Evaluating the safety and efficacy of vaccination

Compilation of scientific abstracts

A collection of article abstracts available through Pubmed and Sciencedirect which explore different facets of vaccination. All articles featured have been peer-reviewed and/or published in reputable scientific journals. Articles are arranged thematically and then chronologically within each section. Relevant points are highlighted in green with secondary points highlighted in yellow.
Vaccination (in general)


Cutaneous reactions to vaccinations.

Rosenblatt AE¹, Stein SL².

**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.

Pediatric anaphylactic adverse events following immunization in Victoria, Australia from 2007 to 2013.

Cheng DR1, Perrett KP2, Choo S3, Danchin M4, Buttery JP5, Crawford NW6.

Author information

Abstract

BACKGROUND:
Anaphylaxis is a rare life-threatening adverse event following immunization (AEFI). Variability in presentation can make differentiation between anaphylaxis and other AEFI difficult. This study summarizes pediatric anaphylaxis AEFI reported to an Australian state-based passive surveillance system.

METHODS:
All suspected and reported pediatric (<18 years) anaphylaxis AEFI notified to SAEFVIC (Surveillance of Adverse Events Following Vaccination In the Community) Melbourne, Australia, between May 2007 to May 2013 were analyzed. Clinical descriptions of the AEFI, using the internationally recognized Brighton Collaboration case definition (BCCD) and final outcome were documented.

RESULTS:
93% (25/27) of AEFI classified as anaphylaxis met BCCD criteria, with 36% (9/25), assessed as the highest level of diagnostic certainty (Level 1). Median age was 4.7 years (range 0.3-16.2); 48% of cases were male. The vaccine antigens administered included: diphtheria, tetanus, acellular pertussis (DTaP) alone or in combination vaccines containing other antigens in 11 of 25 cases (44%); and live attenuated measles mumps rubella (MMR) vaccine for six (five also had other vaccines concomitantly administered). The estimated incidence rate of anaphylaxis for DTaP vaccines was 0.36 cases per 100,000 doses, and 1.25 per 100,000 doses for MMR vaccines. The majority of cases had rapid onset, but in 24% (6/25) of cases, first symptoms of anaphylaxis developed ≥30 min after immunization. In 60% (15/25) of cases, symptoms resolved ≤60 min of presentation. Intramuscular adrenaline was administered in 90% (18/25) of cases. All cases made a full recovery with no sequelae identified.

CONCLUSION:
This comprehensive case series of pediatric anaphylaxis as an AEFI identified that diagnostic criteria are useful when applied to a passive vaccine surveillance system when adequate clinical information is available. Anaphylaxis as an AEFI is rare and usually begins within 30 min of vaccination. However, healthcare professionals and
vaccinees/parents should be aware that onset of anaphylaxis can be delayed beyond 30 min following immunization and that medical attention should be sought promptly if anaphylaxis is suspected.


Maglione MA¹, Das L², Raanen L², Smith A², Chari R², Newberry S², Shanman R², Perry T², Goetz MB³, Gidengil C⁴

Abstract

BACKGROUND:
Concerns about vaccine safety have led some parents to decline recommended vaccination of their children, leading to the resurgence of diseases. Reassurance of vaccine safety remains critical for population health. This study systematically reviewed the literature on the safety of routine vaccines recommended for children in the United States.

METHODS:
Data sources included PubMed, Advisory Committee on Immunization Practices statements, package inserts, existing reviews, manuferacturer information packets, and the 2011 Institute of Medicine consensus report on vaccine safety. We augmented the Institute of Medicine report with more recent studies and increased the scope to include more vaccines. Only studies that used active surveillance and had a control mechanism were included. Formulations not used in the United States were excluded. Adverse events and patient and vaccine characteristics were abstracted. Adverse event collection and reporting was evaluated by using the McHarm scale. We were unable to pool results. Strength of evidence was rated as high, moderate, low, or insufficient.

RESULTS:
Of 20,478 titles identified, 67 were included. Strength of evidence was high for measles/mumps/rubella (MMR) vaccine and febrile seizures; the varicella vaccine was associated with complications in immunodeficient individuals. There is strong evidence that MMR vaccine is not associated with autism. There is moderate evidence that rotavirus vaccines are associated with intussusception. Limitations of the study include that the majority of studies did not investigate or identify risk factors for AEs; and the severity of AEs was inconsistently reported.

