov/34333695/

644. Self-limited myocarditis presenting with chest pain and ST-segment elevation in adolescents after vaccination with BNT162b2 mRNA vaccine:
https://pubmed.ncbi.nlm.nih.gov/34180390/

645. Myocarditis Following Immunization with COVID-19 mRNA Vaccines in Members of the U.S. Military:
https://pubmed.ncbi.nlm.nih.gov/34185045/

646. Myocarditis after BNT162b2 vaccination in a healthy male:
https://pubmed.ncbi.nlm.nih.gov/34229940/

647. Myopericarditis in a previously healthy adolescent male after COVID-19 vaccination: Case report:
https://pubmed.ncbi.nlm.nih.gov/34133825/

648. Acute myocarditis after SARS-CoV-2 mRNA-1273 mRNA vaccination:
https://pubmed.ncbi.nlm.nih.gov/34308326/

649. Chest pain with abnormal electrocardiogram redevelopment after injection of COVID-19 vaccine manufactured by Moderna:
https://pubmed.ncbi.nlm.nih.gov/34866106/

650. Biopsy-proven lymphocytic myocarditis after first vaccination with COVID-19 mRNA in a 40-year-old man: case report:
https://pubmed.ncbi.nlm.nih.gov/34487236/

651. Multimodality imaging and histopathology in a young man presenting with fulminant lymphocytic myocarditis and cardiogenic shock after vaccination with mRNA-1273:
https://pubmed.ncbi.nlm.nih.gov/34848416/

652. Report: a case of myopericarditis after vaccination w/BNT162b2 COVID-19 mRNA in a young Korean male:
https://pubmed.ncbi.nlm.nih.gov/34636504/

653. Acute myocarditis after Comirnaty vaccination in a healthy male with previous SARS-CoV-2 infection:
https://pubmed.ncbi.nlm.nih.gov/34367386/

654. Acute myocarditis in a young adult two days after vaccination with Pfizer:
https://pubmed.ncbi.nlm.nih.gov/34709227/

655. Case report: acute fulminant myocarditis and cardiogenic shock after messenger RNA coronavirus vaccination in 2019 requiring extracorporeal cardiopulmonary resuscitation:
https://pubmed.ncbi.nlm.nih.gov/34778411/

656. Acute myocarditis after 2019 coronavirus disease vaccination: https://pubmed.ncbi.nlm.nih.gov/34734821/
657. A series of patients with myocarditis after vaccination against SARS-CoV-2 with mRNA-1279 and BNT162b2:
https://pubmed.ncbi.nlm.nih.gov/34246585/

658. Myopericarditis after Pfizer messenger ribonucleic acid coronavirus coronavirus disease vaccine in adolescents:
https://pubmed.ncbi.nlm.nih.gov/34228985/

659. Post-vaccination multisystem inflammatory syndrome in adults without evidence of prior SARS-CoV-2 infection:
https://pubmed.ncbi.nlm.nih.gov/34852213/

660. Acute myocarditis defined after vaccination with 2019 mRNA of coronavirus disease:
https://pubmed.ncbi.nlm.nih.gov/34866122/

661. Biventricular systolic dysfunction in acute myocarditis after SARS-CoV-2 mRNA-1273 vaccination:
https://pubmed.ncbi.nlm.nih.gov/34601566/

662. Myocarditis following COVID-19 vaccination: MRI study:
https://pubmed.ncbi.nlm.nih.gov/34739045/

663. Acute myocarditis after COVID-19 vaccination: case report:
https://docs.google.com/document/d/1Hc4bh_qNbZ7UVm5BLxkRdMPnnI9zcCsl/e

664. Association of myocarditis with COVID-19 messenger RNA BNT162b2 vaccine COVID-19 in a case series of children:
https://pubmed.ncbi.nlm.nih.gov/34374740/

665. Clinical suspicion of myocarditis temporally related to COVID-19 vaccination in adolescents and young adults:
https://pubmed.ncbi.nlm.nih.gov/34865500/

666. Myocarditis following vaccination with Covid-19 in a large healthcare organization:
https://pubmed.ncbi.nlm.nih.gov/34614329/

667. AstraZeneca COVID-19 vaccine and Guillain-Barré syndrome in Tasmania: a causal link:
https://pubmed.ncbi.nlm.nih.gov/34560365/

668. COVID-19, Guillain-Barré and vaccineA dangerous mix:
https://pubmed.ncbi.nlm.nih.gov/34108736/

669. Guillain-Barré syndrome after the first dose of Pfizer-BioNTech COVID-19 vaccine: case report and review of reported cases:
https://pubmed.ncbi.nlm.nih.gov/34796417/

670. Guillain-Barre syndrome after BNT162b2 COVID-19 vaccine:
https://link.springer.com/article/10.1007%2Fs10072-021-05523-5

671. COVID-19 adenovirus vaccines and Guillain-Barré syndrome with facial palsy:
https://onlinelibrary.wiley.com/doi/10.1002/ana.26258

672. Association of receipt association of Ad26.COV2.S COVID-19 vaccine with presumed Guillain-Barre syndrome, February-July 2021:
https://jamanetwork.com/journals/jama/fullarticle/2785009

673. A case of Guillain-Barré syndrome after Pfizer COVID-19 vaccine:
https://pubmed.ncbi.nlm.nih.gov/34567447/

674. Guillain-Barré syndrome associated with COVID-19 vaccination:
https://pubmed.ncbi.nlm.nih.gov/34648420/

675. Rate of recurrent Guillain-Barré syndrome after COVID-19 BNT162b2 mRNA vaccine:
https://jamanetwork.com/journals/jamaneurology/fullarticle/2783708

676. Guillain-Barre syndrome after COVID-19 vaccination in an adolescent:
https://www.pedneur.com/article/S0887-8994(21)00221-6/fulltext

677. Guillain-Barre syndrome after ChAdOx1-S / nCoV-19 vaccination:
https://pubmed.ncbi.nlm.nih.gov/34114256/

678. Guillain-Barre syndrome after COVID-19 mRNA-1273 vaccine: case report:
https://pubmed.ncbi.nlm.nih.gov/34767184/

679. Guillain-Barre syndrome following SARS-CoV-2 vaccination in 19 patients:
https://pubmed.ncbi.nlm.nih.gov/34644738/

680. Guillain-Barre syndrome presenting with facial diplegia following vaccination with COVID-19 in two patients:
https://pubmed.ncbi.nlm.nih.gov/34649856/

681. A rare case of Guillain-Barré syndrome after COVID-19 vaccination:
https://pubmed.ncbi.nlm.nih.gov/34671572/

682. Neurological complications of COVID-19: Guillain-Barre syndrome after Pfizer COVID-19 vaccine:
https://pubmed.ncbi.nlm.nih.gov/33758714/

683. COVID-19 vaccine causing Guillain-Barre syndrome, an uncommon potential side effect:
https://pubmed.ncbi.nlm.nih.gov/34484780/

684. Guillain-Barre syndrome after the first dose of COVID-19 vaccination: case report;
https://pubmed.ncbi.nlm.nih.gov/34779385/

685. Miller Fisher syndrome after Pfizer COVID-19 vaccine:
https://pubmed.ncbi.nlm.nih.gov/34817727/

686. Miller Fisher syndrome after 2019 BNT162b2 mRNA coronavirus vaccination:
https://pubmed.ncbi.nlm.nih.gov/34789193/

687. Bilateral facial weakness with a variant of paresthesia of Guillain-Barre syndrome after Vaxzevria COVID-19 vaccine:
https://pubmed.ncbi.nlm.nih.gov/34261746/

688. Guillain-Barre syndrome after the first injection of ChAdOx1 nCoV-19 vaccine: first report:
https://pubmed.ncbi.nlm.nih.gov/34217513/

689. A case of sensory ataxic Guillain-Barre syndrome with immunoglobulin G anti-GM1 antibodies after first dose of COVID-19 BNT162b2 mRNA vaccine (Pfizer):
https://pubmed.ncbi.nlm.nih.gov/34871447/

690. Reporting of acute inflammatory neuropathies with COVID-19 vaccines: subgroup disproportionality analysis in VigiBase:
https://pubmed.ncbi.nlm.nih.gov/34579259/

691. A variant of Guillain-Barré syndrome after SARS-CoV-2 vaccination: AMSAN:
https://pubmed.ncbi.nlm.nih.gov/34370408/

692. A rare variant of Guillain-Barré syndrome after vaccination with Ad26.COV2.S:
https://pubmed.ncbi.nlm.nih.gov/34703690/

693. Guillain-Barré syndrome after SARS-CoV-2 vaccination in a patient with previous vaccine-associated Guillain-Barré syndrome:
https://pubmed.ncbi.nlm.nih.gov/34810163/

694. Guillain-Barré syndrome in an Australian state using mRNA and adenovirus-vector SARS-CoV-2 vaccines:
https://onlinelibrary.wiley.com/doi/10.1002/ana.26218

695. Acute transverse myelitis after SARS-CoV-2 vaccination: case report and review of the literature:
https://pubmed.ncbi.nlm.nih.gov/34482455/

696. Variant Guillain-Barré syndrome occurring after SARS-CoV-2 vaccination:
https://pubmed.ncbi.nlm.nih.gov/34114269/

697. Guillian-Barre syndrome with axonal variant temporally associated with Modern SARS-CoV-2 mRNA-based vaccine:
https://pubmed.ncbi.nlm.nih.gov/34722067/

698. Guillain-Barre syndrome after the first dose of SARS-CoV-2 vaccine: a temporary occurrence, not a causal association:
https://pubmed.ncbi.nlm.nih.gov/33968610/

699. SARS-CoV-2 vaccines can be complicated not only by Guillain-Barré syndrome but also by distal small fiber neuropathy:
https://pubmed.ncbi.nlm.nih.gov/34525410/

700. Clinical variant of Guillain-Barré syndrome with prominent facial diplegia after AstraZeneca 2019 coronavirus disease vaccine:
https://pubmed.ncbi.nlm.nih.gov/34808658/

701. Adverse event reporting and risk of Bell's palsy after COVID-19 vaccination:
https://www.thelancet.com/journals/laninf/article/PIIS1473-3099(21)00646-0/fulltext

702. Bilateral facial nerve palsy and COVID-19 vaccination: causality or coincidence:
https://pubmed.ncbi.nlm.nih.gov/34522557/

703. Left Bell's palsy after the first dose of mRNA-1273 SARS-CoV-2 vaccine: case report:
https://pubmed.ncbi.nlm.nih.gov/34763263/

704. Bell's palsy after inactivated vaccination with COVID-19 in a patient with a history of recurrent Bell's palsy: case report:
https://pubmed.ncbi.nlm.nih.gov/34621891/

705. Neurological complications after the first dose of COVID-19 vaccines and SARS-CoV-2 infection:
https://pubmed.ncbi.nlm.nih.gov/34697502/

706. Type I interferons as a potential mechanism linking COVID-19 mRNA vaccines with Bell's palsy:
https://pubmed.ncbi.nlm.nih.gov/33858693/

707. Acute transverse myelitis following inactivated COVID-19 vaccine:
https://pubmed.ncbi.nlm.nih.gov/34370410/

708. Acute transverse myelitis after COVID-19 vaccination:
https://pubmed.ncbi.nlm.nih.gov/34579245/

709. A case of longitudinally extensive transverse myelitis following Covid-19 vaccination:
https://pubmed.ncbi.nlm.nih.gov/34182207/

710. Post COVID-19 transverse myelitis; a case report with review of the literature:
https://pubmed.ncbi.nlm.nih.gov/34457267/

711. Beware of neuromyelitis optica spectrum disorder after vaccination with inactivated virus for COVID-19:
https://pubmed.ncbi.nlm.nih.gov/34189662/

712. Neuromyelitis optica in a healthy woman after vaccination against severe acute respiratory syndrome coronavirus 2 mRNA-1273:
https://pubmed.ncbi.nlm.nih.gov/34660149/

713. Acute bilateral bilateral optic neuritis/chiasm with longitudinal extensive transverse myelitis in long-standing stable multiple sclerosis after vector-based vaccination against SARS-CoV-2:
https://pubmed.ncbi.nlm.nih.gov/34131771/

714. A case series of acute pericarditis after vaccination with COVID-19 in the context of recent reports from Europe and the United States:
https://pubmed.ncbi.nlm.nih.gov/34635376/

715. Acute pericarditis and cardiac tamponade after vaccination with Covid-19:
https://pubmed.ncbi.nlm.nih.gov/34749492/

716. Myocarditis and pericarditis in adolescents after the first and second doses of COVID-19 mRNA vaccines:
https://pubmed.ncbi.nlm.nih.gov/34849667/

717. Perimyocarditis in adolescents after Pfizer-BioNTech COVID-19 vaccine:
https://pubmed.ncbi.nlm.nih.gov/34319393/

718. Acute myopericarditis after COVID-19 vaccine in adolescents:
https://pubmed.ncbi.nlm.nih.gov/34589238/

719. Pericarditis after administration of the BNT162b2 mRNA vaccine COVID-19:
https://pubmed.ncbi.nlm.nih.gov/34149145/

720. Case report: symptomatic pericarditis post COVID-19 vaccination:
https://pubmed.ncbi.nlm.nih.gov/34693198/

721. An outbreak of Still's disease after COVID-19 vaccination in a 34-year-old patient:
https://pubmed.ncbi.nlm.nih.gov/34797392/

722. Hemophagocytic lymphohistiocytosis following COVID-19 vaccination (ChAdOx1 nCoV-19):
https://pubmed.ncbi.nlm.nih.gov/34862234/

723. Myocarditis after SARS-CoV-2 mRNA vaccination, a case series:
https://pubmed.ncbi.nlm.nih.gov/34396358/

724. Miller-Fisher syndrome and Guillain-Barré syndrome overlap syndrome in a patient after Oxford-Astra-Zeneca SARS-CoV-2 vaccination:
https://pubmed.ncbi.nlm.nih.gov/34848426/

725. Immune-mediated disease outbreaks or new-onset disease in 27 subjects after mRNA/DNA vaccination against SARS-CoV-2:
https://pubmed.ncbi.nlm.nih.gov/33946748/

726. Post-mortem investigation of deaths after vaccination with COVID-19 vaccines:
https://pubmed.ncbi.nlm.nih.gov/34591186/

727. Acute kidney injury with macroscopic hematuria and IgA nephropathy after COVID-19 vaccination:
https://pubmed.ncbi.nlm.nih.gov/34352309/

728. Relapse of immune thrombocytopenia after covid-19 vaccination in young male patient:
https://pubmed.ncbi.nlm.nih.gov/34804803/

729. Immune thrombocytopenic purpura associated with COVID-19 mRNA vaccine Pfizer-BioNTech BNT16B2b2:
https://pubmed.ncbi.nlm.nih.gov/34077572/

730. Retinal hemorrhage after SARS-CoV-2 vaccination:
https://pubmed.ncbi.nlm.nih.gov/34884407/

731. Case report: anti-neutrophil cytoplasmic antibody-associated vasculitis with acute renal failure and pulmonary hemorrhage can occur after COVID-19 vaccination:
https://pubmed.ncbi.nlm.nih.gov/34859017/

732. Intracerebral hemorrhage due to vasculitis following COVID-19 vaccination: case report:
https://pubmed.ncbi.nlm.nih.gov/34783899/

733. Peduncular, symptomatic cavernous bleeding after immune thrombocytopenia-induced SARS-CoV-2 vaccination:
https://pubmed.ncbi.nlm.nih.gov/34549178/

734. Brain death in a vaccinated patient with COVID-19 infection:
https://pubmed.ncbi.nlm.nih.gov/34656887/

735. Generalized purpura annularis telangiectodes after SARS-CoV-2 mRNA vaccination:
https://pubmed.ncbi.nlm.nih.gov/34236717/

736. Lobar hemorrhage with ventricular rupture shortly after the first dose of a SARS-CoV-2 mRNA-based SARS-CoV-2 vaccine:
https://pubmed.ncbi.nlm.nih.gov/34729467/

737. A case of outbreak of macroscopic hematuria and IgA nephropathy after SARS-CoV-2 vaccination:
https://pubmed.ncbi.nlm.nih.gov/33932458/

738. Acral hemorrhage after administration of the second dose of SARS-CoV-2 vaccine. A post-vaccination reaction:
https://pubmed.ncbi.nlm.nih.gov/34092400/742

739. Severe immune thrombocytopenic purpura after SARS-CoV-2 vaccine:
https://pubmed.ncbi.nlm.nih.gov/34754937/

740. Gross hematuria after severe acute respiratory syndrome coronavirus 2 vaccination in 2 patients with IgA nephropathy:
https://pubmed.ncbi.nlm.nih.gov/33771584/

741. Autoimmune encephalitis after ChAdOx1-S SARS-CoV-2 vaccination:
https://pubmed.ncbi.nlm.nih.gov/34846583/

742. COVID-19 vaccine and death: causality algorithm according to the WHO eligibility diagnosis:
https://pubmed.ncbi.nlm.nih.gov/34073536/

743. Bell's palsy after vaccination with mRNA (BNT162b2) and inactivated (CoronaVac) SARS-CoV-2 vaccines: a case series and a nested case-control study:
https://pubmed.ncbi.nlm.nih.gov/34411532/

744. Epidemiology of myocarditis and pericarditis following mRNA vaccines in Ontario, Canada: by vaccine product, schedule, and interval:
https://www.medrxiv.org/content/10.1101/2021.12.02.21267156v1

745. Anaphylaxis following Covid-19 vaccine in a patient with cholinergic urticaria:
https://pubmed.ncbi.nlm.nih.gov/33851711/

746. Anaphylaxis induced by CoronaVac COVID-19 vaccine: clinical features and results of revaccination:
https://pubmed.ncbi.nlm.nih.gov/34675550/

747. Anaphylaxis after Modern COVID-19 vaccine:
https://pubmed.ncbi.nlm.nih.gov/34734159/

748. Association of self-reported history of high-risk allergy with allergy symptoms after COVID-19 vaccination:
https://pubmed.ncbi.nlm.nih.gov/34698847/

749. Sex differences in the incidence of anaphylaxis to LNP-mRNA vaccines COVID-19:
https://pubmed.ncbi.nlm.nih.gov/34020815/

750. Allergic reactions, including anaphylaxis, after receiving the first dose of Pfizer-BioNTech COVID-19 vaccine – United States, December 14 to 23, 2020:
https://pubmed.ncbi.nlm.nih.gov/33641264/

751. Allergic reactions, including anaphylaxis, after receiving the first dose of Modern COVID-19 vaccine – United States, December 21, 2020 to January 10, 2021:
https://pubmed.ncbi.nlm.nih.gov/33641268/

752. Prolonged anaphylaxis to Pfizer 2019 coronavirus disease vaccine: a case report and mechanism of action:
https://pubmed.ncbi.nlm.nih.gov/33834172/

753. Anaphylaxis reactions to Pfizer BNT162b2 vaccine: report of 3 cases of anaphylaxis following vaccination with Pfizer BNT162b2:
https://pubmed.ncbi.nlm.nih.gov/34579211/

754. Biphasic anaphylaxis after first dose of 2019 messenger RNA coronavirus disease vaccine with positive polysorbate 80 skin test result:
https://pubmed.ncbi.nlm.nih.gov/34343674/

755. Acute myocardial infarction and myocarditis after COVID-19 vaccination:
https://pubmed.ncbi.nlm.nih.gov/34586408/

756. Takotsubo syndrome after COVID-19 vaccination:
https://pubmed.ncbi.nlm.nih.gov/34539938/

757. Takotsubo cardiomyopathy after coronavirus 2019 vaccination in patient on maintenance hemodialysis:
https://pubmed.ncbi.nlm.nih.gov/34731486/

758. Premature myocardial infarction or side effect of COVID-19 vaccine:
https://pubmed.ncbi.nlm.nih.gov/33824804/

759. Myocardial infarction, stroke, and pulmonary embolism after BNT162b2 mRNA COVID-19 vaccine in persons aged 75 years or older:
https://pubmed.ncbi.nlm.nih.gov/34807248/

760. Kounis syndrome type 1 induced by inactivated SARS-COV-2 vaccine:
https://pubmed.ncbi.nlm.nih.gov/34148772/

761. Acute myocardial infarction within 24 hours after COVID-19 vaccination: is Kounis syndrome the culprit:
https://pubmed.ncbi.nlm.nih.gov/34702550/

762. Deaths associated with the recently launched SARS-CoV-2 vaccination (Comirnaty®):
https://pubmed.ncbi.nlm.nih.gov/33895650/

763. Deaths associated with recently launched SARS-CoV-2 vaccination:
https://pubmed.ncbi.nlm.nih.gov/34425384/

764. A case of acute encephalopathy and non-ST-segment elevation myocardial infarction after vaccination with mRNA-1273: possible adverse effect:
https://pubmed.ncbi.nlm.nih.gov/34703815/

765. COVID-19 vaccine-induced urticarial vasculitis:
https://pubmed.ncbi.nlm.nih.gov/34369046/

766. ANCA-associated vasculitis after Pfizer-BioNTech COVID-19 vaccine:
https://pubmed.ncbi.nlm.nih.gov/34280507/

767. New-onset leukocytoclastic vasculitis after COVID-19 vaccine:
https://pubmed.ncbi.nlm.nih.gov/34241833/

768. Cutaneous small vessel vasculitis after COVID-19 vaccine:
https://pubmed.ncbi.nlm.nih.gov/34529877/

769. Outbreak of leukocytoclastic vasculitis after COVID-19 vaccine:
https://pubmed.ncbi.nlm.nih.gov/33928638/

770. Leukocytoclastic vasculitis after exposure to COVID-19 vaccine:
https://pubmed.ncbi.nlm.nih.gov/34836739/

771. Vasculitis and bursitis in [18 F] FDG-PET/CT after COVID-19 mRNA vaccine: post hoc ergo propter hoc?;
https://pubmed.ncbi.nlm.nih.gov/34495381/

772. Cutaneous lymphocytic vasculitis after administration of COVID-19 mRNA vaccine:
https://pubmed.ncbi.nlm.nih.gov/34327795

773. Cutaneous leukocytoclastic vasculitis induced by Sinovac COVID-19 vaccine:
https://pubmed.ncbi.nlm.nih.gov/34660867/

774. Case report: ANCA-associated vasculitis presenting with rhabdomyolysis and crescentic Pauci-Inmune glomerulonephritis after vaccination with Pfizer-BioNTech COVID-19 mRNA:
https://pubmed.ncbi.nlm.nih.gov/34659268/

775. Reactivation of IgA vasculitis after vaccination with COVID-19:
https://pubmed.ncbi.nlm.nih.gov/34848431/

776. Varicella-zoster virus-related small-vessel vasculitis after Pfizer-BioNTech COVID-19 vaccination:
https://pubmed.ncbi.nlm.nih.gov/34310759/

777. Imaging in vascular medicine: leukocytoclastic vasculitis after COVID-19 vaccine booster:
https://pubmed.ncbi.nlm.nih.gov/34720009/

778. A rare case of Henoch-Schönlein purpura after a case report of COVID-19 vaccine:
https://pubmed.ncbi.nlm.nih.gov/34518812/

779. Cutaneous vasculitis following COVID-19 vaccination:
https://pubmed.ncbi.nlm.nih.gov/34611627/

780. Possible case of COVID-19 mRNA vaccine-induced small-vessel vasculitis:
https://pubmed.ncbi.nlm.nih.gov/34705320/

781. IgA vasculitis following COVID-19 vaccination in an adult:
https://pubmed.ncbi.nlm.nih.gov/34779011/

782. Propylthiouracil-induced anti-neutrophil cytoplasmic antibody-associated vasculitis following vaccination with COVID-19:
https://pubmed.ncbi.nlm.nih.gov/34451967/

783. Coronavirus disease vaccine 2019 (COVID-19) in systemic lupus erythematosus and neutrophil anti-cytoplasmic antibody-associated vasculitis:
https://pubmed.ncbi.nlm.nih.gov/33928459/

784. Reactivation of IgA vasculitis after COVID-19 vaccination:
https://pubmed.ncbi.nlm.nih.gov/34250509/

785. Clinical and histopathologic spectrum of delayed adverse skin reactions after COVID-19 vaccination:
https://pubmed.ncbi.nlm.nih.gov/34292611/

786. First description of immune complex vasculitis after COVID-19 vaccination with BNT162b2: case report:
https://pubmed.ncbi.nlm.nih.gov/34530771/

787. Nephrotic syndrome and vasculitis after SARS-CoV-2 vaccine: true association or circumstantial:
https://pubmed.ncbi.nlm.nih.gov/34245294/

788. Occurrence of de novo cutaneous vasculitis after vaccination against coronavirus disease (COVID-19):
https://pubmed.ncbi.nlm.nih.gov/34599716/

789. Asymmetric cutaneous vasculitis after COVID-19 vaccination with unusual preponderance of eosinophils:
https://pubmed.ncbi.nlm.nih.gov/34115904/

790. Henoch-Schönlein purpura occurring after vaccination with COVID-19:
https://pubmed.ncbi.nlm.nih.gov/34247902/

791. Henoch-Schönlein purpura following the first dose of COVID-19 viral vector vaccine: case report:
https://pubmed.ncbi.nlm.nih.gov/34696186/

792. Granulomatous vasculitis after AstraZeneca anti-SARS-CoV-2 vaccine:
https://pubmed.ncbi.nlm.nih.gov/34237323/

793. Acute retinal necrosis due to varicella zoster virus reactivation after vaccination w/NT162b2 CoV-2 mRNA:
https://pubmed.ncbi.nlm.nih.gov/34851795/

794. A case of generalized Sweet's syndrome with vasculitis triggered by recent vaccination with COVID-19:
https://pubmed.ncbi.nlm.nih.gov/34849386/

795. Small-vessel vasculitis following Oxford-AstraZeneca vaccination against SARS-CoV-2:
https://pubmed.ncbi.nlm.nih.gov/34310763/

796. Relapse of microscopic polyangiitis after COVID-19 vaccination: case report:
https://pubmed.ncbi.nlm.nih.gov/34251683/

797. Cutaneous vasculitis after severe acute respiratory syndrome coronavirus 2 vaccine:
https://pubmed.ncbi.nlm.nih.gov/34557622/

798. Recurrent herpes zoster after COVID-19 vaccination in patients with chronic urticaria on cyclosporine treatment – A report of 3 cases:
https://pubmed.ncbi.nlm.nih.gov/34510694/

799. Leukocytoclastic vasculitis after coronavirus disease vaccination 2019:
https://pubmed.ncbi.nlm.nih.gov/34713472/803

800. Outbreaks of mixed cryoglobulinemia vasculitis after vaccination against SARS-CoV-2:
https://pubmed.ncbi.nlm.nih.gov/34819272/

801. Cutaneous small-vessel vasculitis after vaccination with a single dose of Janssen Ad26.COV2.S:
https://pubmed.ncbi.nlm.nih.gov/34337124/

802. Case of immunoglobulin A vasculitis after vaccination against coronavirus disease 2019:
https://pubmed.ncbi.nlm.nih.gov/34535924/

803. Rapid progression of angioimmunoblastic T-cell lymphoma after BNT162b2 mRNA booster vaccination: case report:
https://www.frontiersin.org/articles/10.3389/fmed.2021.798095/

804. Covid-19 mRNA vaccination-induced lymphadenopathy mimics lymphoma progression on FDG PET / CT:
https://pubmed.ncbi.nlm.nih.gov/33591026/

805. Lymphadenopathy in COVID-19 vaccine recipients: diagnostic dilemma in oncology patients:
https://pubmed.ncbi.nlm.nih.gov/33625300/

806. Hypermetabolic lymphadenopathy after administration of BNT162b2 mRNA vaccine Covid-19: incidence assessed by [18 F] FDG PET-CT and relevance for study interpretation:
https://pubmed.ncbi.nlm.nih.gov/33774684/

807. Lymphadenopathy after COVID-19 vaccination: review of imaging findings:
https://pubmed.ncbi.nlm.nih.gov/33985872/

808. Evolution of bilateral hypermetabolic axillary hypermetabolic lymphadenopathy on FDG PET/CT after 2-dose COVID-19 vaccination:
https://pubmed.ncbi.nlm.nih.gov/34735411/

809. Lymphadenopathy associated with COVID-19 vaccination on FDG PET/CT: distinguishing features in adenovirus-vectored vaccine:
https://pubmed.ncbi.nlm.nih.gov/34115709/

810. COVID-19 vaccination-induced lymphadenopathy in a specialized breast imaging clinic in Israel: analysis of 163 cases:
https://pubmed.ncbi.nlm.nih.gov/34257025/

811. Covid-19 vaccine-related axillary lymphadenopathy in breast cancer patients: case series w/literature review:
https://pubmed.ncbi.nlm.nih.gov/34836672/

812. Coronavirus disease vaccine 2019 mimics lymph node metastases in patients undergoing skin cancer follow-up: a single-center study:
https://pubmed.ncbi.nlm.nih.gov/34280870/

813. COVID-19 post-vaccination lymphadenopathy: report of fine-needle aspiration biopsy cytologic findings:
https://pubmed.ncbi.nlm.nih.gov/34432391/

814. Regional lymphadenopathy after COVID-19 vaccination: review of the literature and considerations for patient management in breast cancer care:
https://pubmed.ncbi.nlm.nih.gov/34731748/

815. Subclinical axillary lymphadenopathy associated with COVID-19 vaccination on screening mammography:
https://pubmed.ncbi.nlm.nih.gov/34906409/

816. Adverse events of COVID injection that may occur in children.Acute-onset supraclavicular lymphadenopathy coincident with intramuscular mRNA vaccination against COVID-19 may be related to the injection technique of the vaccine, Spain, January and February 2021:
https://pubmed.ncbi.nlm.nih.gov/33706861/

817. Supraclavicular lymphadenopathy after COVID-19 vaccination in Korea: serial follow-up w/ultrasonography:
https://pubmed.ncbi.nlm.nih.gov/34116295/

818. Oxford-AstraZeneca COVID-19 vaccination induced lymphadenopathy on [18F] choline PET / CT, not just an FDG finding:
https://pubmed.ncbi.nlm.nih.gov/33661328/

819. Biphasic anaphylaxis after exposure to the first dose of Pfizer-BioNTech COVID-19 mRNA vaccine COVID-19:
https://pubmed.ncbi.nlm.nih.gov/34050949/

820. Axillary adenopathy associated with COVID-19 vaccination: imaging findings and follow-up recommendations in 23 women:
https://pubmed.ncbi.nlm.nih.gov/33624520/

821. A case of cervical lymphadenopathy following COVID-19 vaccination:
https://pubmed.ncbi.nlm.nih.gov/34141500/

822. Unique imaging findings of neurologic phantosmia after Pfizer-BioNtech Covid vaccination: a case report:
https://pubmed.ncbi.nlm.nih.gov/34096896/

823. Thrombotic adverse events reported for Moderna, Pfizer, and Oxford-AstraZeneca COVID-19 vaccines: comparison of occurrence and clinical outcomes in the EudraVigilance database:
https://pubmed.ncbi.nlm.nih.gov/34835256/

824. Unilateral lymphadenopathy after COVID-19 vaccination: a practical management plan for radiologists of all specialties:
https://pubmed.ncbi.nlm.nih.gov/33713605/

825. Unilateral axillary adenopathy in the setting of COVID-19 vaccination: follow-up:
https://pubmed.ncbi.nlm.nih.gov/34298342/

826. A systematic review of cases of CNS demyelination following COVID-19 vaccination:
https://pubmed.ncbi.nlm.nih.gov/34839149/

827. Supraclavicular lymphadenopathy after COVID-19 vaccination: an increasing presentation in the two-week wait neck lump clinic:
https://pubmed.ncbi.nlm.nih.gov/33685772/

828. COVID-19 vaccine-related axillary and cervical lymphadenopathy in patients with current or previous breast cancer and other malignancies: cross-sectional imaging findings on MRI, CT and PET-CT:
https://pubmed.ncbi.nlm.nih.gov/34719892/

829. Adenopathy after COVID-19 vaccination:
https://pubmed.ncbi.nlm.nih.gov/33625299/

830. Incidence of axillary adenopathy on breast imaging after vaccination with COVID-19:
https://pubmed.ncbi.nlm.nih.gov/34292295/

831. COVID-19 vaccination & lower cervical lymphadenopathy in two-week neck lump clinic: a follow-up audit:
https://pubmed.ncbi.nlm.nih.gov/33947605/

832. Cervical lymphadenopathy after coronavirus disease vaccination 2019: clinical features and implications for head and neck cancer services:
https://pubmed.ncbi.nlm.nih.gov/34526175/

833. Lymphadenopathy associated with the COVID-19 vaccine:
https://pubmed.ncbi.nlm.nih.gov/33786231/

834. Evolution of lymphadenopathy on PET/MRI after COVID-19 vaccination:
https://pubmed.ncbi.nlm.nih.gov/33625301/

835. Autoimmune hepatitis triggered by SARS-CoV-2 vaccination:
https://pubmed.ncbi.nlm.nih.gov/34332438/

836. New-onset nephrotic syndrome after Janssen COVID-19 vaccination: case report and literature review:
https://pubmed.ncbi.nlm.nih.gov/34342187/

837. Massive cervical lymphadenopathy following vaccination with COVID-19:
https://pubmed.ncbi.nlm.nih.gov/34601889/

838. ANCA glomerulonephritis following Modern COVID-19 vaccination:
https://pubmed.ncbi.nlm.nih.gov/34081948/

839. Extensive longitudinal transverse myelitis following AstraZeneca COVID-19 vaccination:
https://pubmed.ncbi.nlm.nih.gov/34507942/

840. Systemic capillary extravasation syndrome after vaccination w/ChAdOx1 nCOV-19 (Oxford-AstraZeneca):
https://pubmed.ncbi.nlm.nih.gov/34362727/

841. Unilateral axillary lymphadenopathy related to COVID-19 vaccine: pattern on screening breast MRI allowing benign evaluation:
https://pubmed.ncbi.nlm.nih.gov/34325221/

842. Axillary lymphadenopathy in patients with recent Covid-19 vaccination: a new diagnostic dilemma:
https://pubmed.ncbi.nlm.nih.gov/34825530/

843. Minimal change disease and acute kidney injury after Pfizer-BioNTech COVID-19 vaccine:
https://pubmed.ncbi.nlm.nih.gov/34000278/

844. COVID-19 vaccine-induced unilateral axillary adenopathy: follow-up evaluation in the USA:
https://pubmed.ncbi.nlm.nih.gov/34655312/

845. Gastroparesis after Pfizer-BioNTech COVID-19 vaccination:
https://pubmed.ncbi.nlm.nih.gov/34187985/

846. Acute-onset supraclavicular lymphadenopathy coincident with intramuscular mRNA vaccination against COVID-19 may be related to the injection technique of the vaccine, Spain, January and February 2021:
https://pubmed.ncbi.nlm.nih.gov/33706861/

847. Supraclavicular lymphadenopathy after COVID-19 vaccination in Korea: serial follow-up by ultrasonography:
https://pubmed.ncbi.nlm.nih.gov/34116295/

848. Oxford-AstraZeneca COVID-19 vaccination induced lymphadenopathy on [18F] choline PET / CT, not just an FDG finding:
https://pubmed.ncbi.nlm.nih.gov/33661328/

849. Biphasic anaphylaxis after exposure to the first dose of Pfizer-BioNTech COVID-19 mRNA vaccine COVID-19:
https://pubmed.ncbi.nlm.nih.gov/34050949/

850. Axillary adenopathy associated with COVID-19 vaccination: imaging findings and follow-up recommendations in 23 women:
https://pubmed.ncbi.nlm.nih.gov/33624520/

851. A case of cervical lymphadenopathy following COVID-19 vaccination:
https://pubmed.ncbi.nlm.nih.gov/34141500/

852. Unique imaging findings of neurologic phantosmia after Pfizer-BioNtech vaccination: a case report:
https://pubmed.ncbi.nlm.nih.gov/34096896/

853. Thrombotic adverse events reported for Moderna, Pfizer, and Oxford-AstraZeneca COVID-19 vaccines: comparison of occurrence and clinical outcomes in the EudraVigilance database:
https://pubmed.ncbi.nlm.nih.gov/34835256/

854. Unilateral lymphadenopathy after COVID-19 vaccination: a practical management plan for radiologists of all specialties:
https://pubmed.ncbi.nlm.nih.gov/33713605/

855. Unilateral axillary adenopathy in the setting of COVID-19 vaccination: follow-up:
https://pubmed.ncbi.nlm.nih.gov/34298342/

856. A systematic review of cases of CNS demyelination following COVID-19 vaccination:
https://pubmed.ncbi.nlm.nih.gov/34839149/

857. Supraclavicular lymphadenopathy after COVID-19 vaccination: an increasing presentation in the two-week wait neck lump clinic:
https://pubmed.ncbi.nlm.nih.gov/33685772/

858. COVID-19 vaccine-related axillary and cervical lymphadenopathy in patients with current or previous breast cancer and other malignancies: cross-sectional imaging findings on MRI, CT and PET-CT:
https://pubmed.ncbi.nlm.nih.gov/34719892/

859. Adenopathy after COVID-19 vaccination:
https://pubmed.ncbi.nlm.nih.gov/33625299/

860. Incidence of axillary adenopathy on breast imaging after vaccination with COVID-19:
https://pubmed.ncbi.nlm.nih.gov/34292295/

861. COVID-19 vaccination & lower cervical lymphadenopathy in two-week neck lump clinic: a follow-up audit:
https://pubmed.ncbi.nlm.nih.gov/33947605/

862. Cervical lymphadenopathy after coronavirus disease vaccination 2019: clinical features and implications for head and neck cancer services:
https://pubmed.ncbi.nlm.nih.gov/34526175/

863. Lymphadenopathy associated with the COVID-19 vaccine:
https://pubmed.ncbi.nlm.nih.gov/33786231/

864. Evolution of lymphadenopathy on PET/MRI after COVID-19 vaccination:
https://pubmed.ncbi.nlm.nih.gov/33625301/

865. Autoimmune hepatitis triggered by SARS-CoV-2 vaccination:
https://pubmed.ncbi.nlm.nih.gov/34332438/

866. New-onset nephrotic syndrome after Janssen COVID-19 vaccination: case report and literature review:
https://pubmed.ncbi.nlm.nih.gov/34342187/

867. Massive cervical lymphadenopathy following vaccination with COVID-19:
https://pubmed.ncbi.nlm.nih.gov/34601889/

868. ANCA glomerulonephritis following Modern COVID-19 vaccination:
https://pubmed.ncbi.nlm.nih.gov/34081948/

869. Extensive longitudinal transverse myelitis following AstraZeneca COVID-19 vaccination:
https://pubmed.ncbi.nlm.nih.gov/34507942/

870. Systemic capillary extravasation syndrome after vaccination w/ChAdOx1 nCOV-19 (Oxford-AstraZeneca):
https://pubmed.ncbi.nlm.nih.gov/34362727/

871. Unilateral axillary lymphadenopathy related to COVID-19 vaccine: pattern on screening breast MRI allowing benign evaluation:
https://pubmed.ncbi.nlm.nih.gov/34325221/

872. Axillary lymphadenopathy in patients with recent Covid-19 vaccination: a new diagnostic dilemma:
https://pubmed.ncbi.nlm.nih.gov/34825530/

873. Minimal change disease and acute kidney injury after Pfizer-BioNTech COVID-19 vaccine:
https://pubmed.ncbi.nlm.nih.gov/34000278/

874. COVID-19 vaccine-induced unilateral axillary adenopathy: follow-up evaluation in the USA: https://pubmed.ncbi.nlm.nih.gov/34655312/

875. Gastroparesis after Pfizer-BioNTech COVID-19 vaccination: https://pubmed.ncbi.nlm.nih.gov/34187985/

876. Abbate, A., Gavin, J., Madanchi, N., Kim, C., Shah, P. R., Klein, K., . . . Danielides, S. (2021). Fulminant myocarditis and systemic hyperinflammation temporally associated with BNT162b2 mRNA COVID-19 vaccination in two patients. Int J Cardiol, 340, 119-121. doi:10.1016/j.ijcard.2021.08.018. https://www.ncbi.nlm.nih.gov/pubmed/34416319

877. Abu Mouch, S., Roguin, A., Hellou, E., Ishai, A., Shoshan, U., Mahamid, L., . . . Berar Yanay, N. (2021). Myocarditis following COVID-19 mRNA vaccination. Vaccine, 39(29), 3790-3793. doi:10.1016/j.vaccine.2021.05.087. https://www.ncbi.nlm.nih.gov/pubmed/34092429

878. Albert, E., Aurigemma, G., Saucedo, J., & Gerson, D. S. (2021). Myocarditis following COVID-19 vaccination. Radiol Case Rep, 16(8), 2142-2145. doi:10.1016/j.radcr.2021.05.033. https://www.ncbi.nlm.nih.gov/pubmed/34025885

879. Aye, Y. N., Mai, A. S., Zhang, A., Lim, O. Z. H., Lin, N., Ng, C. H., . . . Chew, N. W. S. (2021). Acute Myocardial Infarction and Myocarditis following COVID-19 Vaccination. QJM. doi:10.1093/qjmed/hcab252. https://www.ncbi.nlm.nih.gov/pubmed/34586408

880. Azir, M., Inman, B., Webb, J., & Tannenbaum, L. (2021). STEMI Mimic: Focal Myocarditis in an Adolescent Patient After mRNA COVID-19 Vaccine. J Emerg Med, 61(6), e129-e132. doi:10.1016/j.jemermed.2021.09.017. https://www.ncbi.nlm.nih.gov/pubmed/34756746

881. Barda, N., Dagan, N., Ben-Shlomo, Y., Kepten, E., Waxman, J., Ohana, R., . . . Balicer, R. D. (2021). Safety of the BNT162b2 mRNA Covid-19 Vaccine in a Nationwide Setting. N Engl J Med, 385(12), 1078-1090. doi:10.1056/NEJMoa2110475. https://www.ncbi.nlm.nih.gov/pubmed/34432976

882. Bhandari, M., Pradhan, A., Vishwakarma, P., & Sethi, R. (2021). Coronavirus and cardiovascular manifestations- getting to the heart of the matter. World J Cardiol, 13(10), 556-565. doi:10.4330/wjc.v13.i10.556. https://www.ncbi.nlm.nih.gov/pubmed/34754400

883. Bozkurt, B., Kamat, I., & Hotez, P. J. (2021). Myocarditis With COVID-19 mRNA Vaccines. Circulation, 144(6), 471-484. doi:10.1161/CIRCULATIONAHA.121.056135. https://www.ncbi.nlm.nih.gov/pubmed/34281357

884. Buchhorn, R., Meyer, C., Schulze-Forster, K., Junker, J., & Heidecke, H. (2021). Autoantibody Release in Children after Corona Virus mRNA Vaccination: A Risk Factor of Multisystem Inflammatory Syndrome? Vaccines (Basel), 9(11). doi:10.3390/vaccines9111353. https://www.ncbi.nlm.nih.gov/pubmed/34835284

885. Calcaterra, G., Bassareo, P. P., Barilla, F., Romeo, F., & Mehta, J. L. (2022). Concerning the unexpected prothrombotic state following some coronavirus disease 2019 vaccines. J Cardiovasc Med (Hagerstown), 23(2), 71-74. doi:10.2459/JCM.0000000000001232. https://www.ncbi.nlm.nih.gov/pubmed/34366403

886. Calcaterra, G., Mehta, J. L., de Gregorio, C., Butera, G., Neroni, P., Fanos, V., & Bassareo, P. P. (2021). COVID 19 Vaccine for Adolescents. Concern about Myocarditis and Pericarditis. Pediatr Rep, 13(3), 530-533. doi:10.3390/pediatric13030061. https://www.ncbi.nlm.nih.gov/pubmed/34564344

887. Chai, Q., Nygaard, U., Schmidt, R. C., Zaremba, T., Moller, A. M., & Thorvig, C. M. (2022). Multisystem inflammatory syndrome in a male adolescent after his second Pfizer-BioNTech COVID-19 vaccine. Acta Paediatr, 111(1), 125-127. doi:10.1111/apa.16141. https://www.ncbi.nlm.nih.gov/pubmed/34617315

888. Chamling, B., Vehof, V., Drakos, S., Weil, M., Stalling, P., Vahlhaus, C., Yilmaz, A. (2021). Occurrence of acute infarct-like myocarditis following COVID-19 vaccination: just an accidental co-incidence or rather vaccination-associated autoimmune myocarditis? Clin Res Cardiol, 110(11), 1850-1854. doi:10.1007/s00392-021-01916-w. https://www.ncbi.nlm.nih.gov/pubmed/34333695

889. Chang, J. C., & Hawley, H. B. (2021). Vaccine-Associated Thrombocytopenia and Thrombosis: Venous Endotheliopathy Leading to Venous Combined Micro-Macrothrombosis. Medicina (Kaunas), 57(11). doi:10.3390/medicina57111163. https://www.ncbi.nlm.nih.gov/pubmed/34833382

890. Chelala, L., Jeudy, J., Hossain, R., Rosenthal, G., Pietris, N., & White, C. (2021). Cardiac MRI Findings of Myocarditis After COVID-19 mRNA Vaccination in Adolescents. AJR Am J Roentgenol. doi:10.2214/AJR.21.26853. https://www.ncbi.nlm.nih.gov/pubmed/34704459

891. Choi, S., Lee, S., Seo, J. W., Kim, M. J., Jeon, Y. H., Park, J. H., . . . Yeo, N. S. (2021). Myocarditis-induced Sudden Death after BNT162b2 mRNA COVID-19 Vaccination in Korea: Case Report Focusing on Histopathological Findings. J Korean Med Sci, 36(40), e286. doi:10.3346/jkms.2021.36.e286. https://www.ncbi.nlm.nih.gov/pubmed/34664804

892. Chouchana, L., Blet, A., Al-Khalaf, M., Kafil, T. S., Nair, G., Robblee, J., . . . Liu, P. P. (2021). Features of Inflammatory Heart Reactions Following mRNA COVID-19 Vaccination at a Global Level. Clin Pharmacol Ther. doi:10.1002/cpt.2499. https://www.ncbi.nlm.nih.gov/pubmed/34860360

893. Chua, G. T., Kwan, M. Y. W., Chui, C. S. L., Smith, R. D., Cheung, E. C., Tian, T., . . . Ip, P. (2021). Epidemiology of Acute Myocarditis/Pericarditis in Hong Kong Adolescents Following Comirnaty Vaccination. Clin Infect Dis. doi:10.1093/cid/ciab989. https://www.ncbi.nlm.nih.gov/pubmed/34849657

894. Clarke, R., & Ioannou, A. (2021). Should T2 mapping be used in cases of recurrent myocarditis to differentiate between the acute inflammation and chronic scar? J Pediatr. doi:10.1016/j.jpeds.2021.12.026. https://www.ncbi.nlm.nih.gov/pubmed/34933012

895. Colaneri, M., De Filippo, M., Licari, A., Marseglia, A., Maiocchi, L., Ricciardi, A., . . . Bruno, R. (2021). COVID vaccination and asthma exacerbation: might there be a link? Int J Infect Dis, 112, 243-246. doi:10.1016/j.ijid.2021.09.026. https://www.ncbi.nlm.nih.gov/pubmed/34547487

896. Das, B. B., Kohli, U., Ramachandran, P., Nguyen, H. H., Greil, G., Hussain, T., . . . Khan, D. (2021). Myopericarditis after messenger RNA Coronavirus Disease 2019 Vaccination in Adolescents 12 to 18 Years of Age. J Pediatr, 238, 26-32 e21. doi:10.1016/j.jpeds.2021.07.044.
https://www.ncbi.nlm.nih.gov/pubmed/34339728

897. Das, B. B., Moskowitz, W. B., Taylor, M. B., & Palmer, A. (2021). Myocarditis and Pericarditis Following mRNA COVID-19 Vaccination: What Do We Know So Far? Children (Basel), 8(7). doi:10.3390/children8070607.
https://www.ncbi.nlm.nih.gov/pubmed/34356586

898. Deb, A., Abdelmalek, J., Iwuji, K., & Nugent, K. (2021). Acute Myocardial Injury Following COVID-19 Vaccination: A Case Report and Review of Current Evidence from Vaccine Adverse Events Reporting System Database. J Prim Care Community Health, 12, 21501327211029230. doi:10.1177/21501327211029230.
https://www.ncbi.nlm.nih.gov/pubmed/34219532

899. Dickey, J. B., Albert, E., Badr, M., Laraja, K. M., Sena, L. M., Gerson, D. S., . . . Aurigemma, G. P. (2021). A Series of Patients With Myocarditis Following SARS-CoV-2 Vaccination With mRNA-1279 and BNT162b2. JACC Cardiovasc Imaging, 14(9), 1862-1863. doi:10.1016/j.jcmg.2021.06.003.
https://www.ncbi.nlm.nih.gov/pubmed/34246585

900. Dimopoulou, D., Spyridis, N., Vartzelis, G., Tsolia, M. N., & Maritsi, D. N. (2021). Safety and tolerability of the COVID-19 mRNA-vaccine in adolescents with juvenile idiopathic arthritis on treatment with TNF-inhibitors. Arthritis Rheumatol. doi:10.1002/art.41977.
https://www.ncbi.nlm.nih.gov/pubmed/34492161

901. Dimopoulou, D., Vartzelis, G., Dasoula, F., Tsolia, M., & Maritsi, D. (2021). Immunogenicity of the COVID-19 mRNA vaccine in adolescents with juvenile idiopathic arthritis on treatment with TNF inhibitors. Ann Rheum Dis. doi:10.1136/annrheumdis-2021-221607.
https://www.ncbi.nlm.nih.gov/pubmed/34844930

902. Ehrlich, P., Klingel, K., Ohlmann-Knafo, S., Huttinger, S., Sood, N., Pickuth, D., & Kindermann, M. (2021). Biopsy-proven lymphocytic myocarditis following first mRNA COVID-19 vaccination in a 40-year-old male: case report. Clin Res Cardiol, 110(11), 1855-1859. doi:10.1007/s00392-021-01936-6.
https://www.ncbi.nlm.nih.gov/pubmed/34487236

903. El Sahly, H. M., Baden, L. R., Essink, B., Doblecki-Lewis, S., Martin, J. M., Anderson, E. J., . . . Group, C. S. (2021). Efficacy of the mRNA-1273 SARS-CoV-2 Vaccine at Completion of Blinded Phase. N Engl J Med, 385(19), 1774-1785. doi:10.1056/NEJMoa2113017.
https://www.ncbi.nlm.nih.gov/pubmed/34551225

904. Facetti, S., Giraldi, M., Vecchi, A. L., Rogiani, S., & Nassiacos, D. (2021). [Acute myocarditis in a young adult two days after Pfizer vaccination]. G Ital Cardiol (Rome), 22(11), 891-893. doi:10.1714/3689.36746.
https://www.ncbi.nlm.nih.gov/pubmed/34709227

905. Fazlollahi, A., Zahmatyar, M., Noori, M., Nejadghaderi, S. A., Sullman, M. J. M., Shekarriz-Foumani, R., . . . Safiri, S. (2021). Cardiac complications following mRNA COVID-19 vaccines: A systematic review of case reports and case series. Rev Med Virol, e2318. doi:10.1002/rmv.2318.
https://www.ncbi.nlm.nih.gov/pubmed/34921468

906. Fazolo, T., Lima, K., Fontoura, J. C., de Souza, P. O., Hilario, G., Zorzetto, R., . . . Bonorino, C. (2021). Pediatric COVID-19 patients in South Brazil show abundant viral mRNA and strong specific anti-viral responses. Nat Commun, 12(1), 6844. doi:10.1038/s41467-021-27120-y.
https://www.ncbi.nlm.nih.gov/pubmed/34824230

907. Fikenzer, S., & Laufs, U. (2021). Correction to: Response to Letter to the editors referring to Fikenzer, S., Uhe, T., Lavall, D., Rudolph, U., Falz, R., Busse, M., Hepp, P., & Laufs, U. (2020). Effects of surgical and FFP2/N95 face masks on cardiopulmonary exercise capacity. Clinical research in cardiology: official journal of the German Cardiac Society, 1-9. Advance online publication. https://doi.org/10.1007/s00392-020-01704-y. Clin Res Cardiol, 110(8), 1352. doi:10.1007/s00392-021-01896-x.
https://www.ncbi.nlm.nih.gov/pubmed/34170372

908. Foltran, D., Delmas, C., Flumian, C., De Paoli, P., Salvo, F., Gautier, S., . . . Montastruc, F. (2021). Myocarditis and Pericarditis in Adolescents after First and Second doses of mRNA COVID-19 Vaccines. Eur Heart J Qual Care Clin Outcomes. doi:10.1093/ehjqcco/qcab090.
https://www.ncbi.nlm.nih.gov/pubmed/34849667