CONCLUSIONS:
We found evidence that some vaccines are associated with serious AEs however, these events are extremely rare and must be weighed against the protective benefits that vaccines provide.

KEYWORDS:
evidence-based medicine; infectious disease; vaccine/immunization


Anti-laminin-332 mucous membrane pemphigoid developing after a diphtheria tetanus vaccination.

Sezin T, Egozi E, Hillou W, Avitan-Hersh E, Bergman R.

Source

Department of Dermatology, Rambam Health Care Campus, Haifa, Israel.

Abstract

IMPORTANCE:

Bullous pemphigoid (BP) has been previously described to develop after vaccination in 26 patients. Immunoblotting or enzyme-linked immunosorbent assays (ELISAs), which were performed for 7 of these patients, have always shown circulating autoantibodies against BP180 and/or BP230 antigens. A case of anti-laminin-332 mucous membrane pemphigoid (MMP) that developed shortly after a diphtheria tetanus vaccination is described, with a review of the literature on postvaccination BP.

OBSERVATIONS:

A 29-year-old man developed an acute eruption of oral and cutaneous blisters and erosions 2 days after receiving a diphtheria tetanus vaccination. The histopathological, immunohistochemical, immunofluorescent, ELISA, and immunoblotting assay results were compatible with anti-laminin-332 MMP. The serum autoantibodies reacted with the α3 and β3 subunits of laminin-332. The disease was controlled by administering a combination of glucocorticosteroids and dapsone.

CONCLUSIONS AND RELEVANCE:

The development of acute MMP shortly after a diphtheria tetanus vaccination may have been serendipitous, a result of a nonspecific bystander activation of the immune system, or due to structural mimicry between domains of the toxoid molecule and a subunit of laminin-332.

[Surveillance of adverse events following immunization in Henan Province, China between 2010-2011].

Ye Y, Wang CS, Ma YT, Lu MX, Zhang XX, Zhang YY, Guo WS.

Source
Henan Province Center for Disease Control and Prevention, Zhengzhou, China.

Abstract

OBJECTIVE:
To analyze the epidemiological features of adverse events following immunization (AEFI) in Henan Province, China and to evaluate the safety of vaccines currently used in Henan.

METHODS:
The AEFI cases reported in Henan from January 1, 2010 to December 31, 2011 were collected through the China Surveillance System of Information on National Immunization Program. The descriptive method was used for epidemiological analysis.

RESULTS:
A total of 2415 cases of AEFI were reported in Henan from January 1, 2010 to December 31, 2011, and 1238 (51.26%) of them were found in Zhengzhou, Luoyang, and Jiaozuo cities. The male-to-female ratio was 1.32:1. Seven hundred and ninety-nine (33.08%) of these cases were less than one year old. Measles vaccine and DPT vaccine (against diphtheria, pertussis, and tetanus) were the main causes of AEFI, contributing to 61.24% of cases; the incidence rates of AEFI among people receiving measles and DPT vaccines were 30.3/105 and 5.0/105, respectively. 1528 cases (63.27%) developed AEFI after the first dose of vaccination. Inflammation and allergic symptoms were the predominant adverse effects caused by the top 5 vaccines AEFI-causing vaccines, and the clinical manifestations were significantly different among AEFI cases caused by different vaccines ($\chi^2=304.5$, $P<0.001$). Among the 2415 AEFI cases, 1948 (80.58%) had common adverse reaction, 348 (14.41%) had rare adverse reaction, 98 (4.06%) had coupling disease, 13 (0.51%) had psychogenic reaction, and 10 (0.41%) had reaction for unknown reasons. The prognosis of most AEFI cases was good, with a cure rate as high as 90.64%.

CONCLUSIONS:
AEFI occurs mostly in young children and after the first dose of vaccination. This should be brought to the attention of vaccination service personnel and the children's parents.

Distal acquired demyelinating symmetric neuropathy after vaccination.

Gable KL, Afshari Z, Sufit RL, Allen JA.