909. Forgacs, D., Jang, H., Abreu, R. B., Hanley, H. B., Gattiker, J. L., Jefferson, A. M., & Ross, T. M. (2021). SARS-CoV-2 mRNA Vaccines Elicit Different Responses in Immunologically Naive and Pre-Immune Humans. Front Immunol, 12, 728021. doi:10.3389/fimmu.2021.728021.
https://www.ncbi.nlm.nih.gov/pubmed/34646267

910. Furer, V., Eviatar, T., Zisman, D., Peleg, H., Paran, D., Levartovsky, D., . . . Elkayam, O. (2021). Immunogenicity and safety of the BNT162b2 mRNA COVID-19 vaccine in adult patients with autoimmune inflammatory rheumatic diseases and in the general population: a multicentre study. Ann Rheum Dis, 80(10), 1330-1338. doi:10.1136/annrheumdis-2021-220647.
https://www.ncbi.nlm.nih.gov/pubmed/34127481

911. Galindo, R., Chow, H., & Rongkavilit, C. (2021). COVID-19 in Children: Clinical Manifestations and Pharmacologic Interventions Including Vaccine Trials. Pediatr Clin North Am, 68(5), 961-976. doi:10.1016/j.pcl.2021.05.004.
https://www.ncbi.nlm.nih.gov/pubmed/34538306

912. Gargano, J. W., Wallace, M., Hadler, S. C., Langley, G., Su, J. R., Oster, M. E., . . . Oliver, S. E. (2021). Use of mRNA COVID-19 Vaccine After Reports of Myocarditis Among Vaccine Recipients: Update from the Advisory Committee on Immunization Practices – United States, June 2021. MMWR Morb Mortal Wkly Rep, 70(27), 977-982. doi:10.15585/mmwr.mm7027e2.
https://www.ncbi.nlm.nih.gov/pubmed/34237049

913. Gatti, M., Raschi, E., Moretti, U., Ardizzoni, A., Poluzzi, E., & Diemberger, I. (2021). Influenza Vaccination and Myo-Pericarditis in Patients Receiving Immune Checkpoint Inhibitors: Investigating the Likelihood of Interaction through the Vaccine Adverse Event Reporting System and VigiBase. Vaccines (Basel), 9(1). doi:10.3390/vaccines9010019.
https://www.ncbi.nlm.nih.gov/pubmed/33406694

914. Gautam, N., Saluja, P., Fudim, M., Jambhekar, K., Pandey, T., & Al'Aref, S. (2021). A Late Presentation of COVID-19 Vaccine-Induced Myocarditis. Cureus, 13(9), e17890. doi:10.7759/cureus.17890.
https://www.ncbi.nlm.nih.gov/pubmed/34660088

915. Gellad, W. F. (2021). Myocarditis after vaccination against covid-19. BMJ, 375, n3090.
https://www.ncbi.nlm.nih.gov/pubmed/34916217

916. Greenhawt, M., Abrams, E. M., Shaker, M., Chu, D. K., Khan, D., Akin, C., . . . Golden, D. B. K. (2021). The Risk of Allergic Reaction to SARS-CoV-2 Vaccines and Recommended Evaluation and Management: A Systematic Review, Meta-Analysis, GRADE Assessment, and International Consensus Approach. J Allergy Clin Immunol Pract, 9(10), 3546-3567. doi:10.1016/j.jaip.2021.06.006.
https://www.ncbi.nlm.nih.gov/pubmed/34153517

917. Haaf, P., Kuster, G. M., Mueller, C., Berger, C. T., Monney, P., Burger, P., . . . Tanner, F. C. (2021). The very low risk of myocarditis and pericarditis after mRNA COVID-19 vaccination should not discourage vaccination. Swiss Med Wkly, 151, w30087. doi:10.4414/smw.2021.w30087.
https://www.ncbi.nlm.nih.gov/pubmed/34668687

918. Hasnie, A. A., Hasnie, U. A., Patel, N., Aziz, M. U., Xie, M., Lloyd, S. G., & Prabhu, S. D. (2021). Perimyocarditis following first dose of the mRNA-1273 SARS-CoV-2 (Moderna) vaccine in a healthy young male: a case report. BMC Cardiovasc Disord, 21(1), 375. doi:10.1186/s12872-021-02183-3.
https://www.ncbi.nlm.nih.gov/pubmed/34348657

919. Hause, A. M., Gee, J., Baggs, J., Abara, W. E., Marquez, P., Thompson, D., . . . Shay, D. K. (2021). COVID-19 Vaccine Safety in Adolescents Aged 12-17 Years – United States, December 14, 2020-July 16, 2021. MMWR Morb Mortal Wkly Rep, 70(31), 1053-1058. doi:10.15585/mmwr.mm7031e1.
https://www.ncbi.nlm.nih.gov/pubmed/34351881

920. Helms, J. M., Ansteatt, K. T., Roberts, J. C., Kamatam, S., Foong, K. S., Labayog, J. S., & Tarantino, M. D. (2021). Severe, Refractory Immune Thrombocytopenia Occurring After SARS-CoV-2 Vaccine. J Blood Med, 12, 221-224. doi:10.2147/JBM.S307047.
https://www.ncbi.nlm.nih.gov/pubmed/33854395

921. Hippisley-Cox, J., Patone, M., Mei, X. W., Saatci, D., Dixon, S., Khunti, K., . . . Coupland, C. A. C. (2021). Risk of thrombocytopenia and thromboembolism after covid-19 vaccination and SARS-CoV-2 positive testing: self-controlled case series study. BMJ, 374, n1931. doi:10.1136/bmj.n1931.
https://www.ncbi.nlm.nih.gov/pubmed/34446426

922. Ho, J. S., Sia, C. H., Ngiam, J. N., Loh, P. H., Chew, N. W., Kong, W. K., & Poh, K. K. (2021). A review of COVID-19 vaccination and the reported cardiac manifestations. Singapore Med J. doi:10.11622/smedj.2021210.
https://www.ncbi.nlm.nih.gov/pubmed/34808708

923. Iguchi, T., Umeda, H., Kojima, M., Kanno, Y., Tanaka, Y., Kinoshita, N., & Sato, D. (2021). Cumulative Adverse Event Reporting of Anaphylaxis After mRNA COVID-19 Vaccine (Pfizer-BioNTech) Injections in Japan: The First-Month Report. Drug Saf, 44(11), 1209-1214. doi:10.1007/s40264-021-01104-9.
https://www.ncbi.nlm.nih.gov/pubmed/34347278

924. In brief: Myocarditis with the Pfizer/BioNTech and Moderna COVID-19 vaccines. (2021). Med Lett Drugs Ther, 63(1629), e9. Retrieved from https://www.ncbi.nlm.nih.gov/pubmed/34544112
https://www.ncbi.nlm.nih.gov/pubmed/3454412

925. Ioannou, A. (2021a). Myocarditis should be considered in those with a troponin rise and unobstructed coronary arteries following Pfizer-BioNTech COVID-19 vaccination. QJM. doi:10.1093/qjmed/hcab231.
https://www.ncbi.nlm.nih.gov/pubmed/34463755

926. Ioannou, A. (2021b). T2 mapping should be utilised in cases of suspected myocarditis to confirm an acute inflammatory process. QJM. doi:10.1093/qjmed/hcab326. https://www.ncbi.nlm.nih.gov/pubmed/34931681

927. Isaak, A., Feisst, A., & Luetkens, J. A. (2021). Myocarditis Following COVID-19 Vaccination. Radiology, 301(1), E378-E379. doi:10.1148/radiol.2021211766.
https://www.ncbi.nlm.nih.gov/pubmed/34342500

928. Istampoulouoglou, I., Dimitriou, G., Spani, S., Christ, A., Zimmermanns, B., Koechlin, S., . . . Leuppi-Taegtmeyer, A. B. (2021). Myocarditis and pericarditis in association with COVID-19 mRNA-vaccination: cases from a regional pharmacovigilance centre. Glob Cardiol Sci Pract, 2021(3), e202118. doi:10.21542/gcsp.2021.18.
https://www.ncbi.nlm.nih.gov/pubmed/34805376

929. Jaafar, R., Boschi, C., Aherfi, S., Bancod, A., Le Bideau, M., Edouard, S., . . . La Scola, B. (2021). High Individual Heterogeneity of Neutralizing Activities against the Original Strain and Nine Different Variants of SARS-CoV-2. Viruses, 13(11). doi:10.3390/v13112177.
https://www.ncbi.nlm.nih.gov/pubmed/34834983

930. Jain, S. S., Steele, J. M., Fonseca, B., Huang, S., Shah, S., Maskatia, S. A., . . . Grosse-Wortmann, L. (2021). COVID-19 Vaccination-Associated Myocarditis in Adolescents. Pediatrics, 148(5).
https://www.ncbi.nlm.nih.gov/pubmed/34389692

931. Jhaveri, R., Adler-Shohet, F. C., Blyth, C. C., Chiotos, K., Gerber, J. S., Green, M., . . . Zaoutis, T. (2021). Weighing the Risks of Perimyocarditis With the Benefits of SARS-CoV-2 mRNA Vaccination in Adolescents. J Pediatric Infect Dis Soc, 10(10), 937-939. doi:10.1093/jpids/piab061.
https://www.ncbi.nlm.nih.gov/pubmed/34270752

932. Kaneta, K., Yokoi, K., Jojima, K., Kotooka, N., & Node, K. (2021). Young Male With Myocarditis Following mRNA-1273 Vaccination Against Coronavirus Disease-2019 (COVID-19). Circ J. doi:10.1253/circj.CJ-21-0818.
https://www.ncbi.nlm.nih.gov/pubmed/34744118

933. Kaul, R., Sreenivasan, J., Goel, A., Malik, A., Bandyopadhyay, D., Jin, C., . . . Panza, J. A. (2021). Myocarditis following COVID-19 vaccination. Int J Cardiol Heart Vasc, 36, 100872. doi:10.1016/j.ijcha.2021.100872.
https://www.ncbi.nlm.nih.gov/pubmed/34568540

934. Khogali, F., & Abdelrahman, R. (2021). Unusual Presentation of Acute Perimyocarditis Following SARS-COV-2 mRNA-1237 Moderna Vaccination. Cureus, 13(7), e16590. doi:10.7759/cureus.16590.
https://www.ncbi.nlm.nih.gov/pubmed/34447639

935. Kim, H. W., Jenista, E. R., Wendell, D. C., Azevedo, C. F., Campbell, M. J., Darty, S. N., . . . Kim, R. J. (2021). Patients With Acute Myocarditis Following mRNA COVID-19 Vaccination. JAMA Cardiol, 6(10), 1196-1201. doi:10.1001/jamacardio.2021.2828.
https://www.ncbi.nlm.nih.gov/pubmed/34185046

936. Kim, I. C., Kim, H., Lee, H. J., Kim, J. Y., & Kim, J. Y. (2021). Cardiac Imaging of Acute Myocarditis Following COVID-19 mRNA Vaccination. J Korean Med Sci, 36(32), e229. doi:10.3346/jkms.2021.36.e229.
https://www.ncbi.nlm.nih.gov/pubmed/34402228

937. King, W. W., Petersen, M. R., Matar, R. M., Budweg, J. B., Cuervo Pardo, L., & Petersen, J. W. (2021). Myocarditis following mRNA vaccination against SARS-CoV-2, a case series. Am Heart J Plus, 8, 100042. doi:10.1016/j.ahjo.2021.100042.
https://www.ncbi.nlm.nih.gov/pubmed/34396358

938. Klein, N. P., Lewis, N., Goddard, K., Fireman, B., Zerbo, O., Hanson, K. E., . . . Weintraub, E. S. (2021). Surveillance for Adverse Events After COVID-19 mRNA Vaccination. JAMA, 326(14), 1390-1399. doi:10.1001/jama.2021.15072.
https://www.ncbi.nlm.nih.gov/pubmed/34477808

939. Klimek, L., Bergmann, K. C., Brehler, R., Pfutzner, W., Zuberbier, T., Hartmann, K., . . . Worm, M. (2021). Practical handling of allergic reactions to COVID-19 vaccines: A position paper from German and Austrian Allergy Societies AeDA, DGAKI, GPA and OGAI. Allergo J Int, 1-17. doi:10.1007/s40629-021-00165-7.
https://www.ncbi.nlm.nih.gov/pubmed/33898162

940. Klimek, L., Novak, N., Hamelmann, E., Werfel, T., Wagenmann, M., Taube, C., . . . Worm, M. (2021). Severe allergic reactions after COVID-19 vaccination with the Pfizer/BioNTech vaccine in Great Britain and USA: Position statement of the German Allergy Societies: Medical Association of German Allergologists (AeDA), German Society for Allergology and Clinical Immunology (DGAKI) and Society for Pediatric Allergology and Environmental Medicine (GPA). Allergo J Int, 30(2), 51-55. doi:10.1007/s40629-020-00160-4.
https://www.ncbi.nlm.nih.gov/pubmed/33643776

941. Kohli, U., Desai, L., Chowdhury, D., Harahsheh, A. S., Yonts, A. B., Ansong, A., . . . Ang, J. Y. (2021). mRNA Coronavirus-19 Vaccine-Associated Myopericarditis in Adolescents: A Survey Study. J Pediatr. doi:10.1016/j.jpeds.2021.12.025.
https://www.ncbi.nlm.nih.gov/pubmed/34952008

942. Kostoff, R. N., Calina, D., Kanduc, D., Briggs, M. B., Vlachoyiannopoulos, P., Svistunov, A. A., & Tsatsakis, A. (2021a). Erratum to "Why are we vaccinating children against COVID-19?" [Toxicol. Rep. 8C (2021) 1665-1684 / 1193]. Toxicol Rep, 8, 1981. doi:10.1016/j.toxrep.2021.10.003.
https://www.ncbi.nlm.nih.gov/pubmed/34642628

943. Kostoff, R. N., Calina, D., Kanduc, D., Briggs, M. B., Vlachoyiannopoulos, P., Svistunov, A. A., & Tsatsakis, A. (2021b). Why are we vaccinating children against COVID-19? Toxicol Rep, 8, 1665-1684. doi:10.1016/j.toxrep.2021.08.010.
https://www.ncbi.nlm.nih.gov/pubmed/34540594

944. Kremsner, P. G., Mann, P., Kroidl, A., Leroux-Roels, I., Schindler, C., Gabor, J. J., . . . Group, C.-N.-S. (2021). Safety and immunogenicity of an mRNA-lipid nanoparticle vaccine candidate against SARS-CoV-2 : A phase 1 randomized clinical trial. Wien Klin Wochenschr, 133(17-18), 931-941. doi:10.1007/s00508-021-01922-y.
https://www.ncbi.nlm.nih.gov/pubmed/34378087

945. Kustin, T., Harel, N., Finkel, U., Perchik, S., Harari, S., Tahor, M., . . . Stern, A. (2021). Evidence for increased breakthrough rates of SARS-CoV-2 variants of concern in BNT162b2-mRNA-vaccinated individuals. Nat Med, 27(8), 1379-1384. doi:10.1038/s41591-021-01413-7.
https://www.ncbi.nlm.nih.gov/pubmed/34127854

946. Kwan, M. Y. W., Chua, G. T., Chow, C. B., Tsao, S. S. L., To, K. K. W., Yuen, K. Y., . . . Ip, P. (2021). mRNA COVID vaccine and myocarditis in adolescents. Hong Kong Med J, 27(5), 326-327. doi:10.12809/hkmj215120.
https://www.ncbi.nlm.nih.gov/pubmed/34393110

947. Lee, E., Chew, N. W. S., Ng, P., & Yeo, T. J. (2021). Reply to "Letter to the editor: Myocarditis should be considered in those with a troponin rise and unobstructed coronary arteries following PfizerBioNTech COVID-19 vaccination". QJM. doi:10.1093/qjmed/hcab232.
https://www.ncbi.nlm.nih.gov/pubmed/34463770

948. Lee, E. J., Cines, D. B., Gernsheimer, T., Kessler, C., Michel, M., Tarantino, M. D., . . . Bussel, J. B. (2021). Thrombocytopenia following Pfizer and Moderna SARS-CoV-2 vaccination. Am J Hematol, 96(5), 534-537. doi:10.1002/ajh.26132.
https://www.ncbi.nlm.nih.gov/pubmed/33606296

949. Levin, D., Shimon, G., Fadlon-Derai, M., Gershovitz, L., Shovali, A., Sebbag, A., . . . Gordon, B. (2021). Myocarditis following COVID-19 vaccination – A case series. Vaccine, 39(42), 6195-6200. doi:10.1016/j.vaccine.2021.09.004.
https://www.ncbi.nlm.nih.gov/pubmed/34535317

950. Li, J., Hui, A., Zhang, X., Yang, Y., Tang, R., Ye, H., . . . Zhu, F. (2021). Safety and immunogenicity of the SARS-CoV-2 BNT162b1 mRNA vaccine in younger and older Chinese adults: a randomized, placebo-controlled, double-blind phase 1 study. Nat Med, 27(6), 1062-1070. doi:10.1038/s41591-021-01330-9.
https://www.ncbi.nlm.nih.gov/pubmed/33888900

951. Li, M., Yuan, J., Lv, G., Brown, J., Jiang, X., & Lu, Z. K. (2021). Myocarditis and Pericarditis following COVID-19 Vaccination: Inequalities in Age and Vaccine Types. J Pers Med, 11(11). doi:10.3390/jpm11111106.
https://www.ncbi.nlm.nih.gov/pubmed/34834458

952. Lim, Y., Kim, M. C., Kim, K. H., Jeong, I. S., Cho, Y. S., Choi, Y. D., & Lee, J. E. (2021). Case Report: Acute Fulminant Myocarditis and Cardiogenic Shock After Messenger RNA Coronavirus Disease 2019 Vaccination Requiring Extracorporeal Cardiopulmonary Resuscitation. Front Cardiovasc Med, 8, 758996. doi:10.3389/fcvm.2021.758996.
https://www.ncbi.nlm.nih.gov/pubmed/34778411

953. Long, S. S. (2021). Important Insights into Myopericarditis after the Pfizer mRNA COVID-19 Vaccination in Adolescents. J Pediatr, 238, 5. doi:10.1016/j.jpeds.2021.07.057.
https://www.ncbi.nlm.nih.gov/pubmed/34332972

954. Luk, A., Clarke, B., Dahdah, N., Ducharme, A., Krahn, A., McCrindle, B., . . . McDonald, M. (2021). Myocarditis and Pericarditis After COVID-19 mRNA Vaccination: Practical Considerations for Care Providers. Can J Cardiol, 37(10), 1629-1634. doi:10.1016/j.cjca.2021.08.001.
https://www.ncbi.nlm.nih.gov/pubmed/34375696

955. Madelon, N., Lauper, K., Breville, G., Sabater Royo, I., Goldstein, R., Andrey, D. O., . . . Eberhardt, C. S. (2021). Robust T cell responses in anti-CD20 treated patients following COVID-19 vaccination: a prospective cohort study. Clin Infect Dis. doi:10.1093/cid/ciab954.
https://www.ncbi.nlm.nih.gov/pubmed/34791081

956. Mangat, C., & Milosavljevic, N. (2021). BNT162b2 Vaccination during Pregnancy Protects Both the Mother and Infant: Anti-SARS-CoV-2 S Antibodies Persistently Positive in an Infant at 6 Months of Age. Case Rep Pediatr, 2021, 6901131. doi:10.1155/2021/6901131.
https://www.ncbi.nlm.nih.gov/pubmed/34676123

957. Mark, C., Gupta, S., Punnett, A., Upton, J., Orkin, J., Atkinson, A., . . . Alexander, S. (2021). Safety of administration of BNT162b2 mRNA (Pfizer-BioNTech) COVID-19 vaccine in youths and young adults with a history of acute lymphoblastic leukemia and allergy to PEG-asparaginase. Pediatr Blood Cancer, 68(11), e29295. doi:10.1002/pbc.29295.
https://www.ncbi.nlm.nih.gov/pubmed/34398511

958. Martins-Filho, P. R., Quintans-Junior, L. J., de Souza Araujo, A. A., Sposato, K. B., Souza Tavares, C. S., Gurgel, R. Q., . . . Santos, V. S. (2021). Socio-economic inequalities and COVID-19 incidence and mortality in Brazilian children: a nationwide register-based study. Public Health, 190, 4-6. doi:10.1016/j.puhe.2020.11.005. https://www.ncbi.nlm.nih.gov/pubmed/33316478

959. McLean, K., & Johnson, T. J. (2021). Myopericarditis in a previously healthy adolescent male following COVID-19 vaccination: A case report. Acad Emerg Med, 28(8), 918-921. doi:10.1111/acem.14322. https://www.ncbi.nlm.nih.gov/pubmed/34133825

960. Mevorach, D., Anis, E., Cedar, N., Bromberg, M., Haas, E. J., Nadir, E., . . . Alroy-Preis, S. (2021). Myocarditis after BNT162b2 mRNA Vaccine against Covid-19 in Israel. N Engl J Med, 385(23), 2140-2149. doi:10.1056/NEJMoa2109730. https://www.ncbi.nlm.nih.gov/pubmed/34614328

961. Minocha, P. K., Better, D., Singh, R. K., & Hoque, T. (2021). Recurrence of Acute Myocarditis Temporally Associated with Receipt of the mRNA Coronavirus Disease 2019 (COVID-19) Vaccine in a Male Adolescent. J Pediatr, 238, 321-323. doi:10.1016/j.jpeds.2021.06.035. https://www.ncbi.nlm.nih.gov/pubmed/34166671

962. Mizrahi, B., Lotan, R., Kalkstein, N., Peretz, A., Perez, G., Ben-Tov, A., . . . Patalon, T. (2021). Correlation of SARS-CoV-2-breakthrough infections to time-from-vaccine. Nat Commun, 12(1), 6379. doi:10.1038/s41467-021-26672-3. https://www.ncbi.nlm.nih.gov/pubmed/34737312

963. Moffitt, K., Cheung, E., Yeung, T., Stamoulis, C., & Malley, R. (2021). Analysis of Staphylococcus aureus Transcriptome in Pediatric Soft Tissue Abscesses and Comparison to Murine Infections. Infect Immun, 89(4). doi:10.1128/IAI.00715-20. https://www.ncbi.nlm.nih.gov/pubmed/33526560

964. Mohamed, L., Madsen, A. M. R., Schaltz-Buchholzer, F., Ostenfeld, A., Netea, M. G., Benn, C. S., & Kofoed, P. E. (2021). Reactivation of BCG vaccination scars after vaccination with mRNA-Covid-vaccines: two case reports. BMC Infect Dis, 21(1), 1264. doi:10.1186/s12879-021-06949-0. https://www.ncbi.nlm.nih.gov/pubmed/34930152

965. Montgomery, J., Ryan, M., Engler, R., Hoffman, D., McClenathan, B., Collins, L., . . . Cooper, L. T., Jr. (2021). Myocarditis Following Immunization With mRNA COVID-19 Vaccines in Members of the US Military. JAMA Cardiol, 6(10), 1202-1206. doi:10.1001/jamacardio.2021.2833. https://www.ncbi.nlm.nih.gov/pubmed/34185045

966. Murakami, Y., Shinohara, M., Oka, Y., Wada, R., Noike, R., Ohara, H., . . . Ikeda, T. (2021). Myocarditis Following a COVID-19 Messenger RNA Vaccination: A Japanese Case Series. Intern Med. doi:10.2169/internalmedicine.8731-21. https://www.ncbi.nlm.nih.gov/pubmed/34840235

967. Nagasaka, T., Koitabashi, N., Ishibashi, Y., Aihara, K., Takama, N., Ohyama, Y., . . . Kaneko, Y. (2021). Acute Myocarditis Associated with COVID-19 Vaccination: A Case Report. J Cardiol Cases. doi:10.1016/j.jccase.2021.11.006. https://www.ncbi.nlm.nih.gov/pubmed/34876937

968. Ntouros, P. A., Vlachogiannis, N. I., Pappa, M., Nezos, A., Mavragani, C. P., Tektonidou, M. G., . . . Sfikakis, P. P. (2021). Effective DNA damage response after acute but not chronic immune challenge: SARS-CoV-2 vaccine versus Systemic Lupus Erythematosus. Clin Immunol, 229, 108765. doi:10.1016/j.clim.2021.108765. https://www.ncbi.nlm.nih.gov/pubmed/34089859

969. Nygaard, U., Holm, M., Bohnstedt, C., Chai, Q., Schmidt, L. S., Hartling, U. B., . . . Stensballe, L. G. (2022). Population-based Incidence of Myopericarditis After COVID-19 Vaccination in Danish Adolescents. Pediatr Infect Dis J, 41(1), e25-e28. doi:10.1097/INF.0000000000003389. https://www.ncbi.nlm.nih.gov/pubmed/34889875

970. Oberhardt, V., Luxenburger, H., Kemming, J., Schulien, I., Ciminski, K., Giese, S., . . . Hofmann, M. (2021). Rapid and stable mobilization of CD8(+) T cells by SARS-CoV-2 mRNA vaccine. Nature, 597(7875), 268-273. doi:10.1038/s41586-021-03841-4. https://www.ncbi.nlm.nih.gov/pubmed/34320609

971. Park, H., Yun, K. W., Kim, K. R., Song, S. H., Ahn, B., Kim, D. R., . . . Kim, Y. J. (2021). Epidemiology and Clinical Features of Myocarditis/Pericarditis before the Introduction of mRNA COVID-19 Vaccine in Korean Children: a Multicenter Study. J Korean Med Sci, 36(32), e232. doi:10.3346/jkms.2021.36.e232. https://www.ncbi.nlm.nih.gov/pubmed/34402230

972. Park, J., Brekke, D. R., & Bratincsak, A. (2021). Self-limited myocarditis presenting with chest pain and ST segment elevation in adolescents after vaccination with the BNT162b2 mRNA vaccine. Cardiol Young, 1-4. doi:10.1017/S1047951121002547. https://www.ncbi.nlm.nih.gov/pubmed/34180390

973. Patel, Y. R., Louis, D. W., Atalay, M., Agarwal, S., & Shah, N. R. (2021). Cardiovascular magnetic resonance findings in young adult patients with acute myocarditis following mRNA COVID-19 vaccination: a case series. J Cardiovasc Magn Reson, 23(1), 101. doi:10.1186/s12968-021-00795-4. https://www.ncbi.nlm.nih.gov/pubmed/34496880

974. Patone, M., Mei, X. W., Handunnetthi, L., Dixon, S., Zaccardi, F., Shankar-Hari, M., . . . Hippisley-Cox, J. (2021). Risks of myocarditis, pericarditis, and cardiac arrhythmias associated with COVID-19 vaccination or SARS-CoV-2 infection. Nat Med. doi:10.1038/s41591-021-01630-0. https://www.ncbi.nlm.nih.gov/pubmed/34907393

975. Patrignani, A., Schicchi, N., Calcagnoli, F., Falchetti, E., Ciampani, N., Argalia, G., & Mariani, A. (2021). Acute myocarditis following Comirnaty vaccination in a healthy man with previous SARS-CoV-2 infection. Radiol Case Rep, 16(11), 3321-3325. doi:10.1016/j.radcr.2021.07.082. https://www.ncbi.nlm.nih.gov/pubmed/34367386

976. Perez, Y., Levy, E. R., Joshi, A. Y., Virk, A., Rodriguez-Porcel, M., Johnson, M., . . . Swift, M. D. (2021). Myocarditis Following COVID-19 mRNA Vaccine: A Case Series and Incidence Rate Determination. Clin Infect Dis. doi:10.1093/cid/ciab926. https://www.ncbi.nlm.nih.gov/pubmed/34734240

977. Perrotta, A., Biondi-Zoccai, G., Saade, W., Miraldi, F., Morelli, A., Marullo, A. G., . . . Peruzzi, M. (2021). A snapshot global survey on side effects of COVID-19 vaccines among healthcare professionals and armed forces with a focus on headache. Panminerva Med, 63(3), 324-331. doi:10.23736/S0031-0808.21.04435-9. https://www.ncbi.nlm.nih.gov/pubmed/34738774

978. Pinana, J. L., Lopez-Corral, L., Martino, R., Montoro, J., Vazquez, L., Perez, A., . . . Cell Therapy, G. (2022). SARS-CoV-2-reactive antibody detection after SARS-CoV-2 vaccination in hematopoietic stem cell transplant recipients: Prospective survey from the Spanish Hematopoietic Stem Cell Transplantation and Cell Therapy Group. Am J Hematol, 97(1), 30-42. doi:10.1002/ajh.26385.
https://www.ncbi.nlm.nih.gov/pubmed/34695229

979. Revon-Riviere, G., Ninove, L., Min, V., Rome, A., Coze, C., Verschuur, A., . . . Andre, N. (2021). The BNT162b2 mRNA COVID-19 vaccine in adolescents and young adults with cancer: A monocentric experience. Eur J Cancer, 154, 30-34. doi:10.1016/j.ejca.2021.06.002.
https://www.ncbi.nlm.nih.gov/pubmed/34233234

980. Sanchez Tijmes, F., Thavendiranathan, P., Udell, J. A., Seidman, M. A., & Hanneman, K. (2021). Cardiac MRI Assessment of Nonischemic Myocardial Inflammation: State of the Art Review and Update on Myocarditis Associated with COVID-19 Vaccination. Radiol Cardiothorac Imaging, 3(6), e210252. doi:10.1148/ryct.210252.
https://www.ncbi.nlm.nih.gov/pubmed/34934954

981. Schauer, J., Buddhe, S., Colyer, J., Sagiv, E., Law, Y., Mallenahalli Chikkabyrappa, S., & Portman, M. A. (2021). Myopericarditis After the Pfizer Messenger Ribonucleic Acid Coronavirus Disease Vaccine in Adolescents. J Pediatr, 238, 317-320. doi:10.1016/j.jpeds.2021.06.083.
https://www.ncbi.nlm.nih.gov/pubmed/34228985

982. Schneider, J., Sottmann, L., Greinacher, A., Hagen, M., Kasper, H. U., Kuhnen, C., . . . Schmeling, A. (2021). Postmortem investigation of fatalities following vaccination with COVID-19 vaccines. Int J Legal Med, 135(6), 2335-2345. doi:10.1007/s00414-021-02706-9.
https://www.ncbi.nlm.nih.gov/pubmed/34591186

983. Schramm, R., Costard-Jackle, A., Rivinius, R., Fischer, B., Muller, B., Boeken, U., . . . Gummert, J. (2021). Poor humoral and T-cell response to two-dose SARS-CoV-2 messenger RNA vaccine BNT162b2 in cardiothoracic transplant recipients. Clin Res Cardiol, 110(8), 1142-1149. doi:10.1007/s00392-021-01880-5.
https://www.ncbi.nlm.nih.gov/pubmed/34241676

984. Sessa, F., Salerno, M., Esposito, M., Di Nunno, N., Zamboni, P., & Pomara, C. (2021). Autopsy Findings and Causality Relationship between Death and COVID-19 Vaccination: A Systematic Review. J Clin Med, 10(24). doi:10.3390/jcm10245876.
https://www.ncbi.nlm.nih.gov/pubmed/34945172

985. Sharif, N., Alzahrani, K. J., Ahmed, S. N., & Dey, S. K. (2021). Efficacy, Immunogenicity and Safety of COVID-19 Vaccines: A Systematic Review and Meta-Analysis. Front Immunol, 12, 714170. doi:10.3389/fimmu.2021.714170.
https://www.ncbi.nlm.nih.gov/pubmed/34707602

986. Shay, D. K., Gee, J., Su, J. R., Myers, T. R., Marquez, P., Liu, R., . . . Shimabukuro, T. T. (2021). Safety Monitoring of the Janssen (Johnson & Johnson) COVID-19 Vaccine – United States, March-April 2021. MMWR Morb Mortal Wkly Rep, 70(18), 680-684. doi:10.15585/mmwr.mm7018e2.
https://www.ncbi.nlm.nih.gov/pubmed/33956784

987. Shazley, O., & Alshazley, M. (2021). A COVID-Positive 52-Year-Old Man Presented With Venous Thromboembolism and Disseminated Intravascular Coagulation Following Johnson & Johnson Vaccination: A Case-Study. Cureus, 13(7), e16383. doi:10.7759/cureus.16383.
https://www.ncbi.nlm.nih.gov/pubmed/34408937

988. Shiyovich, A., Witberg, G., Aviv, Y., Eisen, A., Orvin, K., Wiessman, M., . . . Hamdan, A. (2021). Myocarditis following COVID-19 vaccination: magnetic resonance imaging study. Eur Heart J Cardiovasc Imaging. doi:10.1093/ehjci/jeab230.
https://www.ncbi.nlm.nih.gov/pubmed/34739045

989. Simone, A., Herald, J., Chen, A., Gulati, N., Shen, A. Y., Lewin, B., & Lee, M. S. (2021). Acute Myocarditis Following COVID-19 mRNA Vaccination in Adults Aged 18 Years or Older. JAMA Intern Med, 181(12), 1668-1670. doi:10.1001/jamainternmed.2021.5511.
https://www.ncbi.nlm.nih.gov/pubmed/34605853

990. Singer, M. E., Taub, I. B., & Kaelber, D. C. (2021). Risk of Myocarditis from COVID-19 Infection in People Under Age 20: A Population-Based Analysis. medRxiv. doi:10.1101/2021.07.23.21260998.
https://www.ncbi.nlm.nih.gov/pubmed/34341797

991. Smith, C., Odd, D., Harwood, R., Ward, J., Linney, M., Clark, M., . . . Fraser, L. K. (2021). Deaths in children and young people in England after SARS-CoV-2 infection during the first pandemic year. Nat Med. doi:10.1038/s41591-021-01578-1.
https://www.ncbi.nlm.nih.gov/pubmed/34764489

992. Snapiri, O., Rosenberg Danziger, C., Shirman, N., Weissbach, A., Lowenthal, A., Ayalon, I., . . . Bilavsky, E. (2021). Transient Cardiac Injury in Adolescents Receiving the BNT162b2 mRNA COVID-19 Vaccine. Pediatr Infect Dis J, 40(10), e360-e363. doi:10.1097/INF.0000000000003235.
https://www.ncbi.nlm.nih.gov/pubmed/34077949

993. Spinner, J. A., Julien, C. L., Olayinka, L., Dreyer, W. J., Bocchini, C. E., Munoz, F. M., & Devaraj, S. (2021). SARS-CoV-2 anti-spike antibodies after vaccination in pediatric heart transplantation: A first report. J Heart Lung Transplant. doi:10.1016/j.healun.2021.11.001.
https://www.ncbi.nlm.nih.gov/pubmed/34911654

994. Starekova, J., Bluemke, D. A., Bradham, W. S., Grist, T. M., Schiebler, M. L., & Reeder, S. B. (2021). Myocarditis Associated with mRNA COVID-19 Vaccination. Radiology, 301(2), E409-E411. doi:10.1148/radiol.2021211430.
https://www.ncbi.nlm.nih.gov/pubmed/34282971

995. Sulemankhil, I., Abdelrahman, M., & Negi, S. I. (2021). Temporal association between the COVID-19 Ad26.COV2.S vaccine and acute myocarditis: A case report and literature review. Cardiovasc Revasc Med. doi:10.1016/j.carrev.2021.08.012.
https://www.ncbi.nlm.nih.gov/pubmed/34420869

996. Tailor, P. D., Feighery, A. M., El-Sabawi, B., & Prasad, A. (2021). Case report: acute myocarditis following the second dose of mRNA-1273 SARS-CoV-2 vaccine. Eur Heart J Case Rep, 5(8), ytab319. doi:10.1093/ehjcr/ytab319.
https://www.ncbi.nlm.nih.gov/pubmed/34514306

997. Takeda, M., Ishio, N., Shoji, T., Mori, N., Matsumoto, M., & Shikama, N. (2021). Eosinophilic Myocarditis Following Coronavirus Disease 2019 (COVID-19) Vaccination. Circ J. doi:10.1253/circj.CJ-21-0935.
https://www.ncbi.nlm.nih.gov/pubmed/34955479

998. Team, C. C.-R., Food, & Drug, A. (2021). Allergic Reactions Including Anaphylaxis After Receipt of the First Dose of Pfizer-BioNTech COVID-19 Vaccine – United States, December 14-23, 2020. MMWR Morb Mortal Wkly Rep, 70(2), 46-51. doi:10.15585/mmwr.mm7002e1.
https://www.ncbi.nlm.nih.gov/pubmed/33444297

999. Thompson, M. G., Burgess, J. L., Naleway, A. L., Tyner, H., Yoon, S. K., Meece, J., . . . Gaglani, M. (2021). Prevention and Attenuation of Covid-19 with the BNT162b2 and mRNA-1273 Vaccines. N Engl J Med, 385(4), 320-329. doi:10.1056/NEJMoa2107058.
https://www.ncbi.nlm.nih.gov/pubmed/34192428

1000. Tinoco, M., Leite, S., Faria, B., Cardoso, S., Von Hafe, P., Dias, G., . . . Lourenco, A. (2021). Perimyocarditis Following COVID-19 Vaccination. Clin Med Insights Cardiol, 15, 11795468211056634. doi:10.1177/11795468211056634.
https://www.ncbi.nlm.nih.gov/pubmed/34866957

1001. Truong, D. T., Dionne, A., Muniz, J. C., McHugh, K. E., Portman, M. A., Lambert, L. M., . . . Newburger, J. W. (2021). Clinically Suspected Myocarditis Temporally Related to COVID-19 Vaccination in Adolescents and Young Adults. Circulation. doi:10.1161/CIRCULATIONAHA.121.056583.
https://www.ncbi.nlm.nih.gov/pubmed/34865500

1002. Tutor, A., Unis, G., Ruiz, B., Bolaji, O. A., & Bob-Manuel, T. (2021). Spectrum of Suspected Cardiomyopathy Due to COVID-19: A Case Series. Curr Probl Cardiol, 46(10), 100926. doi:10.1016/j.cpcardiol.2021.100926.
https://www.ncbi.nlm.nih.gov/pubmed/34311983

1003. Umei, T. C., Kishino, Y., Shiraishi, Y., Inohara, T., Yuasa, S., & Fukuda, K. (2021). Recurrence of myopericarditis following mRNA COVID-19 vaccination in a male adolescent. CJC Open. doi:10.1016/j.cjco.2021.12.002.
https://www.ncbi.nlm.nih.gov/pubmed/34904134

1004. Vidula, M. K., Ambrose, M., Glassberg, H., Chokshi, N., Chen, T., Ferrari, V. A., & Han, Y. (2021). Myocarditis and Other Cardiovascular Complications of the mRNA-Based COVID-19 Vaccines. Cureus, 13(6), e15576. doi:10.7759/cureus.15576.
https://www.ncbi.nlm.nih.gov/pubmed/34277198

1005. Visclosky, T., Theyyunni, N., Klekowski, N., & Bradin, S. (2021). Myocarditis Following mRNA COVID-19 Vaccine. Pediatr Emerg Care, 37(11), 583-584. doi:10.1097/PEC.0000000000002557.
https://www.ncbi.nlm.nih.gov/pubmed/34731877

1006. Warren, C. M., Snow, T. T., Lee, A. S., Shah, M. M., Heider, A., Blomkalns, A., . . . Nadeau, K. C. (2021). Assessment of Allergic and Anaphylactic Reactions to mRNA COVID-19 Vaccines With Confirmatory Testing in a US Regional Health System. JAMA Netw Open, 4(9), e2125524. doi:10.1001/jamanetworkopen.2021.25524.
https://www.ncbi.nlm.nih.gov/pubmed/34533570

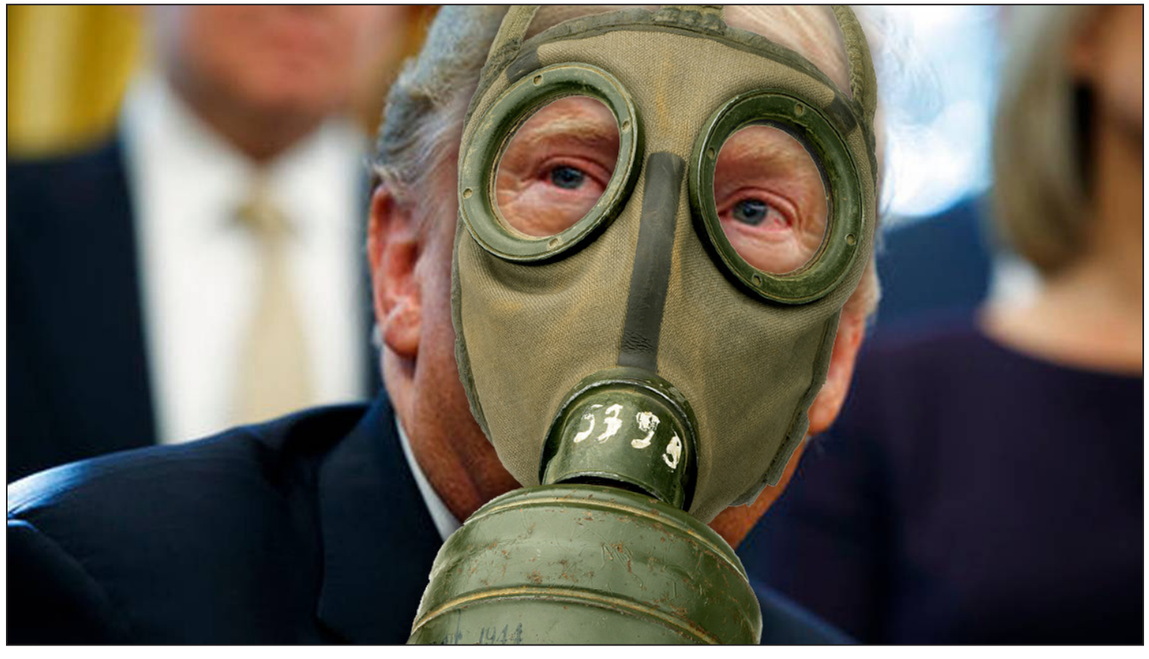
1007. Watkins, K., Griffin, G., Septaric, K., & Simon, E. L. (2021). Myocarditis after BNT162b2 vaccination in a healthy male. Am J Emerg Med, 50, 815 e811-815 e812. doi:10.1016/j.ajem.2021.06.051.
https://www.ncbi.nlm.nih.gov/pubmed/34229940

1008. Weitzman, E. R., Sherman, A. C., & Levy, O. (2021). SARS-CoV-2 mRNA Vaccine Attitudes as Expressed in U.S. FDA Public Commentary: Need for a Public-Private Partnership in a Learning Immunization System. Front Public Health, 9, 695807. doi:10.3389/fpubh.2021.695807.
https://www.ncbi.nlm.nih.gov/pubmed/34336774

1009. Welsh, K. J., Baumblatt, J., Chege, W., Goud, R., & Nair, N. (2021). Thrombocytopenia including immune thrombocytopenia after receipt of mRNA COVID-19 vaccines reported to the Vaccine Adverse Event Reporting System (VAERS). Vaccine, 39(25), 3329-3332. doi:10.1016/j.vaccine.2021.04.054.
https://www.ncbi.nlm.nih.gov/pubmed/34006408

1010. Witberg, G., Barda, N., Hoss, S., Richter, I., Wiessman, M., Aviv, Y., . . . Kornowski, R. (2021). Myocarditis after Covid-19 Vaccination in a Large Health Care Organization. N Engl J Med, 385(23), 2132-2139. doi:10.1056/NEJMoa2110737.
https://www.ncbi.nlm.nih.gov/pubmed/34614329

1011. Zimmermann, P., & Curtis, N. (2020). Why is COVID-19 less severe in children? A review of the proposed mechanisms underlying the age-related difference in severity of SARS-CoV-2 infections. Arch Dis Child. doi:10.1136/archdischild-2020-320338.
https://www.ncbi.nlm.nih.gov/pubmed/33262177



CHAPTER TWO

THE LOST PEER REVIEW

I've included this chapter to use the older peer review to show the reader that we've known about a number of components related to the manufacturing of injectible biologics that can and do cause harms, adverse events and even deaths. These vulnerable points in the manufacturing process apply to the CoV-2 injectible mRNA product as well as all vaccines on the current vaccine schedule. The manufacturing of injectible biologics is a complex process and what can only be accurately described as a dirty process where potential for undetected contamination lurks everywhere and where bacthes are not always the same as one would expect. As regards contamination by various animal viruses and bacteria known to be harmful to human beings, and batches or lots differing in content and known and accepted harms directly attributed to vaccines, the following peer review speaks for itslef. And while some of these reports date back to the 90s nothing has changed and they're as valid as if they were written today. You'll also see first hand how the terms "***Primary Vaccine Failure***" and "***Secondary Vaccine Failure***" have been replaced by the media with "Breakthrough Cases" as though the CoV-2 Investigative injections are working extremely well but a virus with a better survival rate than Influenza managed to sneak by all of the defenses. Bullshit. We're talking about ***Primary and Secondary Vaccine Failure*** as described in Centers for Disease Control (CDC) documents, which you'll be reading shortly.

I call this the lost peer review yet it's simply peer review the world never noticed. A number of factors may be involved in the variations in immune responses you'll read about here which include age, gender, race, amount and quality of the antigen, the dose administered and to some extent the route of administration, and genetics of the individuals immune system. For this reason a one-size-fits-all vaccine, as researchers well know, will inevitably result in human harms.

Therefore, vaccine harm is ubiquitous.

Washington DC National Academies Press (US) 1991
The National Academies Collection

Reports funded by National Institutes of Health
By Howson CP, Howe CJ, Fineberg HV, editors

Adverse Effects of Pertussis and Rubella Vaccines: A Report of the Committee to Review the Adverse Consequences of Pertussis and Rubella Vaccines

Excerpt

Parents have come to depend on vaccines to protect their children from a variety of diseases. Some evidence suggests, however, that vaccination against pertussis (whooping cough) and rubella (German measles) is, in a small number of cases, associated with increased risk of serious illness. This book examines the controversy over the evidence and offers a comprehensively documented assessment of the risk of illness following immunization with vaccines against pertussis and rubella. Based on extensive review of the evidence from epidemiologic studies, case histories, studies in animals, and other sources of information, the book examines: The relation of pertussis vaccines to a number of serious adverse events, including encephalopathy and other central nervous system disorders, sudden infant death syndrome, autism, Guillain-Barre syndrome, learning disabilities, and Reye syndrome. The relation of rubella vaccines to arthritis, various neuropathies, and thrombocytopenic purpura. The volume, which includes a description of the committee's methods for evaluating evidence and directions for future research, will be important reading for public health officials, pediatricians, researchers, and concerned parents.

http://www.ncbi.nlm.nih.gov/pubmed/25121241

"that the evidence is consistent with a causal relation between DPT vaccine and acute encephalopathy, shock and "unusual shock-like state," and between RA 27/3 rubella vaccine and chronic arthritis; and that the evidence indicates a causal relation between DPT vaccine and anaphylaxis, between the pertussis component of DPT vaccine and protracted, inconsolable crying, and between RA 27/3 rubella vaccine and acute arthritis."

[RA 27/3 rubella is still in use today]

JAMA • January 1992

Adverse events following pertussis and rubella vaccines Summary of a report of the Institute of Medicine

By Howson CP1, Fineberg HV.

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Abstract

In August 1991, the Institute of Medicine released a report entitled Adverse Effects of Pertussis and Rubella Vaccines, which examined 18 adverse events in relation to diphtheria-tetanus-pertussis (DTP) vaccine and four adverse events in relation to the currently used rubella vaccine strain, RA 27/3. The committee spent 20 months reviewing a wide range of information sources, including case series and individual case reports, both published and unpublished, epidemiologic studies, studies in animals, and other laboratory studies. The committee found that the evidence indicates a causal relation between DTP vaccine and anaphylaxis and between the pertussis component of DTP vaccine and extended periods of inconsolable crying or screaming. The committee also reported that the evidence indicates a causal relation between the rubella vaccine and acute arthritis in adult women. The committee found the available evidence weaker but still consistent with a causal relation between DTP vaccine and two conditions: acute encephalopathy and hypotonic, hyporesponsive episodes, and between rubella vaccine and chronic arthritis in adult women. Estimated incidence rates of these adverse events following vaccination are provided, where possible. The committee found that the evidence does not indicate a causal relation between the DTP vaccine and infantile spasms, hypsarrhythmia, Reye's syndrome, and sudden infant death syndrome. The committee found insufficient evidence to indicate either the presence or absence of a causal relation between DTP vaccine and chronic neurologic damage, aseptic meningitis, erythema multiforme or other rash, Guillain-Barré syndrome, hemolytic anemia, juvenile diabetes, learning disabilities and attention-deficit disorder, peripheral mononeuropathy, or thrombocytopenia, and between rubella vaccine and radiculoneuritis and other neuropathies or thrombocytopenic purpura. The committee's evaluative methods are briefly described and a summary of research needs is provided

http://www.ncbi.nlm.nih.gov/pubmed/1727962

"The committee found that the evidence indicates a causal relation between DTP vaccine and anaphylaxis and between the pertussis component of DTP vaccine and extended periods of inconsolable crying or screaming.
The committee also reported that the evidence indicates a causal relation between the rubella vaccine and acute arthritis in adult women. The committee found the available evidence weaker but still consistent with a causal relation between DTP vaccine and two conditions—acute encephalopathy and hypotonic, hyporesponsive episodes—and between rubella vaccine and chronic arthritis in adult women."

Vaccine • October 1991

Adverse reactions after injection of adsorbed diphtheria-pertussis-tetanus (DPT) vaccine are not due only to pertussis organisms or pertussis components in the vaccine

By Gupta RK1, Relyveld EH.

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Abstract

Reactions to adsorbed diphtheria-pertussis-tetanus (DPT) vaccine have mostly been attributed to the pertussis organisms or pertussis components in the vaccine. Nevertheless reactions may also be due to other factors such as sensitization induced by aluminium adjuvants and impurities present in crude toxoids that cannot be removed by purification of toxoids after formalinization. Aluminium compounds such as aluminium phosphate and aluminium hydroxide are the most commonly used adjuvants with vaccines for human use. Due to the increasing concern about the toxicity of aluminium, other adjuvants like calcium phosphate may be evaluated as an alternative to aluminium adjuvants. To minimize reactions after immunization with DPT vaccine due to impurities in the toxoids, the use of toxoided purified toxins is suggested.

http://www.ncbi.nlm.nih.gov/pubmed/?term=1759487

"... reactions may also be due to other factors such as sensitization induced by aluminium adjuvants and impurities present in crude toxoids that cannot be removed by purification of toxoids after formalinization."

Pace Environmental Law Review, vol. 28, no. 2 • 2011

Unanswered Questions
A Review of Compensated Cases of Vaccine-Induced Brain Injury

by Mary Holland, Louis Conte, Robert Krakow and Lisa Colin

Executive Summary

In 1986, Congress created the Vaccine Injury Compensation Program (VICP) under the National Childhood Vaccine Injury Act (1986 Law). This Program has original jurisdiction for children's claims of vaccine injury. Because almost all children receive multiple vaccinations for daycare and school, it is critically important that the Program provides fundamental fairness, due process and transparency. This empirical investigation, published in a peer-reviewed law journal, examines claims that the VICP compensated for vaccine-induced encephalopathy and seizure disorder. The VICP has compensated approximately 2,500 claims of vaccine injury since the inception of the program. This study found 83 cases of acknowledged vaccine-induced brain damage that include autism, a disorder that affects speech, social communication and behavior. In 21 published cases of the Court of Federal Claims, which administers the VICP, the Court stated that the petitioners had autism or described autism unambiguously. In 62 remaining cases, the authors identified settlement agreements where Health and Human Services (HHS) compensated children with vaccine-induced brain damage, who also have autism or an autism spectrum disorder. Parents reported the existence of autism in telephone interviews and supplied supplemental materials including medical diagnoses, school records, and completed, standard autism screening questionnaires to verify their reports. In 39 of the 83 cases, or 47% of the cases of vaccine injury reviewed, there is confirmation of autism or autism spectrum disorder beyond parental report. This finding of autism in compensated cases of vaccine injury is significant. U.S. government spokespeople have been asserting no vaccine-autism link for more than a decade. This finding calls into question the decisions of the Court of Federal Claims in the Omnibus Autism Proceeding in 2009 and 2010 and the statement of Health and Human Services on its website that "HHS has never concluded in any case that autism was caused by vaccination."

Using publicly available information, the investigation shows that the VICP has been compensating cases of vaccine-induced brain damage associated with autism for more than twenty years. This investigation suggests that officials at HHS, the Department of Justice and the Court of Federal Claims may have been aware of this associa- tion but failed to publicly disclose it. The study calls on Congress to thoroughly investigate the VICP, including a medical investigation of compen- sated claims of vaccine injury. This investigation calls on Congress to get answers to these critically important unanswered questions.

http://www.ebcala.org/unanswered-questions

"Using publicly available information, the investigation shows that the Vaccine Injury Compensation Program (VICP) has been compensating cases of vaccine-induced brain damage associated with autism for more than twenty years. This investigation suggests that officials at HHS, the Department of Justice and the Court of Federal Claims may have been aware of this association but failed to publicly disclose it."

American Journal Of Public Health • April 1989

The role of secondary vaccine failures in measles outbreaks

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Abstract

An outbreak of measles in 1985-86 in a community where measles vaccine trials had been carried out from 1974-76 allowed the assessment of the role of ***secondary vaccine failures*** in previously immunized children. A total of 188 children from the vaccine trial were followed. Of these, 175 seroconverted initially while 13 (6 per cent) required re-immunization (***primary failure***). A total of 13 cases of measles, eight of which were laboratory and/or physician-confirmed, were reported in this cohort. Of these, nine cases occurred in the 175 subjects who had hemagglutination inhibition test (HI) and neutralizing antibody responses following the initial immunization. These nine cases represent ***secondary vaccine failures***. An additional four cases occurred in the 13 subjects with ***primary vaccine failure***. We conclude that ***secondary vaccine failures occur*** and that while ***primary failures account for most cases, secondary vaccine failures contribute*** to the occurrence of measles cases in an epidemic. A booster dose of measles vaccine may be necessary to reduce susceptibility to a sufficiently low level to allow the goal of measles elimination to be achieved.

http://www.ncbi.nlm.nih.gov/pubmed/2929807

"These nine cases represent secondary vaccine failures. An additional four cases occurred in the 13 subjects with primary vaccine failure. We conclude that secondary vaccine failures occur and that while primary failures account for most cases, secondary vaccine failures contribute to the occurrence of measles cases in an epidemic."

Pediatric Infectious Disease Journal • March 1991

Aseptic meningitis as a complication of mumps vaccination

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National Institute of Health Tokyo, Japan

Abstract

In 1989 a nationwide surveillance of neurologic complications after the administration of mumps vaccine was conducted in Japan, based on the notification of cases and the testing of mumps viruses isolated from cerebrospinal fluid for their relatedness to the vaccine by nucleotide sequence analysis. Among 630,157 recipients of measles-mumps-rubella trivalent (MMR) vaccine containing the Urabe Am9 mumps vaccine, there were at least 311 meningitis cases suspected to be vaccine-related. In 96 of these 311 cases, mumps virus related to the vaccine was isolated from cerebrospinal fluid. The unusually high incidence may have been partly a result of the adverse media publicity of the problem at the time of surveillance. We analyzed clinical features of 165 and 27 laboratory-confirmed mumps vaccine-related meningitis cases that occurred among the recipients of MMR and monovalent mumps vaccines, respectively, during a 1-year period after the introduction of MMR vaccine. The incidence of vaccine-related meningitis was similar among the recipients of MMR and monovalent Urabe Am9 mumps vaccines. Meningitis was generally mild and there were no sequelae from the illness. The complication was more frequent among male than among female children.

http://www.ncbi.nlm.nih.gov/pubmed/2041668

"Among 630,157 recipients of measles-mumps-rubella trivalent (MMR) vaccine containing the Urabe Am9 mumps vaccine, there were at least 311 meningitis cases suspected to be vaccine-related. In 96 of these 311 cases, mumps virus related to the vaccine was isolated from cerebrospinal fluid."

This outbreak demonstrates that transmission of measles can occur within a school population with a documented immunization level of 100%. This level was validated during the outbreak investigation. Previous investigations of measles outbreaks among highly immunized populations have revealed risk factors such as improper storage or handling of vaccine, vaccine administered to children under 1 year of age, use of globulin with vaccine, and use of killed virus vaccine (1-5). However, these risk factors did not adequately explain the occurrence of this outbreak.

If waning immunity is not a problem, this outbreak suggests that measles transmission can occur within the ***2%-10% of expected vaccine failures*** (5,7). However, transmission was not sustained beyond 36 days in this outbreak, and community spread was principally among unvaccinated preschool children. The infrequent occurrence of measles among highly vaccinated persons suggests that this outbreak may have resulted from chance clustering of otherwise randomly distributed ***vaccine failures in the community***. That measles transmission can occur among ***vaccine failures*** makes it even more important to ensure persons are adequately vaccinated.

http://www.cdc.gov/mmwr/preview/mmwrhtml/00000359.htm

“This outbreak demonstrates
that transmission of measles can occur
within a school population with a
documented immunization level of 100%.
This level was validated during the outbreak investigation.”

Polysorbate 80 and E-Ferol toxicity

By Alade SL, Brown RE, Paquet A Jr.

Abstract

The relatively recent introduction and use of an intravenous form of a vitamin E preparation (E-Ferol) has been associated with the development of an unusual syndrome and fatalities among low birth weight (less than 1,500 g), premature infants in neonatal intensive care units. We have observed an inhibitory effect by this vitamin E preparation on the in vitro response of human lymphocytes to phytohemagglutinin (PHA). E-Ferol suppressed the expected response to low doses of PHA. However, this suppression was not due to the alpha-tocopherol acetate (vitamin E) component, because alpha-tocopherol acetate by itself was not inhibitory; in fact, it often enhanced the PHA response. Because a mixture of polysorbate 80 and polysorbate 20 is used as a carrier in E-Ferol, these components were also tested and were found to be responsible for the suppression, especially the polysorbate 80. Concurrent with this suppression of PHA-induced mitogenesis was a decrease in the percentage of T11 lymphocytes.

http://www.ncbi.nlm.nih.gov/pubmed/3960626

“The relatively recent introduction and use
of an intravenous form of a vitamin E preparation
has been associated with the development of an unusual
syndrome and fatalities among low birth weight (less than
1,500 g), premature infants in neonatal intensive care units ...
polysorbate 80 and polysorbate 20 ... were found to be
responsible for the suppression,
especially the polysorbate 80.”

Journal Of The American Medical Association (JAMA) • July 2010 Medical News and Perspectives

FDA:
Benefits of Rotavirus Vaccination Outweigh Potential Contamination Risk

by Bridget M. Kuehn

On March 22, the FDA had recommended that physicians suspend the use of Rotarix after the agency learned that academic researchers made the unexpected finding that the vaccine contained DNA from porcine circovirus 1 (PCV1), a virus that is common in US swine but not associated with illness in pigs or humans (Victoria JG et al. J Virol. 2010;84[12]:6033-6040). This finding was confirmed by scientists from the FDA and the vaccine's maker, GlaxoSmithKline.

http://jama.jamanetwork.com/article.aspx?articleid=186166

"Recently discovered contamination
of 2 rotavirus vaccines by pig viruses
is unlikely to pose a human health threat,
according to the US Food and Drug Administration (FDA)."

Toxicology • December 2010

Interindividual variations
in the efficacy and toxicity of vaccines

Thomas C1, Moridani M.

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School of Pharmacy, Lake Erie College of Osteopathic Medicine
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Abstract

A number of currently available vaccines have shown significant differences in the magnitude of immune responses and toxicity in individuals undergoing vaccination. A number of factors may be involved in the variations in immune responses, which include age, gender, race, amount and quality of the antigen, the dose administered and to some extent the route of administration, and genetics of immune system. Hence, it becomes imperative that researchers have tools such as genomics and proteomics at their disposal to predict which set of population is more likely to be non-responsive or develop toxicity to vaccines. In this article, we briefly review the influence of pharmacogenomics biomarkers on the efficacy and toxicity of some of the most frequently reported vaccines that showed a high rate of variability in response and toxicity towards hepatitis B, measles, mumps, rubella, influenza, and AIDS/HIV.

http://www.ncbi.nlm.nih.gov/pubmed/19837123

"A number of currently available vaccines
have shown significant differences in the magnitude
of immune responses and toxicity
in individuals undergoing vaccination."

Canadian Medical Association Journal • November 1975

Analysis of a measles epidemic: possible role of vaccine failures

By W. E. Rawls, M. L. Rawls, and M. A. Chernesky

Abstract

A measles epidemic occurred in the Greensville (Ont.) Unit schools during January and February 1975. There were 47 cases of measles in 403 students: 26 (55%) of the children had a history of being vaccinated and 18 (38%) had not been vaccinated. Among children known to have been vaccinated at less than 1 year of age 7 of 13 contracted measles, while among the 48 children who had not been vaccinated 18 contracted measles. The attack rate among vaccinees increased with increasing time since vaccination. The observations of this study as well as those of similar studies suggest that ***vaccine failures contributed to the genesis of the epidemic***. It is recommended that all children initially vaccinated at less than 1 year of age should be revaccinated with live attenuated measles virus vaccine.

http://www.ncbi.nlm.nih.gov/pmc/articles/PMC1956577/

"The observations of this study
as well as those of similar studies
suggest that vaccine failures
contributed to the genesis of the epidemic."

New England Journal Of Medicine • January 1984

Abnormal T-lymphocyte subpopulations in healthy subjects after tetanus booster immunization

By Eibl MM, Mannhalter JW, Zlabinger G.

"By way of explanation, a vaccine safety test is one in which before-and-after vaccine tests are performed, specifically designed to test for possible adverse effects on the neurological, immunological, hematologic, genetic, and other systems of the body, in sufficient numbers of test subjects and controls to be statistically significant. As an example, in a little noted study from Germany by Eibl et al. [11], a significant, though temporary, drop of T-Helper lymphocytes was found in 11 healthy adults following routine tetanus booster vaccinations. Special concern rests in the fact that, in four of the subjects, T-helper lymphocytes fell to levels seen in active AIDS patients."

http://www.ncbi.nlm.nih.gov/pubmed/?term=6228737

"As an example, in a little noted study from Germany
by Eibl et al., a significant, though temporary, drop of
T-Helper lymphocytes was found in 11 healthy adults
following routine tetanus booster vaccinations.
Special concern rests in the fact that, in four of the subjects,
T-helper lymphocytes fell to levels seen
in active AIDS patients."

Lancet • April 1987

Possible Role Of Pestiviruses In Microcephaly Author Information

By BarbaraJ. Potts, JohnL. Sever, NancyR. Tzan, David Huddleston, GregoryA. Elder

Infectious Diseases Branch
National Institute of Neurological and Communicative Disorders and Stroke
National Institutes of Health, Bethesda, Maryland 20892, USA

Abstract

"The background of this suggestion was that, first, although usually a pathogen in cattle and sheep, pestivirus infection can occur in children (Yolken et al. 1989). Second, an association has been reported between pestivirus exposure and microcephaly in newborns (Potts et al. 1987), which might be due to a generalized reduction in white matter bulk. Third, dysmyelination (Potts et al. 1985, Anderson et al. 1987b), frank brain damage (Hewicker-Trautwein and Trautwein 1994), and hypothyroxinemia (Anderson et al. 1987a) are characteristics of perinatal pestivirus infection in lamb models, are found in preterm infants (Leviton and Gilles 1996, Reuss et al. 1997), and are associated with each other among preterm infants (Den Ouden et al. 1996, Leviton et al. 1999). "

Report available for purchase
http://www.thelancet.com/journals/lancet/article/PIIS0140-6736(87)90311-4/abstract

"... an association has been reported between pestivirus exposure and microcephaly in newborns, which might be due to a generalized reduction in white matter bulk. Third, dysmyelination, frank brain damage and hypothyroxinemia are characteristics of perinatal pestivirus infection in lamb models, are found in preterm infants, and are associated with each other among preterm infants ..."

Developments In Biological Standardization • 1991

Bovine viral diarrhea virus contamination of nutrient serum, cell cultures and viral vaccines

By Levings RL1, Wessman SJ.

National Veterinary Services Laboratories Animal and Plant Health Inspection Service
USDA, Ames, IA 50010

Abstract

Bovine viral diarrhea virus (BVDV) infection is common in the bovine population. Infection in utero leads to virus and antibody contamination of the fetal bovine serum used in cell cultures. These contaminants can interfere with diagnosis of viral infection. The high frequency of virus and antibody detection in individual animal or small pool samples suggests that any large pool of unscreened sera will be contaminated. Infection of cell cultures with BVDV can lead to interference with the growth of other viruses. Vaccine produced on contaminated cells may in turn be contaminated, leading to seroconversion or disease in the vaccine. The safety, purity, and efficacy of viral vaccines require BVDV testing of ingredients, cell substrates and final product. Methods for detection of BVDV in nutrient serum, cell cultures, seed viruses, and viral vaccines, and the frequency of their detection at the National Veterinary Services Laboratories are discussed.

http://www.ncbi.nlm.nih.gov/pubmed/1665461

"Vaccine produced on contaminated cells
may in turn be contaminated,
leading to seroconversion or disease in the vaccine."

Journal Of Clinical Microbiology • June 1994

Evidence of pestivirus RNA in human virus vaccines

By Harasawa R1, Tomiyama T.

Animal Center for Biomedical Research Faculty of Medicine
University of Tokyo, Japan

Abstract

We examined live virus vaccines against measles, mumps, and rubella for the presence of pestivirus RNA or of pestiviruses by reverse transcription PCR. Pestivirus RNA was detected in two measles-mumps-rubella combined vaccines and in two monovalent vaccines against mumps and rubella. Nucleotide sequence analysis of the PCR products indicated that a modified live vaccine strain used for immunization of cattle against bovine viral diarrhea is not responsible for the contamination of the vaccines.

http://www.ncbi.nlm.nih.gov/pubmed/?term=8077414

“Pestivirus RNA was detected in two measles-mumps-rubella combined vaccines and in two monovalent vaccines against mumps and rubella.”

Biologicals • December 1996

Application of PCR for detection of mycoplasma DNA and pestivirus RNA in human live viral vaccines

By Sasaki T1, Harasawa R, Shintani M, Fujiwara H, Sasaki Y, Horino A, Kenri T, Asada K, Kato I, Chino F.

Department of Safety Research on Biologics National Institute of Health, Tokyo, Japan

Abstract

PCR techniques were applied for the detection of mycoplasma DNA and pestivirus RNA to 43 lots of live viral vaccines (measles, mumps, rubella, and oral poliomyelitis) produced by six manufacturers in Japan. Although mycoplasma DNA was not detected in any of the vaccines tested, pestivirus RNA was detected in 12 lots (28%). The incidence of contamination among the four viral vaccines was in the range of 20 to 37%, and the incidence among the six manufacturers varied from 0 to 56%.

http://www.ncbi.nlm.nih.gov/pubmed/9088554

“The incidence of contamination among the four viral vaccines was in the range of 20 to 37%, and the incidence among the six manufacturers varied from 0 to 56%.”

Monaldi Archives Of Chest Disease • April 1998

The biological activities of simian virus 40 large-T antigen and its possible oncogenic effects in humans

By Matker CM1, Rizzo P, Pass HI, Di Resta I, Powers A, Mutti L, Kast WM, Carbone M.

Cardinal Bernardin Cancer Center Loyola University of Chicago Maywood, IL 60153, USA

Abstract

Simian virus 40 (SV40) is an oncogenic virus which induces tumors in hamsters and transforms human cells in tissue culture. Between 1955 and 1963, polio vaccines and adenovaccines were contaminated with SV40; therefore, millions of people were exposed to this oncogenic virus. The SV40 proteins responsible for in vivo oncogenesis and in vitro cell transformation are encoded by the early region of the virus. These proteins are called T (tumor) antigens (Tags), because animals with tumors induced by SV40 have antibodies against these viral proteins. Recently, we and other research laboratories have found SV40 in specific types of human tumors: mesothelioma, ependymoma and choroid plexus tumors, osteosarcoma and sarcoma. The same tumor types will develop in hamsters which have been injected systemically with SV40. SV40 causes cell transformation in tissue culture and tumors in animals, because SV40 Tag binds and inactivates the cellular tumor suppressor gene products, Rb and p53. We found that SV40 Tag binds p53 and Rb in human mesotheliomas, possibly contributing to the malignant phenotype.

http://www.ncbi.nlm.nih.gov/pubmed/9689808

"Between 1955 and 1963, polio vaccines and adenovaccines were contaminated with SV40; therefore, millions of people were exposed to this oncogenic [cancer causing] virus."

Anticancer Research • May 1999

Cancer risk associated with simian virus 40 contaminated polio vaccine

By Fisher SG1, Weber L, Carbone M.

Cancer Cause and Prevention Program
Loyola University Medical Center Maywood, Illinois 60153, USA

Abstract

BACKGROUND

The presence of SV40 in monkey cell cultures used in the preparation of the polio vaccine from 1955 through 1961 is well documented. Investigations have consistently demonstrated the oncogenic behavior of SV40 in animal models. Early epidemiologic studies were inadequate in demonstrating an increase in cancer incidence associated with contaminated vaccine. Recently, investigators have provided persuasive evidence that SV40 is present in human ependymomas, choroid plexus tumors, bone tumors, and mesotheliomas, however, the etiologic role of the virus in tumorigenesis has not been established.

MATERIALS AND METHODS

Using data from SEER, we analyzed the incidence of brain tumors, bone tumors, and mesotheliomas from 1973-1993 and the possible relationship of these tumors with the administration of the SV40 contaminated vaccine.

RESULTS

Our analysis indicates increased rates of ependymomas (37%), osteogenic sarcomas (26%), other bone tumors (34%) and mesothelioma (90%) among those in the exposed as compared to the unexposed birth cohort.

CONCLUSIONS

These data suggest that there may be an increased incidence of certain cancers among the 98 million persons exposed to contaminated polio vaccine in the U.S.; further investigations are clearly justified.

http://www.ncbi.nlm.nih.gov/pubmed/10472327

"These data suggest that there may be an increased incidence of certain cancers among the 98 million persons exposed to contaminated polio vaccine in the U.S."

Journal Of Veterinary Medical Science • July 2001

Genotypes of pestivirus RNA detected in live virus vaccines for human use

By Giangaspero M1, Vacirca G, Harasawa R, Büttner M, Panuccio A,
De Giuli Morghen C, Zanetti A, Belloli A, Verhulst A.

Institute of Special Pathology and Veterinary Medical Clinic
Faculty of Veterinary Medicine, The University of Milan, Italy

Abstract

Live virus vaccines for human use, 29 monovalent vaccines against measles, mumps, rubella or polio, eight polyvalent vaccines against measles-mumps-rubella and one bacterial polyvalent vaccine against Streptococcus pneumoniae, were tested by reverse transcriptase-nested PCR for the presence of petivirus or pestivirus RNA. Twenty-four samples were selected from European manufacturers, ten were from U.S.A. and four from Japan. Five (13.1%) out of 38 tested samples were positive for pestivirus RNA. Three vaccines (rubella and two measles) were from Europe and two (mumps and rubella) from Japan. The 5'-untranslated genomic region of the contaminant pestivirus RNA were amplified by reverse transcription-PCR and sequenced. Analyses based on primary nucleotide sequence homology and on secondary structures, characteristic to genotypes, revealed that the cDNA sequences belonged to bovine viral diarrhea virus (BVDV). A cDNA sequence, detected from one measles sample, belonged to BVDV-1b genotype. Pestiviral cDNA detected from the Japanese mumps and rubella vaccine samples, belonged to the BVDV genotypes 1a and 1c, respectively. Analysis on two cDNA sequences detected from measles and rubella vaccine samples from Europe showed their appurtenance to a new genotype, BVDV-1d. These findings indicate that contamination by animal pestivirus may occur in biological products for human use.

http://www.ncbi.nlm.nih.gov/pubmed/11503899

"Twenty-four samples were selected
from European manufacturers, ten were from U.S.A.
and four from Japan. Five (13.1%) out of 38 tested samples
were positive for pestivirus RNA. Three vaccines (rubella and
two measles) were from Europe and
two (mumps and rubella) from Japan."

Anticancer Research • November 2002

SV40 in human tumors: new documents shed light on the apparent controversy

By MacLachlan DS.

MacLachlan Law Offices LLC
487 Goffle Road Ridgewood, New Jersey 07450, USA

Abstract
CONCLUSION

The facts indicating that Dr. Shah's laboratory technique was not sufficiently sensitive to detect SV40 were not made available to the other laboratories participating in the study and were not published. Instead, according to Dr. Shah's testimony, Dr. Strickler, the VEB multi-center study coordinator, compromised the masked positive controls and knowingly permitted Dr. Shah to re-test and adjust his technique during pre-trial testing. The actual negative pre-trial test results were never published alongside the published trial results indicating Dr. Shah's laboratory had the most sensitive technique to detect SV40 among the nine participating laboratories.

http://www.ncbi.nlm.nih.gov/pubmed/12552945

"When one of the participating laboratories
questioned irregularities in the data from Dr. Shah's
laboratory and directly questioned Dr. Strickler,
the study organizer, about the potential irregularity,
Dr. Strickler and Dr. Shah offered letters stating that
such irregularities had not occurred and re-confirmed
that they had not deviated from the standard protocol."

[it was subsequently found that they had lied]

Developments In Biologicals (Basel) • 2006

Vaccine cell substrates: bovine and porcine virus considerations

By Wessman SJ

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Center for Veterinary Biologics
Ames, Iowa 50010, USA
stephen.j.wessman@aphis.usda.gov

Abstract

The use of materials of animal origin to supplement cell cultures used in vaccine production, viral diagnostic testing, or materials testing may lead to contamination of the vaccines, with seroconversion or disease in the vaccinated animals, and possible misdiagnosis of diagnostic samples or incorrect test results. The methods used by the Center for Veterinary Biologics to monitor serum and cell cultures are described. Considerations for the use of animal origin materials, especially bovine and porcine, as substrates or additives, plus the possibility of crossovers to humans are discussed.

http://www.ncbi.nlm.nih.gov/pubmed/16566453

“The use of materials of animal origin
to supplement cell cultures used in vaccine production,
viral diagnostic testing, or materials testing
may lead to contamination of the vaccines,
with seroconversion or disease in the vaccinated animals,
and possible misdiagnosis of diagnostic samples
or incorrect test results.”

Archives de Pediatrie • February 2006

Pharmacovigilance of vaccines

Autret-Leca E1, Bensouda-Grimaldi L, Jonville-Béra AP, Beau-Salinas F.

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Abstract

Safety of vaccines must be excellent to make vaccine’s strategy acceptable, since it usually has a deferred individual benefit but immediate adverse drug reactions (ADRs). Pharmacovigilance of vaccines after their marketing is crucial because, prior to its availability on the market, the size of clinical trials is insufficient to identify rare or deferred adverse effects. The Pharmacovigilance is based on “spontaneous reporting” of ADRs to the Pharmacovigilance Regional Centre (PVRC) which establishes a relationship between each drug taken by the patient and the ADRs occurrence (imputability). This method is crucial to generate alerts, but under-estimates the real frequency of ADRs (1 to 10% of severe ADRs are reported). Thus pharmacoepidemiology studies are necessary to confirm the alerts identified by spontaneous reporting. ADRs can be specific, related to the antigen of an attenuated alive virus vaccine (lymphocyte meningitis after anti-mumps vaccine) or non-specific, related to a component different from the antigen (aluminium hydroxide involved in the “macrophagic myofasciitis”, allergic reactions to neomycin, latex, egg or gelatine). Importance of Pharmacovigilance of vaccines is illustrated. Data, especially case-control studies, about the relationship between multiple sclerosis and hepatitis B vaccine are summarised. Data about the relationship between Crohn’s disease or autism and MMR vaccine are analysed. As vaccines are used in healthy people, their safety must be excellent to be accepted. To monitor them after their marketing is the unique way to detect rare ADRs. This surveillance is made through reporting of ADRs to the PVRC. However, an active and intensive surveillance of ADRs as the one set up from the marketing of Prevenar should be systematic.

http://www.ncbi.nlm.nih.gov/pubmed/16343870

“Pharmacovigilance of vaccines
after their marketing is crucial because,
prior to its availability on the market,
the size of clinical trials is insufficient
to identify rare or deferred adverse effects.”

Immunology Letters • June 2007

Mycoplasma contamination and viral immunomodulatory activity: dendritic cells open Pandora's box

By Alves MP1, Carrasco CP, Balmelli C, Ruggli N, McCullough KC, Summerfield A.

Institute of Virology and Immunoprophylaxis
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Abstract

During in vitro investigations on the interaction of classical swine fever virus (CSFV)-- an immunosuppressive viral pathogen--with monocyte-derived dendritic cells (MoDC) a soluble factor with a strong anti-proliferative activity for T lymphocytes was found. This activity, with an inhibitory dilution 50% (ID(50)) of 10(3)-10(7), was induced after virus infection of monocytes differentiating into DC. UV--inactivation of the supernatants and blocking experiments with a monoclonal antibody against the E2 envelope protein of CSFV initially indicated a virus-dependency. However, further investigations including filtration and centrifugation experiments as well as antibiotic treatment demonstrated the involvement of mycoplasma. This was confirmed by a Hoechst 33258 staining, PCR and mycoplasma cultures--Mycoplasma hyorhinis was identified as the contaminant. Elucidation of a mycoplasma presence occurred under conditions in which the original virus stocks prepared in SK6 cells were negative for mycoplasma using the above tests. Moreover, conventional passage of the virus on the SK6 cells used for this purpose did not reveal any mycoplasma. It was the passage of virus in MoDC rather than SK6 cells that was required to expose the contamination. Three passages of the anti-proliferative supernatants on MoDC cultures increased the ID(50) 10(3)-fold; only when these MoDC-derived supernatants were employed was the mycoplasma contaminant also detectable on SK6 cells. In conclusion, these data demonstrate that regular testing of cell lines and virus stocks for mycoplasma does not necessarily identify their presence, and that application of passage in MoDC cultures could prove an aid for identifying initially undetectable levels of mycoplasma contamination.

http://www.ncbi.nlm.nih.gov/pubmed/?term=17532055

"... these data demonstrate
that regular testing of cell lines
and virus stocks for mycoplasma
does not necessarily identify their presence ..."

International Journal Of Nanomedicine • June 2008

Drug delivery and nanoparticles: Applications and hazards

By Wim H De Jong1 and Paul JA Borm2,3

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National Institute for Public Health and the Environment (RIVM), Bilthoven, The Netherlands
2. Zuyd University, Centre of Expertise in Life Sciences Heerlen, The Netherlands
3. Magnamedics GmbH, Aachen, Germany

Abstract

The use of nanotechnology in medicine and more specifically drug delivery is set to spread rapidly. Currently many substances are under investigation for drug delivery and more specifically for cancer therapy. Interestingly pharmaceutical sciences are using nanoparticles to reduce toxicity and side effects of drugs and up to recently did not realize that carrier systems themselves may impose risks to the patient. The kind of hazards that are introduced by using nanoparticles for drug delivery are beyond that posed by conventional hazards imposed by chemicals in classical delivery matrices. For nanoparticles the knowledge on particle toxicity as obtained in inhalation toxicity shows the way how to investigate the potential hazards of nanoparticles. The toxicology of particulate matter differs from toxicology of substances as the composing chemical(s) may or may not be soluble in biological matrices, thus influencing greatly the potential exposure of various internal organs. This may vary from a rather high local exposure in the lungs and a low or neglectable exposure for other organ systems after inhalation. However, absorbed species may also influence the potential toxicity of the inhaled particles. For nanoparticles the situation is different as their size opens the potential for crossing the various biological barriers within the body. From a positive viewpoint, especially the potential to cross the blood brain barrier may open new ways for drug delivery into the brain. In addition, the nanosize also allows for access into the cell and various cellular compartments including the nucleus. A multitude of substances are currently under investigation for the preparation of nanoparticles for drug delivery, varying from biological substances like albumin, gelatine and phospholipids for liposomes, and more substances of a chemical nature like various polymers and solid metal containing nanoparticles. It is obvious that the potential interaction with tissues and cells, and the potential toxicity, greatly depends on the actual composition of the nanoparticle formulation. This paper provides an overview on some of the currently used systems for drug delivery. Besides the potential beneficial use also attention is drawn to the questions how we should proceed with the safety evaluation of the nanoparticle formulations for drug delivery. For such testing the lessons learned from particle toxicity as applied in inhalation toxicology may be of use. Although for pharmaceutical use the current requirements seem to be adequate to detect most of the adverse effects of nanoparticle formulations, it can not be expected that all aspects of nanoparticle toxicology will be detected. So, probably additional more specific testing would be needed.

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2527668/

"for pharmaceutical use the current requirements seem to be adequate to detect most of the adverse effects of nanoparticle formulations, it can not be expected that all aspects of nanoparticle toxicology will be detected."

BMJ • March 2009

Suspected contamination leads to recall of meningitis C vaccine

By Caroline White

Two batches of meningitis C vaccine distributed to general practices across England have been recalled by the medicines watchdog amid fears that they may have been contaminated. The manufacturer, Novartis Vaccines, raised the alarm last week after routine sampling of a shipment of doses from the same two batches air freighted to the United States showed contamination with Staphylococcus aureus. The sterility of the solvent, aluminium hydroxide, which is used to mix the vaccine, had been compromised.

http://www.bmj.com/content/338/bmj.b896.long

"The sterility of the solvent,
aluminium hydroxide,
which is used to mix the vaccine,
had been compromised."

Pharmacoepidemiological Drug Safety • March 2010

Safety assessment of recalled Haemophilus influenzae type b (Hib) conjugate vaccines United States, 2007-2008

By Huang WT1, Chang S, Miller ER, Woo EJ, Hoffmaster AR, Gee JE, Clark TA, Iskander JK, Ball R, Broder KR.

Epidemic Intelligence Service
Career Development Division Office of the Workforce and Career Development
Centers for Disease Control and Prevention (CDC) Atlanta, GA 30333, USA

Abstract

PURPOSE

On 13 December 2007, Merck & Co., Inc. voluntarily recalled 1.2 million doses of Haemophilus influenzae type b (Hib) vaccines that had been distributed since April 2007 for concerns regarding potential Bacillus cereus contamination. Enhanced postrecall surveillance was conducted to detect vaccine-associated B. cereus infections.

CONCLUSIONS

No evidence of vaccine-associated B. cereus infection had been found in recipients of recalled Hib vaccines. Conducting laboratory surveillance through Epi-X was feasible and may enhance public health response capacities for future vaccine safety emergencies.

http://www.ncbi.nlm.nih.gov/pubmed/20084617

"On 13 December 2007, Merck & Co., Inc.
voluntarily recalled 1.2 million doses
of Haemophilus influenzae type b (Hib) vaccines
that had been distributed since April 2007 ..."

Veterinary Microbiology • April 2010

Atypical 'HoBi'-like pestiviruses— recent findings and implications thereof

By Ståhl K1, Beer M, Schirrmeier H, Hoffmann B, Belák S, Alenius S.

The Joint R&D Division in Virology
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The Swedish University of Agricultural Sciences (SLU) Uppsala, Sweden
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Abstract

In 2004, an atypical pestivirus named D32/00_'HoBi', isolated from foetal calf serum (FCS) originating from Brazil, was described (Schirrmeier et al., 2004). A few years later, a closely related virus (Th/04_KhonKaen) was detected in serum from a calf in Thailand, indicating that this group of atypical pestiviruses already is spread in cattle populations in various regions of the world. At the Friedrich-Loeffler-Institute, Insel Riems, Germany, FCS batches are regularly tested for pestivirus contamination, in general with positive PCR results, and in some cases the contaminants have been typed as 'HoBi'-like. At the National Veterinary Institute (SVA) in Uppsala, Sweden, a recent event with contaminated FCS ruined much of the ongoing cell culture work. From the FCS and the contaminated cells we were able to amplify and sequence nucleic acid from three different pestivirus strains, including BVDV-1, -2 and 'HoBi'-like; this in a commercial FCS that had been tested free from pestivirus by the manufacturer. In this short communication we review the current status of atypical 'HoBi'-like pestiviruses, describe recent findings and discuss the implications thereof.

http://www.ncbi.nlm.nih.gov/pubmed/?term=19857934

"From the Fetal Calf Serum and the contaminated cells
we were able to amplify and sequence nucleic acid
from three different pestivirus strains, including BVDV-1, -2
and 'HoBi'-like; this in a commercial FCS [foetal calf serum]
that had been tested free from pestivirus by the manufacturer."

[Note: FCS is a component in vaccine manufacturing]

Journal Of Virology • June 2010

Viral Nucleic Acids in Live-Attenuated Vaccines: Detection of Minority Variants and an Adventitious Virus

By Joseph G. Victoria,1,2 Chunlin Wang,3 Morris S. Jones,4
Crystal Jaing,5 Kevin McLoughlin,5 Shea Gardner,5 and Eric L. Delwart1,2*

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Travis AFB, California 94535 5. Lawrence Livermore National Laboratory
Livermore, California 94551

Because the chemical inactivation used in the manufacture of killed-virus vaccines is also likely to inactivate adventitious viruses, we focused on eight live-attenuated viruses, OPV (Biopolio), rubella (Meruvax-II), measles (Attenuvax), yellow fever (YF-Vax), human herpesvirus 3 (HHV-3) (Varivax), rotavirus (Rotarix and Rotateq), and multivalent measles/ mumps/rubella (MMR-II), to resequence the attenuated viruses and test for the presence of adventitious viruses after viral particle purification, massively parallel pyrosequencing, and viral sequence similarity searches. Vaccine nucleic acids were also analyzed using a panmicrobial microarray.

Published ahead of print on 7th April 2010
The authors have paid a fee to allow immediate free access to this article.

http://jvi.asm.org/content/84/12/6033.full.pdf

"In very rare instances,
one attenuated viral vaccine,
the oral poliovirus vaccine (OPV),
can accumulate mutations as well as recombine
with other coinfecting enteroviruses
and revert to a pathogenic state."

National Academies Press US • 1994

DPT Vaccine and Chronic Nervous System Dysfunction: A New Analysis

Institute of Medicine US Committee to Study New Research on Vaccines
Editors
Kathleen R. Stratton, Cynthia J. Howe, and Richard B. Johnston, Jr. Washington, DC

EXCERPT

The National Childhood Encephalopathy Study data are consistent with the possibility that some children without underlying brain or metabolic abnormalities might experience serious acute neurologic illness within 7 days after receiving DPT and that acute neurologic illness will have chronic nervous system sequelae. The NCES data also are consistent with the possibility that some children with underlying brain or metabolic abnormalities (which foster a "triggering" by DPT of an acute neurologic illness) might go on to develop chronic nervous system dysfunction due to a DPT-triggered acute illness. Therefore, the committee concludes that the balance of evidence is consistent with a causal relation between DPT and the forms of chronic nervous system dysfunction described in the NCES in those children who experience a serious acute neurologic illness within 7 days after receiving DPT vaccine. This serious acute neurologic response to DPT is a rare event. The excess risk has been estimated to range from 0 to 10.5 per million immunizations (IOM, 1991). The evidence does not "establish" or "prove" a causal relation. The evidence remains insufficient to indicate the presence or absence of a causal relation between DPT and chronic nervous system dysfunction under any other circumstances. That is, because the NCES is the only systematic study of long-term dysfunctions after DPT, the committee can only comment on the causal relation between DPT and those long-term dysfunctions under the conditions studied by the NCES. In particular, it should be noted that the long-term dysfunctions associated with DPT followed a serious acute neurologic illness that occurred in children within 7 days after receiving DPT.

http://www.ncbi.nlm.nih.gov/books/NBK225452/

"... it should be noted that the long-term dysfunctions associated with DPT followed a serious acute neurologic illness that occurred in children within 7 days after receiving DPT."

JAMA • May 1994

Adverse events associated with childhood vaccines other than pertussis and rubella Summary of a report from the Institute of Medicine

By Stratton KR1, Howe CJ, Johnston RB Jr.

Institute of Medicine
National Academy of Sciences Washington, DC

Abstract

In September 1993, the Institute of Medicine released a report entitled Adverse Events Associated With Childhood Vaccines: Evidence Bearing on Causality. The report examined putative serious adverse consequences associated with administration of diphtheria and tetanus toxoids; measles, mumps, and measles-mumps-rubella vaccines; oral polio vaccine and inactivated polio vaccine; hepatitis B vaccines; and Haemophilus influenzae type b (Hib) vaccines. The committee spent 18 months reviewing all available scientific and medical data, from individual case reports (published and unpublished) to controlled clinical trials. The committee found that the evidence favored the rejection of a causal relation between diphtheria and tetanus toxoids and encephalopathy, infantile spasms, and sudden infant death syndrome, and between conjugate Hib vaccines and susceptibility to Hib disease. The committee found that the evidence favored acceptance of a causal relation between diphtheria and tetanus toxoids and Guillain-Barré syndrome and brachial neuritis, between measles vaccine and anaphylaxis, between oral polio vaccine and Guillain-Barré syndrome, and between unconjugated Hib vaccine and susceptibility to Hib disease. The committee found that the evidence established causality between diphtheria and tetanus toxoids and anaphylaxis, between measles vaccine and death from measles vaccine-strain viral infection, between measles-mumps-rubella vaccine and thrombocytopenia and anaphylaxis, between oral polio vaccine and poliomyelitis and death from polio vaccine-strain viral infection, and between hepatitis B vaccine and anaphylaxis. For five vaccine-related adverse events, there was no evidence identified. For the remaining 33 vaccine-related adverse events, the evidence was inadequate to accept or reject a causal relation.

http://www.ncbi.nlm.nih.gov/pubmed/8182813

"The committee found that the evidence favored acceptance of a causal relation between diphtheria and tetanus toxoids and Guillain-Barré syndrome and brachial neuritis, between measles vaccine and anaphylaxis, between oral polio vaccine and Guillain-Barré syndrome, and between unconjugated Hib vaccine and susceptibility to Hib disease. The committee found that the evidence established causality between diphtheria and tetanus toxoids and anaphylaxis, between measles vaccine and death from measles vaccine-strain viral infection, between measles-mumps-rubella vaccine and thrombocytopenia and anaphylaxis, between oral polio vaccine and poliomyelitis and death from polio vaccine-strain viral infection, and between hepatitis B vaccine and anaphylaxis."

ON AUTOIMMUNITY

In the peer reviewed report,

'Novel Pebbles In The Mosaic Of Autoimmunity'

the authors write,

"An entirely new syndrome,
the autoimmune/inflammatory syndrome
induced by adjuvants (ASIA), has been recently described.
This is the new wind blowing within
the branches of autoimmunity ...".

The International Journal of Environmental Research and Public Health • January 2015

Exposure to mercury and aluminum in early life: developmental vulnerability as a modifying factor in neurologic and immunologic effects

By Dr. JG Dorea

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http://www.ncbi.nlm.nih.gov/pubmed/25625408

"Currently, ethylmercury (EtHg) and adjuvant-Al are the dominating interventional exposures encountered by fetuses, newborns, and infants due to immunization with Thimerosal-containing [and aluminum containing] vaccines (TCVs & ACVs).

Despite their long use as active agents of medicines and fungicides, the safety levels of these substances have never been determined, either for animals or for adult humans—much less for fetuses, newborns, infants, and children."

Immunotherapy • January 2014

Are there negative Central Nervous System impacts of aluminum adjuvants used in vaccines and immunotherapy?

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Abstract

In spite of a common view that aluminum (Al) salts are inert and therefore harmless as vaccine adjuvants or in immunotherapy, the reality is quite different. In the following article we briefly review the literature on Al neurotoxicity and the use of Al salts as vaccine adjuvants and consider not only direct toxic actions on the nervous system, but also the potential impact for triggering autoimmunity. Autoimmune and inflammatory responses affecting the CNS appear to underlie some forms of neurological disease, including developmental disorders. Al has been demonstrated to impact the CNS at every level, including by changing gene expression. These outcomes should raise concerns about the increasing use of Al salts as vaccine adjuvants and for the application as more general immune stimulants.

http://www.ncbi.nlm.nih.gov/pubmed/25428645

"These outcomes should raise concerns about the increasing use of Al" salts as vaccine adjuvants."

From the Journal Lupus • September 2015

Human adjuvant-related syndrome or autoimmune/inflammatory syndrome induced by adjuvants. Where have we come from? Where are we going? A proposal for new diagnostic criteria

By Alijotas J-Reig J.

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Abstract

In 1964, Miyoshi reported a series of patients with diverse symptoms after receiving treatment with silicone or paraffin fillers. Miyoshi named this condition 'human adjuvant disease'. Since then, the literature has been flooded with case reports and case series of granulomatous and systemic autoimmune disorders related to vaccines, infection or other adjuvants such as silicone and other biomaterials. A new term, autoimmune/inflammatory syndrome induced by adjuvants [ASIA] - has recently been coined for a process that includes several clinical features previously described by Miyoshi plus other clinical and laboratory parameters related to exposure to diverse external stimuli. Disorders such as siliconosis, Gulf War syndrome, macrophagic myofasciitis syndrome, sick building syndrome and post-vaccination syndrome have been included in autoimmune/inflammatory syndrome induced by adjuvants. Disorders such as Spanish toxic oil syndrome and Ardystil syndrome could also be included. Furthermore, biomaterials other than silicone should also be considered as triggering factors for these adjuvant-related syndromes. New diagnostic criteria in this field have been proposed. Nevertheless, many of these criteria are too subjective, leading to some patients being diagnosed with chronic fatigue syndrome or other 'central sensitization syndromes'. Diagnostic criteria based only on objective clinical and laboratory data to be further discussed and validated are proposed herein.

http://www.ncbi.nlm.nih.gov/pubmed/25813870

"Since then, the literature has been flooded with case reports and case series of granulomatous and systemic autoimmune disorders related to vaccines ..."

Journal of Trace Elements in Medicine and Biology • October 2012

Aluminium overload after 5 years in skin biopsy following post-vaccination with subcutaneous pseudolymphoma

By Guillard O1, Fauconneau B, Pineau A, Marrauld A, Bellocq JP, Chenard MP.

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Abstract

Aluminium hydroxide is used as an effective adjuvant in a wide range of vaccines for enhancing immune response to the antigen. The pathogenic role of aluminium hydroxide is now recognized by the presence of chronic fatigue syndrome, macrophagic myofasciitis and subcutaneous pseudolymphoma, linked to intramuscular injection of aluminium hydroxide-containing vaccines. The aim of this study is to verify if the subcutaneous pseudolymphoma observed in this patient in the site of vaccine injection is linked to an aluminium overload. Many years after vaccination, a subcutaneous nodule was discovered in a 45-year-old woman with subcutaneous pseudolymphoma. In skin biopsy at the injection site for vaccines, aluminium (Al) deposits are assessed by Morin stain and quantification of Al is performed by Zeeman Electrothermal Atomic Absorption Spectrophotometry. Morin stain shows Al deposits in the macrophages, and Al assays (in µg/g, dry weight) were 768.10±18 for the patient compared with the two control patients, 5.61±0.59 and 9.13±0.057. Given the pathology of this patient and the high Al concentration in skin biopsy, the authors wish to draw attention when using the Al salts known to be particularly effective as adjuvants in single or repeated vaccinations. The possible release of Al may induce other pathologies ascribed to the well-known toxicity of this metal.

http://www.ncbi.nlm.nih.gov/pubmed/22425036

"Aluminium hydroxide is used as an effective adjuvant in a wide range of vaccines for enhancing immune response to the antigen. The pathogenic role of aluminium hydroxide is now recognized by the presence of chronic fatigue syndrome, macrophagic myofasciitis and subcutaneous pseudolymphoma, linked to intramuscular injection of aluminum hydroxide-containing vaccines."

From the Journal Medical Hypotheses • 2009

A role for the body burden of aluminium in vaccine-associated macrophagic myofasciitis and chronic fatigue syndrome

By Exley C, Swarbrick L, Gherardi RK, Authier FJ.

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Abstract

Macrophagic myofasciitis and chronic fatigue syndrome are severely disabling conditions which may be caused by adverse reactions to aluminium-containing adjuvants in vaccines. While a little is known of disease aetiology both conditions are characterised by an aberrant immune response, have a number of prominent symptoms in common and are coincident in many individuals. Herein, we have described a case of vaccine-associated chronic fatigue syndrome and macrophagic myofasciitis in an individual demonstrating aluminium overload. This is the first report linking the latter with either of these two conditions and the possibility is considered that the coincident aluminium overload con- tributed significantly to the severity of these conditions in this individual. This case has highlighted potential dangers associated with aluminium-containing adjuvants and we have elucidated a possible mechanism whereby vaccination involving aluminium-containing adjuvants could trigger the cascade of immunological events which are associated with autoimmune conditions including chronic fatigue syndrome and macrophagic myofasciitis.

http://www.ncbi.nlm.nih.gov/pubmed/19004564

"This case has highlighted potential dangers associated with aluminium-containing adjuvants and we have elucidated a possible mechanism whereby vaccination involving aluminium-containing adjuvants could trigger the cascade of immunological events which are associated with autoimmune conditions including chronic fatigue syndrome and macrophagic myofasciitis."

From the Journal Pharmacological Research • August 2015

Vaccines, adjuvants and autoimmunity

By Guimarães LE1, Baker B1, Perricone C2, Shoenfeld Y3.

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Abstract

Vaccines and autoimmunity are linked fields. Vaccine efficacy is based on whether host immune response against an antigen can elicit a memory T-cell response over time. Although the described side effects thus far have been mostly transient and acute, vaccines are able to elicit the immune system towards an autoimmune reaction. The diagnosis of a definite autoimmune disease and the occurrence of fatal outcome post-vaccination have been less frequently reported. Since vaccines are given to previously healthy hosts, who may have never developed the disease had they not been immunized, adverse events should be carefully accessed and evaluated even if they represent a limited number of occurrences. In this review of the literature, there is evidence of vaccine-in- duced autoimmunity and adjuvant-induced autoimmunity in both experimental models as well as human patients. Adjuvants and in- fectious agents may exert their immune-enhancing effects through various functional activities, encompassed by the adjuvant effect. These mechanisms are shared by different conditions triggered by adjuvants leading to the autoimmune/inflammatory syndrome induced by adjuvants (ASIA syndrome). In conclusion, there are several case reports of autoimmune diseases following vaccines, however, due to the limited number of cases, the different classi- fications of symptoms and the long latency period of the diseases, every attempt for an epidemiological study has so far failed to deliver a connection. Despite this, efforts to unveil the connection between the triggering of the immune system by adjuvants and the development of autoimmune conditions should be undertaken. Vaccinomics is a field that may bring to light novel customized, personalized treatment approaches in the future.

http://www.ncbi.nlm.nih.gov/pubmed/26275795

"In this review of the literature, there is evidence of vaccine-induced autoimmunity and adjuvant-induced autoimmunity in both experimental models as well as human patients ... leading to the autoimmune/inflammatory syndrome induced by adjuvants (ASIA syndrome)."

From the Journal Brain • September 2001

Macrophagic myofasciitis lesions assess long-term persistence of vaccine-derived aluminium hydroxide in muscle

By Gherardi RK, Coquet M, Cherin P, Belec L,
Moretto P, Dreyfus PA, Pellissier JF, Chariot P, Authier FJ.

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Abstract

Macrophagic myofasciitis (MMF) is an emerging condition of unknown cause, detected in patients with diffuse arthromyalgias and fatigue, and characterized by muscle infiltration by granular periodic acid-Schiff's reagent-positive macrophages and lymphocytes. Intracytoplasmic inclusions have been observed in macrophages of some patients. To assess their significance, electron microscopy was performed in 40 consecutive cases and chemical analysis was done by microanalysis and atomic absorption spectrometry. Inclusions were constantly detected and corresponded to aluminium hydroxide, an immunostimulatory compound frequently used as a vaccine adjuvant. A lymphocytic component was constantly observed in MMF lesions. Serological tests were compatible with exposure to aluminium hydroxide-containing vaccines. History analysis revealed that 50 out of 50 patients had received vaccines against hepatitis B virus (86%), hepatitis A virus (19%) or tetanus toxoid (58%), 3-96 months (median 36 months) before biopsy. Diffuse myalgias were more frequent in patients with than without an MMF lesion at deltoid muscle biopsy ($P < 0.0001$). Myalgia onset was subsequent to the vaccination (median 11 months) in 94% of patients. MMF lesion was experimentally reproduced in rats. We conclude that the MMF lesion is secondary to intramuscular injection of aluminium hydroxide-containing vaccines, shows both long-term persistence of aluminium hydroxide and an ongoing local immune reaction, and is detected in patients with systemic symptoms which appeared subsequently to vaccination.

http://www.ncbi.nlm.nih.gov/pubmed/11522584

"We conclude that the MMF lesion
is secondary to intramuscular injection
of aluminium hydroxide-containing vaccines."

Critical Reviews In Toxicology • October 2014

Systematic review of potential health risks posed by pharmaceutical, occupational and consumer exposures to metallic and nanoscale aluminum, aluminum oxides, aluminum hydroxide and its soluble salts

By Willhite CC, Karyakina NA, Yokel RA, Yenugadhati N, Wisniewski TM
Arnold IM, Momoli F, Krewski D.

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Abstract

Abstract Aluminum (Al) is a ubiquitous substance encountered both naturally (as the third most abundant element) and intentionally (used in water, foods, pharmaceuticals, and vaccines); it is also present in ambient and occupational airborne particulates. Existing data underscore the importance of Al physical and chemical forms in relation to its uptake, accumulation, and systemic bioavailability. The present review represents a systematic examination of the peer-reviewed literature on the adverse health effects of Al materials published since a previous critical evaluation compiled by Krewski et al. (2007) . Challenges encountered in carrying out the present review reflected the experimental use of different physical and chemical Al forms, different routes of administration, and different target organs in relation to the magnitude, frequency, and duration of exposure. Wide variations in diet can result in Al intakes that are often higher than the World Health Organization provisional tolerable weekly in- take (PTWI), which is based on studies with Al citrate. Comparing daily dietary Al exposures on the basis of "total Al" assumes that gastrointestinal bioavailability for all dietary Al forms is equivalent to that for Al citrate, an approach that requires validation. Current occupational exposure limits (OELs) for identical Al substances vary as much as 15-fold. The toxicity of different Al forms depends in large measure on their physical behavior and relative solubility in water. The toxicity of soluble Al forms depends upon the delivered dose of Al(+3) to target tissues. Trivalent Al reacts with water to produce bidentate superoxide coordination spheres [Al(O2)(H2O4)(+2) and Al(H2O)6 (+3)] that after complexation with O2(•-), generate Al superoxides [Al(O2(•))](H2O5)](+2). Semireduced AlO2(•) radicals deplete mitochondrial Fe and promote generation of H2O2, O2 (•-) and OH(•). Thus, it is the Al(+3)-induced formation of oxygen radicals that accounts for the oxidative damage that leads to intrinsic apoptosis. In contrast, the toxicity of the insoluble Al oxides depends primarily on their behavior as particulates. Aluminum has been held responsible for human morbidity and mortality, but there is no consistent and convincing evidence to associate the Al found in food and drinking water at the doses and chemical forms presently consumed by people living in North America and Western Europe with increased risk for Alzheimer's disease (AD). Neither is there clear evidence to show use of Al-containing underarm antiperspirants or cosmetics increases the risk of AD or breast cancer. Metallic Al, its oxides, and common Al salts have not been shown to be either genotoxic or carcinogenic. Aluminum exposures during neonatal and pediatric parenteral nutrition (PN) can impair bone mineralization and delay neurological development. Adverse effects to vaccines with Al adjuvants have occurred; however, recent controlled trials found that the immunologic response to certain vaccines with Al adjuvants was no greater, and in some cases less than, that after identical vaccination without Al adjuvants. The scientific literature on the adverse health effects of Al is extensive. Health risk assessments for Al must take into account individual co-factors (e.g., age, renal function, diet, gastric pH). Conclusions from the current review point to the need for refinement of the PTWI, reduction of Al contamination in PN solutions, justification for routine addition of Al to vaccines, and harmonization of OELs for Al substances.

http://www.ncbi.nlm.nih.gov/pubmed/25233067

"The scientific literature on the
adverse health effects of Al [aluminum] is extensive."

CHAPTER THREE

Institutional Corruption of Pharmaceuticals and the Myth of Safe and Effective Drugs

This is a business gentlemen,
we're a corporation with shareholders.

We're in it to make money, plain and simple.
By capitalizing on the least expensive
research and development expenditures,
the lowest outlay for sales and marketing
while using the cheapest possible ingredients
to manufacture our products and while all is at
the taxpayers expense, we'll clean house.

Vaccines Are Our Holy Grail

~ Overheard at a Davos meeting

Journal of Law, Medicine and Ethics, June 1, 2013, Vol. 14, No. 3:590-610

Institutional Corruption of Pharmaceuticals and the Myth of Safe and Effective Drugs

By Donald W. Light, Ph.D., a fellow for 2012-2013 at the Edmond J. Safra Center for Ethics at Harvard University in Cambridge, MA. He received his Ph.D. in sociology from Brandeis University and is a professor of comparative health policy at Rowan University, School of Osteopathic Medicine.

By Joel Lexchin, M.Sc., M.D., who has been teaching health policy for 12 years at York University in Toronto, ON. He received his M.D. from the University of Toronto in 1977 and since 1988 has been an emergency physician at the University Health Network in Toronto.

By Jonathan J. Darrow, J.D., M.B.A., LL.M., S.J.D., who is a research fellow at Harvard Medical School and a lecturer on law at Bentley University in Waltham, MA. He received his S.J.D. from Harvard in 2013.

Over the past 35 years, patients have suffered from a largely hidden epidemic of side effects from drugs that usually have few offsetting benefits. The pharmaceutical industry has corrupted the practice of medicine through its influence over what drugs are developed, how they are tested, and how medical knowledge is created. Since 1906, heavy commercial influence has compromised Congressional legislation to protect the public from unsafe drugs. The authorization of user fees in 1992 has turned drug companies into the FDA's prime clients, deepening the regulatory and cultural capture of the agency. Industry has demanded shorter average review times and, with less time to thoroughly review evidence, increased hospitalizations and deaths have resulted. Meeting the needs of the drug companies has taken priority over meeting the needs of patients. Unless this corruption of regulatory intent is reversed, the situation will continue to deteriorate. We offer practical suggestions including: separating the funding of clinical trials from their conduct, analysis, and publication: independent FDA leadership; full public funding for all FDA activities; measures to discourage R&D on drugs with few if any new clinical benefits; and the creation of a National Drug Safety Board.

Institutional corruption is a normative concept of growing importance that embodies the systemic dependencies and informal practices that distort an institution's societal mission. An extensive range of studies and lawsuits already documents strategies by which pharmaceutical companies hide, ignore, or misrepresent evidence about new drugs; distort the medical literature; and misrepresent products to prescribing physicians. We focus on the consequences for patients: millions of adverse reactions. After defining institutional corruption, we focus on evidence that it lies behind the epidemic of harms and the paucity of benefits.

It is our thesis that institutional corruption has occurred at three levels. First, through large-scale lobbying and political contributions, the pharmaceutical industry has influenced Congress to pass legislation that has compromised the mission of the Food and Drug Administration (FDA). Second, largely as a result of industry pressure, Congress has underfunded FDA enforcement capacities since 1906, and turning to industry-paid "user fees" since 1992 has biased funding to limit the FDA's ability to protect the public from serious adverse reactions to drugs that have few offsetting advantages. Finally, industry has commercialized the role of physicians and undermined their position as independent, trusted advisers to patients.

Institutional Integrity: The Baseline of Corruption

If "corruption" is defined as an impairment of integrity or moral principle, then institutional corruption is an institution's deviation from a baseline of integrity. In the case of Congress, integrity demands that democratically elected representatives should be dedicated solely to the best interests of the people they represent.

According to seminal essays on institutional corruption by Dennis Thompson and Larry Lessig, this baseline of integrity is corrupted because elections are not publicly funded. As a result, congressional representatives must constantly raise funds from a tiny percent of the population and respond to their priorities. This dependency corruption creates an "economy of influence," even if individual actors are well-intentioned. Lessig's examples portray how secrecy and rationalizations disguise distortions in the democratic process and mission. The concept of institutional corruption highlights numerous distinctions — between what is legal and illegal; between good people doing bad things, not bad people doing bad things; between influence, not money, affecting decisions. These are the ends of continua, and there is a need to recognize degrees of corruption in between. Special interests also influence members of Congress to make legal what has been illegal or else to game the rules, thereby blurring the line between legal and illegal as well as making it hard to determine the law's intent.

Just as a proper electoral democracy is devoted to the public good, health care systems are founded on the moral principles of beneficence, nonmaleficence (" first, do no harm"), respect for autonomy, and the just distribution of scarce resources. Based on these principles, health care workers are obliged to use the best medical science to relieve suffering and pain, treat illness, and address risks to health. The institutional corruption of health care consists of deviations from these principles. The major patent-based research pharmaceutical companies also nominally commit themselves to improving health and relieving suffering. For example, Merck promises "to provide innovative, distinctive products that save and improve lives ... and to provide investors with a superior rate of return." Pfizer is dedicated "to applying science and our global resources to improve health and well-being at every stage of life." Pharmaceutical companies continuously emphasize how deeply society depends on their development of innovative products to improve health. But in fact, these companies are mostly developing drugs that are little better than existing products but have the potential to cause widespread adverse reactions even when appropriately prescribed.

This deviation from the principles of health care by institutions allegedly dedicated to health care is institutional corruption. We present evidence that industry has a hidden business model to maximize profits on scores of drugs with clinically minor additional benefits. Physician commitment to better health is compromised as the industry spends billions to create what Lessig calls a "gift economy" of interdependent reciprocation. New research finds that truly innovative new drugs sell themselves in the absence of such gift-economy marketing. Regulators such as the FDA and the Environmental Protection Agency arise when unregulated competition is perceived to cause serious harm to society and government regulation is needed to address the problem. The FDA was founded to protect the public's health from the fraudulent cures peddled in the 19th century. Through a series of legislative enactments, often in response to a drug disaster, the pharmaceutical regulatory side of the FDA has acquired ever-wider responsibilities to ensure that new drugs do more good than harm. Institutional corruption consists of distortions of these responsibilities, such as approving drugs that are mostly little better than existing medications, failing to ensure sufficient testing for serious risks, and inadequately guarding the public from harmful side effects. These distortions serve commercial interests well and public health poorly.

For the past 50 years, patent-based research companies have objected to the FDA's gatekeeping function as being too rigid and too slow. They have claimed that an obsessive concern about safety has undermined patient access to drugs that could save lives or reduce the burdens of ill health. This message is increasingly being accepted by the FDA.

Flooding the Market with Drugs of Little Benefit

In response to the emphasis by pharmaceutical companies, their lobbyists, and their trade association — the Pharmaceutical Research Manufacturers of America (PhRMA) — on the high risk and cost of research and development (R&D), Congress has authorized billions in taxpayer contributions to support R&D, exemptions

from market competition, and special privileges. Patents, of course, can be found in all industries, but lobbyists for the pharmaceutical industry have successfully pressured Congress to provide several forms of market protection beyond patents.

Therapeutic Value of Drugs Marketed in France, 2002-2011

The industry measures "innovation" in terms of new molecular entities (NMEs), but most NMEs provide at best minor clinical advantages over existing ones and may lawfully be approved by the FDA even if they are inferior to previously approved drugs. The preponderance of drugs without significant therapeutic gain dates back at least 35 years. From the mid-1970s through the mid-1990s, multiple assessments have found that only 11 to 15.6 percent of NMEs provide an important therapeutic gain. Millions of patients benefit from the one out of six drugs that are therapeutically significant advances; but most R&D dollars are devoted to developing molecularly different but therapeutically similar drugs, which tends to involve less risk and cost for manufacturers. These drugs are then sold through competition based on brand name, patent status, and newness, rather than on their therapeutic merits.

An analysis of data from the National Science Foundation by Donald Light and Joel Lexchin indicates that patent-based pharmaceutical companies — often deemed by Congress, the press, the public, and themselves to be "innovative" — in fact devote only 1.3 percent of revenues, net of taxpayer subsidies, to discovering new molecules. The 25 percent of revenues spent on promotion is about 19 times more than the amount spent on discovering new molecules. In short, the term "R&D" as used by industry primarily means "development" of variations rather than the path-breaking "research" that onlookers might like to imagine.

The independent drug bulletin, La revue Prescrire, analyzes the clinical value of every new drug product or new indication approved in France. From 1981 to 2001, it found that about 12 percent offered therapeutic advantages. But in the following decade, 2002- 2011, only 8 percent offered some advantages and nearly twice that many — 15.6 percent – were judged to be more harmful than beneficial. A mere 1.6 percent offered substantial advantages. Assessments by the Canadian advisory panel to the Patented Medicine Prices Review Board and by a Dutch general practice drug bulletin have come to similar conclusions. No comparable review has been done in the United States on the 229 NMEs approved by the FDA between 2002 and 2011. This decrease does not come from the "innovation crisis" of fewer new molecules entering trials or eventually being approved but from fewer new drugs being clinically superior. The number of products put into trials has actually increased as the number of clinically superior drugs has decreased. These facts provide evidence that companies are using patents and other protections from market competition primarily to develop drugs with few if any new therapeutic benefits and to charge inflated prices protected by their strong IP rights.

Despite the small number of clinically superior drugs, sales and profits have soared as successful marketing persuades physicians to prescribe the much more costly new products that are at best therapeutically equivalent to established drugs. Both an American and a Canadian study found that 80 percent of the increase in drug expenditures went to paying for these minor-variation new drugs, not for important advances. Companies claim that R&D costs are "unsustainable." But over the past 15 years, revenues have increased six times faster than has investment in R&D.

Almost a decade ago, Jerry Avorn, a widely respected pharmacoepidemiologist and author of a book on the risks of drugs, described how the big pharmaceutical companies exploited patents and concluded that "[l]aws designed to encourage and protect meaningful innovation had been turned into a system that rewarded trivial pseudo-innovation even more profitably than important discoveries." He also noted that efforts in Congress to introduce a "reasonable pricing clause" that would reflect large taxpayer contributions to new drugs were defeated by industry lobbyists.

An Epidemic of Harmful Side Effects

Most new drugs approved and promoted since the 1970s lack additional clinical advantag es over existing drugs and — as with all drugs — they have been accompanied by harmful side effects. A systematic review of the 39 methodologically strongest studies performed in the U.S. between 1964 and 1995 examined patients who were hospitalized due to a serious adverse drug reaction (ADR) or who experienced an ADR while in the hospital.

The review found that 4.7 percent of hospital admissions were due to serious reactions from prescription drugs that had been appropriately prescribed and used. In addition, 2.1 percent of in-hospital patients who received correctly prescribed medications experienced a serious ADR, for a total of 6.8 percent of hospital patients having serious ADRs. Applying this 6.8 percent hospital ADR rate to the 40 million annual admissions in U.S. acute care hospitals indicates that up to 2.7 million hospitalized Americans each year have experienced a serious adverse reaction. Of all hospitalized patients, 0.32 percent died due to ADRs, which means that an estimated 128,000 hospitalized patients died annually, matching stroke as the 4th leading cause of death. Deaths and serious reactions outside of hospitals would significantly increase the totals.

An analysis conducted in 2011, based on a year of ADRs reported to the FDA, came to similar conclusions: Americans experienced "***2.1 million serious injuries, including 128,000 patient deaths.***"

Other studies reveal that one in every five NMEs eventually caused enough serious harm in patients to warrant a severe warning or withdrawal from the market.

Of priority drugs that were reviewed in slightly more than half the normal time, at least one in three of them caused serious harm.

The public health impacts are even greater when milder adverse reactions are taken into account. Given estimates that about 30 ADRs occur for every one that leads to hospitalization, about 81 million side effects are currently experienced every year by the 170 million Americans who use pharmaceuticals. Groups such as pregnant women, elderly patients, and those who are taking multiple medications are especially at risk. Most of these medically minor adverse reactions are never brought to clinical attention, but even minor reactions can impair productivity or functioning, lead to falls, and cause potentially fatal motor vehicle accidents.

Contributors to More Harm and Less Benefit

Are the adverse side effects we have just been describing simply the "price of progress or an unavoidable risk of drug therapy?" In fact, evidence suggests that commercial distortions of the review process and aggressive marketing contribute to both undermining beneficence as health care's raison d'être and to the epidemic of harm to patients.

Distorting, Limiting, and Circumventing Safety Regulations

Since at least the 1890s, the public has clamored for Congress to regulate contaminated or adulterated foods and harmful or ineffective medicines (medicines that may delay truly useful treatments). At that time, lobbyists — paid from drug profits — argued that even bills to require accurate listing of secret ingredients would destroy the industry. These lobbyists had managed to have earlier bills sent to die in the Committee on Manufactures until President Roosevelt intervened to secure passage of the 1906 Food and Drug Act, which

still only required that statements on labels be true and provided no budget for enforcement. Work on what would become the 1938 food and drug law began in 1933 with a bill that would prohibit misstatements in advertising and require manufacturers to prove to the FDA that drugs were safe before being allowed to sell them. The companies' two trade associations launched "well-choreographed screams of protest" and letter-writing campaigns to mislead Congress and to distort its mission to protect its constituents from harm. Employees of drug makers wrote to Congress, arguing that requiring companies to make honest claims about safe drugs would put thousands out of work. The FDA staff wanted the legislation passed but were stopped by threats of prosecution if they campaigned for it. Then a manufacturer added diethylene glycol (antifreeze) to a sulfa drug to make a sweet-tasting elixir and children started dying. Public response trumped industry lobbyists and Congress passed the 1938 law, requiring that drugs be safe but leaving it to companies to decide how to define and test for safety.

For the next 25 years, drugs were approved within 180 days unless the FDA objected, based on the companies' tests and reports of safety. Some companies "tested" their products by sending samples out to providers for feedback, keeping no records of the results, and denying serious harms when reported by doctors. Daniel Carpenter, the author of a book considered to be a definitive work on the politics of the FDA, has detailed how the FDA staff dedicated themselves to enforcing the rules and developing better criteria for safety and efficacy. But as Malcolm Salter, at the Harvard Business School emphasizes, companies institutionalize corruption by getting legislative and administrative rules shaped to serve their interests, either directly or by crafting rules in ways they can game.

In his review of new pharmaceutical products in the 1940s and 1950s, Dr. Henry Dowling, an AMA senior officer and expert, found that companies launched 200-400 a year but only three on average were clinically useful. Physicians, swamped with far more drugs than they could know much about, relied on sales reps to brief them, entertain them, and leave an ample supply of free samples as gifts that the physicians could then give to their patients — a two-stage economy of reciprocation. In effect, through political pressure and lobbying, companies minimized the role of the FDA as the protector of public health for its first 56 years.

Following the 1962 amendments, propelled to passage by the thalidomide tragedy, the FDA commissioned the National Research Council, as part of the National Academy of Sciences, to review the effectiveness of all 2820 drugs (available in 4350 different versions) approved between 1938 to 1962. Companies were required to submit substantial evidence of effectiveness. The review concluded that seven percent of the drugs reviewed were completely ineffective for every claim they made and a further 50 percent were only effective for some of the claims made for them. Although the FDA has acted to remove many of these ineffective drugs from the market, some pre-1962 drugs are — more than 50 years later — still under-going review and are among the "several thousand drug products" that, according to a 2011 FDA guidance document, are today "marketed illegally without required FDA approval."

Regulatory capture begins with the dependency corruption of Congress, which passes the regulations and provides the funding for agencies to protect the public. While the 1962 amendments ushered in the modern era of testing for safety and efficacy before a drug can be approved, three key features of the modern drug-testing system actually work for industry profits and against the development of safe drugs that improve health. First, three criteria used by the FDA contribute to the large number of new drugs approved with few therapeutic advantages. New drugs are often tested against placebos rather than against established effective treatments, and the use of surrogate or substitute end points, rather than actual effects on patients' health. Noninferiority trials that merely show that the product is not worse than another drug used to treat the same condition by more than a specified margin are accepted, rather than requiring superiority trials. Silvio Garattini, founder of the Mario Negri Institute for Pharmacological Research, points out that placebo and noninferiority trials violate international ethical standards and provide no useful information for prescribing. Second, allowing companies to test their own products has led them — as rational economic actors — to design trials in ways that minimize detection and reporting of harms and maximize evidence of benefits. Furthermore, clinical trials for new drugs are designed to test primarily for efficacy and generally are not able to detect less common adverse events.

Industry-friendly rules allow companies to exclude those patients most likely to have adverse reactions, while including those most likely to benefit, so that drugs look safer and more effective than they are in practice. Approvals based on scientifically compromised trials underlie the large number of heavily marketed new drugs with few or no new therapeutic benefits to offset their under-tested risks of harm.

Third, companies have created what can be characterized as the trial-journal pipeline because companies treat trials and journals as marketing vehicles. They design trials to produce results that support the marketing profile for a drug and then hire "publication planning" teams of editors, statisticians, and writers to craft journal articles favorable to the sponsor's drug. Articles that present the conclusions of commercially funded clinical trials are at least 2.5 times more likely to favor the sponsor's drug than are the conclusions in articles discussing non-commercially funded clinical trials. Yet, journal approval is deemed to certify what constitutes medical knowledge. Published papers legitimate the pharmaceutical products emerging from the R&D pipeline and provide the key marketing materials.

Furthermore, companies are much less likely to publish negative results, and they have threatened researchers who break the code of secrecy and confidentiality about those results. Positive results are sometimes published twice — or even more often — under different guises. This further biases meta-analyses — a method of statistically combining the results of multiple studies — and clinical guidelines used for prescribing. The result is "a massive distortion of the clinical evidence."

For decades, the FDA has kept silent about these practices and about the discrepancies between the data submitted to the FDA by companies and the findings published in journal articles, to the detriment of patients but much to the benefit of the companies. In sum, testing and FDA criteria approval provide little or no information to clinicians on how to prescribe new drugs, a vacuum filled by company-shaped "evidence" that misleads physicians to prescribe drugs that are less safe and effective than indicated by evidence that the FDA possesses.

PDUFA: Conflict-of-Interest Payments

In 1992, after years of underfunding and cuts in the 1980s that contributed to drug review times ballooning from 6 to 30 months, Congress passed the Prescription Drug User Fee Act (PDUFA), authorizing the FDA to collect "user fees" from drug companies that would allow it to hire 600 more reviewers and thereby speed up drug review. Supporters claimed that fees would increase incentives for innovation and improve health; but aside from clearing the backlog of NMEs waiting for approval, industry fees have not increased innovation as measured by clinically superior drugs.

In return for paying user fees, companies required the FDA to guarantee that it would review priority applications within six months and standard applications within 12 months of submission. Shortened review times led to substantial increases in serious harms. An in-depth analysis found that each 10-month reduction in review time — which could take up to 30 months — resulted in an 18.1-percent increase in serious adverse reactions, a 10.9- percent increase in hospitalizations, and a 7.2-percent increase in deaths. Now, 20 years later, what Carpenter calls "corrosive capture" has set in — a weakened application of regulatory tools and a cultural capture of rhetoric about saving lives by getting new drugs to patients more quickly.

For the FDA, the reduction in review time combined with the fear that missing review deadlines will jeopardize continued PDUFA funding has also led to an increase in "up against the wall" approvals as review deadlines

approach. Carpenter and his colleagues found that "the probability of a drug approved in the two months before the deadline receiving a new black-box warning (the most serious safety warning that the FDA can issue) is 3.27 times greater than a drug approved at some other time" and the likelihood of a drug being withdrawn from the market because of serious adverse events is 6.92 times greater.

These detailed studies corroborate what FDA staff told the Office of the Inspector General, namely, that concerns arising near the end of the review period are not adequately addressed, that needed meetings with advisory committees are not held, and that label warnings and contraindications are hastily written. As a result, there are "tens of thousands of additional hospitalizations, adverse drug reactions, and deaths."

The 1998 withdrawal of five drugs, used by 19.8 million Americans, prompted critical reflection. Three distinguished physicians were struck by how little information had been gathered about the harmful side effects of these drugs before they were withdrawn. They attributed inaction to the FDA's lack of interest in safety, lack of funds, and to "the lack of a proactive, comprehensive and independent system to evaluate the long-term safety, efficacy, and toxicity of drugs" after FDA approval.

To compensate for the FDA's failures, they called for an independent National Drug Safety Board — akin to the National Transportation Safety Board that investigates each plane crash and holds public meetings — so that the same part of the FDA that approves drugs, the Center for Drug Evaluation and Research (CDER), would not later be asked to decide whether that drug should be restricted or withdrawn. In other words, public health would not depend on FDA officials' willingness to admit their own mistakes. Such an independent board should establish an active monitoring system and gather comparative data across a given therapeutic class so it could provide objective information and develop better strategies for addressing adverse reactions as a major cause of death.

In 1997, a year before these five withdrawals, Congress had passed PDUFA II and companies had insisted that none of the fees collected be spent on post-market surveillance or on drug-safety programs. PDUFA II, III, IV, and V and related legislation provided the FDA with steeply increasing user fees but included lower criteria for approval, mandated that an industry representative be on FDA scientific advisory committees, lowered barriers to promotional efforts by companies, and required FDA officers to consult and negotiate with industry on the agency's goals and plans. Offsetting the harms associated with PDUFA I's shortened approval framework are several tools created in PDUFA III through V for detecting, managing, and raising awareness of risks such as the Sentinel system and the Risk Evaluation and Mitigation Strategies; but there is no clear evidence these are reducing the epidemic of harms. These tools are inadequate to counterbalance the increase in risks — let alone to improve safety.

The additional $10 million of funding provided by PDUFA III for the Office of Drug Safety and the $7.5 million provided for the FDA's advertising enforcement arm are tiny in comparison to the more than $690 million in user fees that flow to the FDA each year. In sum, PDUFA allocates user fees overwhelmingly to ensure speedy review of new drug applications while leaving safety and enforcement dependent on grossly inadequate funding, perpetuating a history of underfunding safety.

Granting priority status to more drugs further increases the number of drugs reviewed in the shortest time and the chance of a major safety issue increases from one drug in five to one in three. Between 1999 and 2008, the FDA gave priority review status to almost 47 percent (114 of 244) of new drug applications, more than four times the proportion of drugs found to have superior clinical effects by independent review groups. Reflecting the cultural and corrosive capture of the FDA, its Commissioner said recently that "an increasing number of treatments are being approved under the agency's fast-track, priority review ... to get critical and innovative medicines to market more rapidly." Quicker reviews and less evidence of clinical benefit have rewarded the hidden business model of developing still more drugs with minor benefits.

The FDA's obligation to serve the public is being corroded by pressures to serve the companies it regulates. As for post-market surveillance — "the single most important function...for protecting the public against the dangers of harmful drugs" — it is put largely in the hands of the manufacturers and the FDA Center for Drug Evaluation and Research (CDER), the part of the FDA that companies pay to review their new drug applications.

After approval, aggressive marketing of new drugs to doctors for both approved and unapproved uses before good safety information is available maximizes the number of patients exposed to risks from the roughly 25 to 40 new NMES approved annually.

Field studies find that most drug representatives do not discuss adverse side effects. Although the law requires companies to submit some marketing materials for review, Congress and the FDA allocate only a small budget and staff to review about 75,000 submissions a year for false or misleading information. Further, the small stream of letters ordering that inaccuracies be corrected is subject to a review process that delays their reaching the companies.

Marketing for unapproved or "off-label" uses worsens the balance of harm and benefit and undermines the purpose of testing to show that a drug is effective and safe for a specific use. While trying drugs for new uses is clinically important, especially for certain populations such as children and cancer patients, 75 percent of off-label prescribing is neither supported by sound evidence nor accompanied by an organized means for gathering such evidence. Companies retain leading experts to expand use, broaden clinical guidelines, and conduct small, short sham trials that companies get published and hand out to their physician-customers as "evidence."

A 15-month investigation by the Committee on Government Reform of the U.S. House of Representatives found "a growing laxity in FDA's surveillance and enforcement procedures, a dangerous decline in regulatory vigilance, and an obvious unwillingness to move forward even on claims from its own field offices." The resulting 2006 report also documented a 53.7-percent decline in warning letters. Since then, FDA leadership has shifted to talking about being a "partner" with industry to get more drugs to patients more quickly. For the reasons we explained above, the proportion of new products with clinical advantages seems to have moved from about 1 in 8 down to 1 in 12, while the proportion with serious harms has gone up from 1 in 5 towards 1 in 3 as the number of drugs given priority status increases.

REFERENCES

https://app.box.com/s/5414zf7lufhtwf3czjfo9msafnoz6ht5

https://www.academia.edu/6750219/Institutional_Corruption_and_the_Myth_of_Safe_and_Effective_Drugs

http://ethics.harvard.edu/news/institutional-corruption-and-pharmaceutical-policy

CHAPTER FOUR

THE OTHER PEER REVIEW

The Dissenters

Innate Immune Suppression by SARS-CoV-2 mRNA Vaccinations: The role of G-quadruplexes, exosomes and microRNAs

January 2022

By Dr. Stephanie Seneff, MIT., Greg Nigh, Immersion Health,
Anthony Kyriakopoulos, Nasco AD Biotech Lab and Dr. Peter McCullough

Abstract

The mRNA SARS-CoV-2 vaccines were brought to market in response to the widely perceived public health crises of Covid-19. The utilization of mRNA vaccines in the context of infectious disease had no precedent, but desperate times seemed to call for desperate measures. The mRNA vaccines utilize genetically modified mRNA encoding spike proteins. These alterations hide the mRNA from cellular defenses, promote a longer biological half-life for the proteins, and provoke higher overall spike protein production. However, both experimental and observational evidence reveals a very different immune response to the vaccines compared to the response to infection with SARS-CoV-2. As we will show, the genetic modifications introduced by the vaccine are likely the source of these differential responses. In this paper, we present the evidence that vaccination, unlike natural infection, induces a profound impairment in type I interferon signaling, which has diverse adverse consequences to human health. We explain the mechanism by which immune cells release into the circulation large quantities of exosomes containing spike protein along with critical microRNAs that induce a signaling response in recipient cells at distant sites. We also identify potential profound disturbances in regulatory control of protein synthesis and cancer surveillance. These disturbances are shown to have a potentially direct causal link to neurodegenerative disease, myocarditis, immune thrombocytopenia, Bell's palsy, liver disease, impaired adaptive immunity, increased tumorigenesis, and DNA damage. We show evidence from adverse event reports in the VAERS database supporting our hypothesis. We believe a comprehensive risk/benefit assessment of the mRNA vaccines excludes them as positive contributors to public health, even in the context of the Covid-19 pandemic.

https://www.researchgate.net/publication/357994624_Innate_Immune_Suppression_by_SARS-CoV-2_mRNA_Vaccinations_The_role_of_G-quadruplexes_exosomes_and_microRNAs

"We also identify potential profound disturbances in regulatory control of protein synthesis and cancer surveillance. These disturbances are shown to have a potentially direct causal link to neurodegenerative disease, myocarditis, immune thrombocytopenia, Bell's palsy, liver disease, impaired adaptive immunity, increased tumorigenesis, and DNA damage."

America's desperate need for wellbeing

Stephan A. Schwartz

The Schwartzreport tracks emerging trends that will affect the world, particularly the United States. For EXPLORE it focuses on matters of health in the broadest sense of that term, including medical issues, changes in the biosphere, technology, and policy considerations, all of which will shape our culture and our lives.

It is a near universal article of faith amongst Americans that the United States is the best country in the world at nearly everything. It isn't true, and the reason it isn't can be clearly defined. We, as a culture, have made something other than fostering wellbeing our number one priority. Instead, everything is geared to profit and the power it bestows, Did that offend you? Let me be clear, I am not interested in partisan politics except anthropologically. Do not misread me. What I care about and have talked about for the 16 years I have been writing in Explore is wellbeing as measured by objectively verifiable data, social outcome data. Decades of social outcome research has proven to me that if you always choose the option that best fosters wellbeing at every level of earth's matrix of life, you will always get the best outcome. Every other option places something else first and ends up diminishing wellbeing; it does not foster it.

So, let's start with some social outcome data that defines us today. Although I could pick many more incarceration, obesity, maternal mortality, infant mortality, life span, come immediately to mind since this is an essay and not a book, I'll just cite four categories of social outcome data to make my point: healthcare, happiness, justice and childcare. I have chosen these four because Benjamin Franklin, America's most enlightened Founder, made the point they are essential to a nation's wellbeing and its ability to maintain a healthy democracy.1
Healthcare: As the Covid pandemic has shown, there are in the United States many highly skilled and deeply dedicated men and women working in healthcare. It is not the individual, but the system that is failing. There are nuanced differences in the way various research entities rank the healthcare of each nation.

The World Population Review looked at all of them. This is what they concluded:

"There are some trends that one can identify in comparing the various data sets. The northern European countries tend to fare well in the more recent reports. Whether it's Norway, Denmark, Switzerland, or a neighbor, it's clear that Northern Europe is working hard to keep its people healthy. East Asian countries also represent well, with South Korea, Japan, and Singapore all making appearances.

"Finally, it's difficult to overlook the absence of the United States in every list. While the U.S. certainly has its share of first-class doctors and facilities, higher costs and lower availability of care continue to impact its ranking—especially when compared to countries with some form of universal health care."2

Where does America rank, how does America compare with 10 other developed nations? We rank last.

According to a 2017 publication from the Commonwealth Fund, The USA is ranked last out of 11 Countries.

In the 2021 rankings the U.S. is still 11th of the 11 developed nations. We are an outlier in the correct sense of the word.

They said, "Among the 11 nations studied in this report Australia, Canada, the Netherlands, Germany, Switzerland, France, New Zealand, Norway, Sweden, the United Kingdom, and the United States—the U.S. ranks last, as it did in 2010, 2007, 2006, and 2014"3

Childcare

There can be no question that children are a nation's future. So, you would think it would follow that children would be a societal priority. That would be incorrect in the United States.

Deniers of these facts may delude themselves all they want, but the social outcome data tells the real story, the real truth. Americans do not like children except their own progeny, and anti-choice people particularly do not care for children.4 You may not believe or like that truth but the facts are what they are. And here is a chart that defines the whole.

The New York Times examined child care policies and expenditures nation by nation and concluded, "In the developed world, the United States is an outlier in its low levels of financial support for young children's care — something Democrats, with their safety net spending bill, are trying to change. The U.S. spends 0.2% of its G.D.P. on child care for children 2 and under — which amounts to about $200 a year for most families, in the form of a once-a-year tax credit for parents who pay for care.

"The other wealthy countries in the Organization for Economic Cooperation and Development spend an average of 0.7% of G.D.P. on toddlers, mainly through heavily subsidized child care. Denmark, for example, spends $23,140 annually per child on care for children 2 and under."5

And if that is not definitive enough, consider this: according to the U.S. Department of Agriculture, "among children, food insecurity and very low food security increased significantly from 2019. Children and adults were food insecure in 7.6% of U.S. households with children in 2020 (up from 6.5% in 2019); very low food security among children was 0.8% (up from 0.6% in 2019). In 2020, the typical food-secure household spent 18% more on food than the typical food-insecure household of the same size and household composition in 2019. About 55% of food-insecure households participated in one or more of the three largest Federal nutrition assistance programs: Supplemental Nutrition Assistance Program (SNAP, formerly food stamps); Special Supplemental Nutrition Program for Women, Infants, and Children (WIC); and the National School Lunch Program during the month prior to the 2020 survey."6 That means in a nation so rich that competing private individuals could finance their own space programs, more than 38 million Americans faced food insecurity in 2020, a nearly 9% increase over 2019. Close to one in five U.S. residents received some kind of charitable food assistance and one in seven children could not be sure where their next meals was coming from.

According to Joel Berg, CEO of Hunger Free America, "The new federal data tells us two things. First, while hunger was already a massive, systemic problem in all 50 states before Covid-19 hit the U.S., domestic hunger surged during the pandemic. Second, while tens of million of Americans suffered mightily from food hardship in 2020— and are still suffering mightily—the nation avoided mass starvation mostly because the federal government stepped in to dramatically increase food and cash aid. This safety net was a giant food life preserver."7

Justice

The World Justice Project is considered the leading source "for original, independent data on the rule of law. Covering 128 countries and jurisdictions, the Index relies on national surveys of more than 130,000 households and 4000 legal practitioners and experts to measure how the rule of law is experienced and perceived worldwide."8

As with healthcare, the nations that top the list are the Nordic countries, Denmark, Norway, and Finland. They reported further that, "This year (2020), for the first time, the United States fell out of the top 20 countries, replaced by Spain."9

Happiness

When you put aside all the politics and ideological arguments and get down to the quality of life and happiness of the individuals of each country, something very revealing emerges: The Nordic Exceptionalism. "The World Happiness Report is a publication of the Sustainable Development Solutions Network, powered by data from the Gallup World Poll and Lloyd's Register Foundation, who provided access to the World Risk Poll."10 For the last 8 years the Report has ranked the nations of the world on the basis of the happiness of their people. The results, like all the other topics I am covering in this essay are incredibly revealing and also instructive. They tell is what works. Finland, Denmark, Norway, Sweden, and Iceland have consistently been in the top ten, and slightly different combinations of them have been ranked as the top three in 2017, 2018, and 2019. And close to them the Netherlands and Switzerland. A ranking calculated on a range of criteria. The United States is ranked 10th.11

And what makes the people of the Nordic countries so happy? The Report concludes, ". . .reviewing the existing studies, theories, and data behind the World Happiness Report, we find that the most prominent explanations include factors related to the quality of institutions, such as reliable and extensive welfare benefits, low corruption, and well-functioning democracy and state institutions. Furthermore, Nordic citizens experience a high sense of autonomy and freedom, as well as high levels of social trust towards each other, which play an important role in determining life satisfaction. On the other hand, we show that a few popular explanations for Nordic happiness such as the small population and homogeneity of the Nordic countries, and a few counterarguments against Nordic happiness such as the cold weather and the suicide rates, actually don't seem to have much to do with Nordic happiness."12

Conclusion

Just a few more facts to close. The media tells us constantly that America is the richest nation in the world, and that is true although China is about to surpass us; but that is not really a very meaningful statistic. What matters to most people is not how rich their country is, but how rich they are. So let's look at that. The average income in Norway is 78,250 US, while in the U.S. it is 65,910 US$. The reality is that when one deals with data and not ideology, or nationalism based on objectively verifiable data, it is very clear that the best managed nations in the world are Norway, Finland, Sweden, Denmark, Iceland, the Netherlands, Finland, Switzerland and New Zealand. Why? Because they explicitly design their national policies to foster wellbeing. The question one has to ask is why doesn't the United States do that? I think it is because of an existential sense of isolated individuality, a gross distortion of what the Founders intended. We are no longer a "We" culture, it is every person for themselves, and our culture's first priority as a society is profit and the power it bestows.

The only way to change this, again based on data, particularly in a democracy, is to change the culture's consciousness. And the consciousness of a culture is the aggregate of individual consciousnesses. This is not a theory, there is objectively measurable data confirming this process.

Princeton researcher Roger Nelson, Director and founder of the Global Consciousness Project, an international collaboration of researchers has been working for decades to collect and analyze objectively measurable effects of events that stimulate us to integrate around an event as a world-wide consciousness focused on that event. The GCP monitors changes in collective consciousness 24/7, and the work has shown that when individual consciousness around an event like Princess Diana's death, or a tsunami in Japan occurs and receives international attention there is a measurable effect in the informational architecture that makes up a culture, be it for wellbeing or disaster. If something changes how individuals think and react to an event or a worldview, the culture changes for good or ill.

What the Nordic nations and the few others I have listed have discovered is that positive, life-affirming be-

ingness is the core of a social transformation strategy based on nonviolence, and that it can be invoked by creating social policies that foster wellbeing.

Let me quote myself, "No one else in modern history has understood and articulated this approach better than Mahatma Gandhi. Just before Gandhi was assassinated, a young reporter had the opportunity to interview him at the Sabarmati Ashram in Gujarat. His editors had told him to ask this question: How did you force the British to leave India?

Britain had dominated the subcontinent for centuries. Gandhi had no army, no money to speak of, no official position, none of the trappings that normally confer authority and power. Yet he had made the most powerful nation of his day leave its most valuable colonial possession, without a war.

Gandhi answered the young reporter's question in this way. It perfectly articulates the power of beingness.

"It was not what we did that mattered," he told the reporter, "although that mattered.

"It was not what we said that mattered," he added, "although that mattered.

"It was the nature of our character that caused the British to choose to leave India."13

In 2021 the United States is a nation on the verge of losing its democracy, deeply unhappy, and desperately in need of a change in culture. Where can we start? With the truth. If we won't tell ourselves the truth about ourselves how can we ever hope to make things better? I think the question every American faces in 2022, with an election just in front of us, is how can I change my personal consciousness and the choices it leads me to make so that everything I do or say, my beingness, supports and fosters wellbeing. The Nordic nations and a few others have figured this out. Can Americans do the same?

On COVID vaccines: why they cannot work, and irrefutable evidence of their causative role in deaths after vaccination

Sucharit Bhakdi, MD and Arne Burkhardt, MD

This text is a written summary of Dr. Bhakdi's and Dr. Burkhardt's presentations at the Doctors for COVID Ethics symposium that was live-streamed by UKColumn on December 10th, 2021. The two presentations can be viewed at the very beginning of the video recording of the symposium.

The Authors

Dr. Bhakdi has spent his life practicing, teaching and researching medical microbiology and infectious diseases. He chaired the Institute of Medical Microbiology and Hygiene at the Johannes Gutenberg Unversity of Mainz, Germany, from 1990 until his retirement in 2012. He has published over 300 research articles in the fields of immunology, bacteriology, virology and parasitology, and served from 1990 to 2012 as Editor-in-Chief of Medical Microbiology and Immunology, one of the first scientific journals of this field that was founded by Robert Koch in 1887.

Dr. Arne Burkhardt is a pathologist who has taught at the Universities of Hamburg, Berne and Tübingen. He was invited for visiting professorships/study visits in Japan (Nihon University), the United States (Brookhaven National Institute), Korea, Sweden, Malaysia and Turkey. He headed the Institute of Pathology in Reutlingen

for 18 years. Subsquently, he worked as an independent practicing pathologist with consulting contracts with laboratories in the US. Burkhardt has published more than 150 scientific articles in German and international scientific journals as well as contributions to handbooks in German, English and Japanese. Over many years he has audited and certified institutes of pathology in Germany.

The Evidence

We herewith present scientific evidence that calls for an immediate stop of the use of gene-based COVID-19 vaccines. We first lay out why the agents cannot protect against viral infection. While no positive effects can be expected, we show that the vaccines can trigger self-destructive processes that lead to debilitating illness and death.

Why the vaccines cannot protect against infection

A fundamental mistake underlying the development of the COVID-19 vaccines was to neglect the functional distinction between the two major categories of antibodies which the body produces in order to protect itself from pathogenic microbes.

The first category (secretory IgA) is produced by immune cells (lymphocytes) which are located directly underneath the mucous membranes that line the respiratory and intestinal tract. The antibodies produced by these lymphocytes are secreted through and to the surface of the mucous membranes.

These antibodies are thus on site to meet air-borne viruses, and they may be able to prevent viral binding and infection of the cells.

The second category of antibodies (IgG and circulating IgA) occur in the bloodstream. These antibodies protect the internal organs of the body from infectious agents that try to spread via the bloodstream.

Vaccines that are injected into the muscle – i.e., the interior of the body – will only induce IgG and circulating IgA, not secretory IgA. Such antibodies cannot and will not effectively protect the mucous membranes from infection by SARS-CoV-2. Thus, the currently observed "breakthrough infections" among vaccinated individuals merely confirm the fundamental design flaws of the vaccines. Measurements of antibodies in the blood can never yield any information on the true status of immunity against infection of the respiratory tract.

The inability of vaccine-induced antibodies to prevent coronavirus infections has been reported in recent scientific publications.

The vaccines can trigger self-destruction

A natural infection with SARS-CoV-2 (coronavirus) will in most individuals remain localized to the respiratory tract. In contrast, the vaccines cause cells deep inside our body to express the viral spike protein, which they were never meant to do by nature. Any cell which expresses this foreign antigen will come under attack by the immune system, which will involve both IgG antibodies and cytotoxic T- lymphocytes.

This may occur in any organ. We are seeing now that the heart is affected in many young people, leading to myocarditis or even sudden cardiac arrest and death. How and why such tragedies might causally be linked to vaccination has remained a matter of conjecture because scientific evidence has been lacking. This situation has now been rectified.

Histopathologic Studies: The Patients

Histopathologic analyses have been performed on the organs of 15 persons who died after vaccination. The age, gender, vaccination record, and time of death after injection of each patient are listed in the table on the next page. The following points are of utmost importance:

• Prior to death, only 4 of the 15 patients had been treated in the ICU for more than 2 days. The majority were never hospitalized and died at home (5), on the street (1), at work (1), in the car (1), or in home-care facilities (1). Therefore, in most cases, therapeutic intervention is unlikely to have significantly influenced the post-mortem findings.

• Not a single death was brought into any possible association with the vaccination by the coroner or the public prosecutor; this association was only established by our autopsy findings.

• The initially performed conventional post-mortems also uncovered no obvious hints to a possible role of vaccination, since the macroscopic appearance of the organs was overall unremarkable. In most cases, "rhythmogenic heart failure" was postulated as the cause of death.

But our subsequent histopathological analyses then brought about a complete turnaround. A summary of the fundamental findings follows.

Case #	Gender	Age (years)	Vaccine (injections)	Time of death after last injection
1	female	82	Moderna (1. and 2.)	37 days
2	male	72	Pfizer (1.)	31 days
3	female	95	Moderna (1. and 2.)	68 days
4	female	73	Pfizer (1.)	unknown
5	male	54	Janssen (1.)	65 days
6	female	55	Pfizer (1. and 2.)	11 days
7	male	56	Pfizer (1. and 2.)	8 days
8	male	80	Pfizer (1. and 2.)	37 days
9	female	89	Unknown (1. and 2.)	6 months
10	female	81	Unknown (1. and 2.)	unknown
11	male	64	AstraZeneca (1. and 2.)	7 days
12	female	71	Pfizer (1. and 2.)	20 days
13	male	28	AstraZeneca (1.), Pfizer (2.)	4 weeks
14	male	78	Pfizer (1. and 2.)	65 days
15	female	60	Pfizer (1.)	23 days

Histopathologic Studies: Findings

Histopathologic findings of a similar nature were detected in organs of 14 of the 15 deceased. Most frequently afflicted were the heart (14 of 15 cases) and the lung (13 of 15 cases). Pathologic alterations were furthermore observed in the liver (2 cases), thyroid gland (Hashimoto's thyroiditis, 2 cases), salivary glands (Sjögren`s Syndrome; 2 cases) and brain (2 cases).

A number of salient aspects dominated in all affected tissues of all cases:

1. inflammatory events in small blood vessels (endothelitis), characterized by an abundance of T- lymphocytes and sequestered, dead endothelial cells within the vessel lumen;

2. the extensive perivascular accumulation of T-lymphocytes;

3. a massive lymphocytic infiltration of surrounding non-lymphatic organs or tissue with T- lymphocytes. Lymphocytic infiltration occasionally occurred in combination with intense lymphocytic activation and follicle formation. Where these were present, they were usually accompanied by tissue destruction.

This combination of multifocal, T-lymphocyte-dominated pathology that clearly reflects the process of immunological self-attack is without precedent. Because vaccination was the single common denominator between all cases, there can be no doubt that it was the trigger of self-destruction in these deceased individuals.

Conclusion

Histopathologic analysis show clear evidence of vaccine-induced autoimmune-like pathology in multiple organs. That myriad adverse events deriving from such auto-attack processes must be expected to very frequently occur in all individuals, particularly following booster injections, is self-evident.

Beyond any doubt, injection of gene-based COVID-19 vaccines places lives under threat of illness and death. We note that both mRNA and vector-based vaccines are represented among these cases, as are all four major manufacturers.

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Letter:
The epidemiological relevance of the COVID-19-vaccinated population is increasing

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High COVID-19 vaccination rates were expected to reduce transmission of SARS-CoV-2 in populations by reducing the number of possible sources for transmission and thereby to reduce the burden of COVID-19 disease. Recent data, however, indicate that the epidemiological relevance of COVID-19 vaccinated individuals is increasing. In the UK it was described that secondary attack rates among household contacts exposed to fully vaccinated index cases was similar to household contacts exposed to unvaccinated index cases (25% for vaccinated vs 23% for unvaccinated). 12 of 31 infections in fully vaccinated household contacts (39%) arose

from fully vaccinated epidemiologically linked index cases. Peak viral load did not differ by vaccination status or variant type [1]. In Germany, the rate of symptomatic COVID-19 cases among the fully vaccinated ("breakthrough infections") is reported weekly since 21. July 2021 and was 16.9% at that time among patients of 60 years and older [2]. This proportion is increasing week by week and was 58.9% on 27. October 2021 providing clear evidence of the increasing relevance of the fully vaccinated as a possible source of transmission. A similar situation was described for the UK. Between week 39 and 42, a total of 100.160 COVID-19 cases were reported among citizens of 60 years or older. 89.821 occurred among the fully vaccinated (89.7%), 3.395 among the unvaccinated (3.4%) [3]. One week before, the COVID-19 case rate per 100.000 was higher among the subgroup of the vaccinated compared to the subgroup of the unvaccinated in all age groups of 30 years or more. In Israel a nosocomial outbreak was reported involving 16 healthcare workers, 23 exposed patients and two family members. The source was a fully vaccinated COVID-19 patient. The vaccination rate was 96.2% among all exposed individuals (151 healthcare workers and 97 patients). Fourteen fully vaccinated patients became severely ill or died, the two unvaccinated patients developed mild disease [4]. The US Centres for Disease Control and Prevention (CDC) identifies four of the top five counties with the highest percentage of fully vaccinated population (99.984.3%) as "high" transmission counties [5]. Many decisionmakers assume that the vaccinated can be excluded as a source of transmission. It appears to be grossly negligent to ignore the vaccinated population as a possible and relevant source of transmission when deciding about public health control measures.

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3.395 among the unvaccinated (3.4%)."

Journal Pre-proof

A Report on Myocarditis Adverse Events in the U.S. Vaccine Adverse Events Reporting System (VAERS) in Association with COVID-19 Injectable Biological Products

By Jessica Rose PhD, MSc, BSc , Peter A. McCullough MD, MPH

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Abstract

Following the global rollout and administration of the Pfizer Inc./BioNTech BNT162b2 and Moderna mRNA-1273 vaccines on December 17, 2020, in the United States, and of the Janssen Ad26.COV2.S product on April 1st, 2021, in an unprecedented manner, hundreds of thousands of individuals have reported adverse events (AEs) using the Vaccine Adverse Events Reports System (VAERS). We used VAERS data to examine cardiac AEs, primarily myocarditis, reported following injection of the first or second dose of the COVID-19 injectable products. Myocarditis rates reported in VAERS were significantly higher in youths between the ages of 13 to 23 ($p<0.0001$) with ~80% occurring in males. Within 8 weeks of the public offering of COVID-19 products to the 12-15-year-old age group, we found 19 times the expected number of myocarditis cases in the vaccination volunteers over background myocarditis rates for this age group. In addition, a 5-fold increase in myocarditis rate was observed subsequent to dose 2 as opposed to dose 1 in 15-year-old males. A total of 67% of all cases occurred with BNT162b2. Of the total myocarditis AE reports, 6 individuals died (1.1%) and of these, 2 were under 20 years of age - 1 was 13. These findings suggest a markedly higher risk for myocarditis subsequent to COVID-19 injectable product use than for other known vaccines, and this is well above known background rates for myocarditis. COVID-19 injectable products are novel and have a genetic, pathogenic mechanism of action causing uncontrolled expression of SARS-CoV-2 spike protein within human cells. When you combine this fact with the temporal relationship of AE occurrence and reporting, biological plausibility of cause and effect, and the fact that these data are internally and externally consistent with emerging sources of clinical data, it supports a conclusion that the COVID-19 biological products are deterministic for the myocarditis cases observed after injection.

Conclusions

These data are derived from a rushed, non-FDA-approved, ongoing investigational product rollout, and our conclusions are thus limited by the information at hand. In addition to the 12-15-year-old age group data being very early, it is vital to acknowledge that these reports represent a fraction of the actual total. Thus, due to both the problems of under-reporting and the known lag in report processing, this analysis reveals a strong signal from the VAERS data that the risk of suffering CIRM – especially males is unacceptably high. Again, chil-

dren are not a high-risk group for COVID-19 respiratory illness, and yet they are the high-risk group for CIRM. Efficacy of these products needs to be assessed by immunological assays and long-term studies are required, while safety needs to be evaluated by rigorous clinical, laboratory and imaging assessments of severe reported adverse events such as CIRM. Autopsies should be done in cases of cardiovascular-related deaths temporally associated with COVID-19 injectables. It is reasonable to use the precautionary principle in this particular setting since an alarming number of reports are coming from young males between the ages of 12 and 15. Boys of these ages should be carefully monitored for warning signs of myocarditis which many may pass off such as pallor, chest pain, shortness of breath or lethargy, following dose 1 with the aim of seeking prompt evaluation and avoiding dose 2.

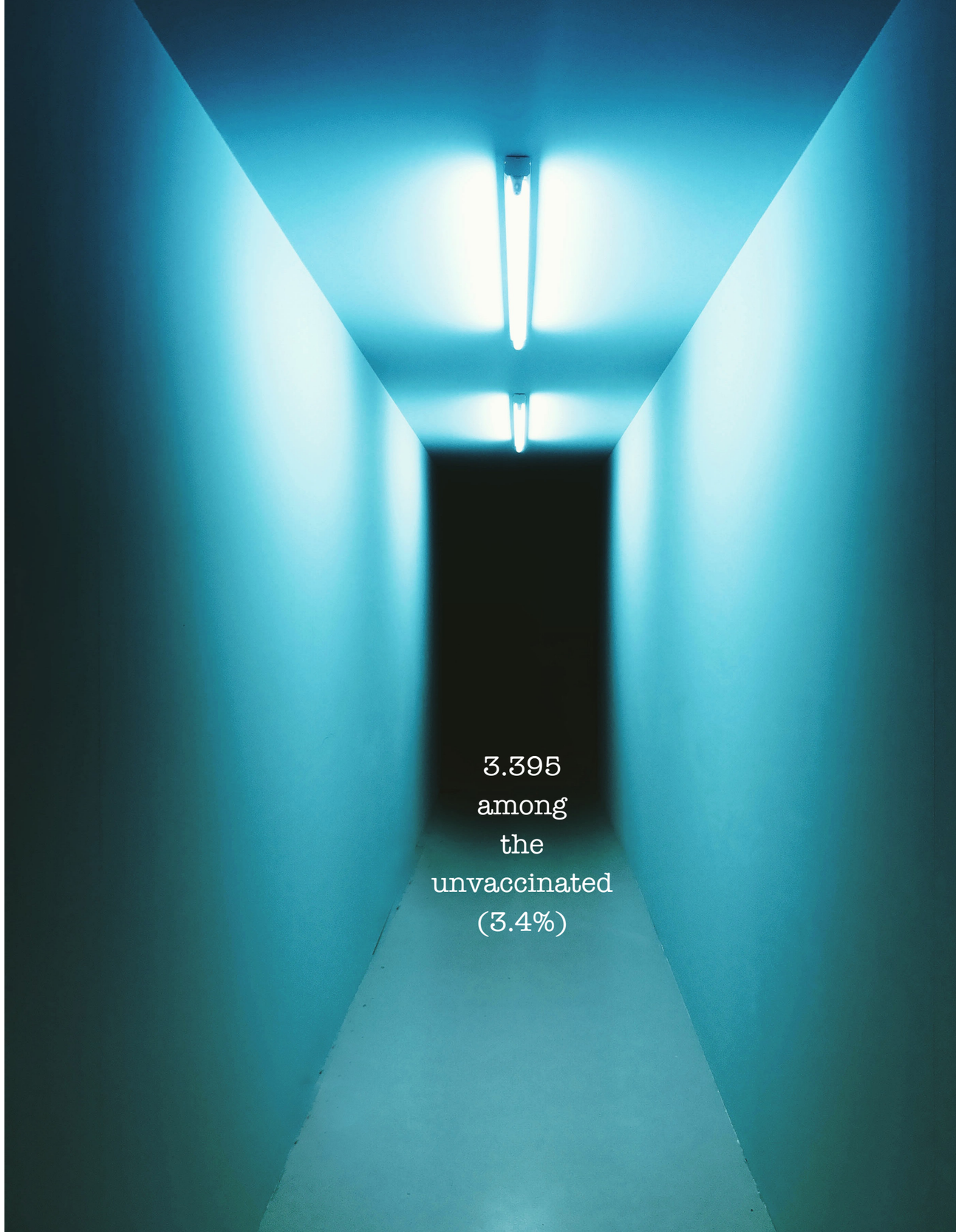
Effective multidrug therapy is available for rare case of serious COVID-19 respiratory illness in the forms of antivirals, immunomodulators, and anthrombotics. *59,60,61,62,63,64,65,66,67,68,69,70,71,72+ The combination of a low IFR in children indicating effective and robust immune responses *73,74,75,76,77,78,79,80,81,82,83+, and the ability to treat with medical therapy, should the need arise, bodes well for clinical outcomes in children *69,70,71,72+.

As part of any risk/benefit analysis which must be completed in the context of experimental products, the points herein must be considered before a decision can be made pertaining to agreeing to 2-dose injections of these experimental COVID-19 products, especially into children and by no means, should parental consent be waived under any circumstances to avoid children volunteering for injections with products that do not have proven safety or efficacy.

Future work may include on-site clinical observations of Troponin, BNP, galectin-3, ST2, IL-6 and D-dimer levels to corroborate temporal effects of onset of myocarditis following injections with particular COVID-19 products. Delineation between COVID-19 respiratory infection with mild ICU-related cardiac injury and true CIRM using these and other clinical diagnostic markers would be incredibly useful for clinicians and should become the standard for differential diagnosis of suspected CIRM. Correcting the inherent limitations of the VAERS dataset must be a priority as part of future studies. Incomplete VAERS dataset field entries describing prior COVID-19 infection and diagnostic tests such as cardiac MRIs in individuals diagnosed with myocarditis, for example, would make this particular study even more potent. However, despite these limitations, and the limitation of using the VAERS dataset for studies like this one, the usable sample sizes have good statistical power. Ultimately, it remains vital to share the results herein to allow true pharmacovigilance to take place.



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VACCINES ARE MADE FOR PROFIT NOT FOR YOUR HEALTH