Source

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Abstract

Neuropathy after vaccination is a rare event. Chronic immune-mediated polyneuropathy developing in the postvaccination period is distinctly unusual and not well described. Almost all such patients have been reported as having typical chronic inflammatory demyelinating polyneuropathy. Distal acquired demyelinating symmetric neuropathy, unlike classic chronic inflammatory demyelinating polyneuropathy, is characterized by distally predominant sensory symptoms with no or mild distal weakness. We describe the clinical, laboratory, and neurophysiological findings of 2 patients who developed distal acquired demyelinating symmetric neuropathy after vaccination. Immunomodulatory therapy led to clinical improvement in both cases. The literature is reviewed with attention to the clinical features of chronic immune-mediated neuropathies that follow vaccination.

Nonspecific effects of vaccines and the reduction of mortality in children.

Shann F.

Abstract

There is now strong evidence that vaccines have substantial nonspecific (heterologous) effects in children in high-mortality regions. The hypothesis states that, until a different vaccine is given: (1) live vaccines induce a protective nonspecific immune response, whereas inactivate vaccines cause a harmful nonspecific immune response; (2) Bacillus Calmette-Guerin (BCG) vaccine approximately halves mortality from infections other than tuberculosis; (3) provided vitamin A was not given at birth, measles vaccine approximately halves mortality from infections other than measles (this effect may be stronger if the child still has maternal antibody); and (4) whole-cell diphtheria-tetanus-pertussis (DTP) vaccine increases mortality from infections other than diphtheria, tetanus, and pertussis (this effect is stronger in girls than boys). These observations suggest that minor modifications to the routine immunization schedule could reduce child mortality by at least 30%, and they have important implications for the design of randomized trials of vaccines in high-mortality regions.

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Vaccine adverse events reported during the first ten years (1998-2008) after introduction in the state of Rondonia, Brazil.

Cunha MP, Dória JG, Marques RC, Leão RS.

Source
Department of Nursing, Fundação Universidade Federal de Rondônia, 76801-974 Porto Velho, RO, Brazil.

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 Calmette-Guérin), HB (hepatitis B), DTwP/Hib (diphtheria-tetanus-pertussis+Hemophilus 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.

Annual report: Surveillance of adverse events following immunisation in Australia, 2011.

Mahajan D, Cook J, Dey A, Macartney K, Menzies RI.

Author information

- National Centre for Immunisation Research and Surveillance of Vaccine Preventable Diseases, University of Sydney and The Children's Hospital at Westmead, Sydney, New South Wales.

Abstract

This report summarises Australian passive surveillance data for adverse events following immunisation (AEFI) reported to the Therapeutic Goods Administration (TGA) for 2011, and describes reporting trends over the 12-year period 2000 to 2011. There were 2,327 AEFI records for vaccines administered in 2011, a decrease of 40% from 3,894 in 2010. The decrease in 2011 was attributable to a decline in reporting following seasonal influenza (2,354 to 483) and pandemic H1N1 (pH1N1) influenza vaccines (514 to 2). However, reporting rates for some other vaccines were higher in 2011 compared with 2010. The 13-valent pneumococcal conjugate vaccine (13vPCV) replaced the 7-valent pneumococcal conjugate vaccine (7vPCV) and was suspected of involvement in 236 AEFI cases (48 per 100,000 doses). An increase in the number of reports following rotavirus (from 40 to 56 per 100,000 doses), and the hexavalent infant vaccine (from 27 to 40 per 100,000 doses), may have been due at least in part to co-administration with 13vPCV. Reports following DTPa-IPV also increased (from 94 to 139 per 100,000 doses), continuing a trend since 2009. AEFI reports following receipt of the 23-valent pneumococcal vaccine also increased markedly in those aged ≥65 years, from 155 to 288 records. In response to the increase in reports following 23vPPV, boosters are no longer recommended for those without medical risk factors. The most commonly reported reactions were injection site reactions, fever, allergic reactions and malaise. Only 7% of all the reported adverse events were categorised as serious, as per the database definitions, although some events classified as non-serious may have caused severe illness. Three deaths were temporally associated with vaccination; however, all were attributed to causes other than vaccination. The increase in 2011 was predominately due to reports of injection site reactions (49% increase in 2011). Increases in some instances may also be partly attributable to an increasing propensity to report AEFI.

**Hypersensitivity reactions to vaccine constituents: a case series and review of the literature.**

Leventhal JS, Berger EM, Brauer JA, Cohen DE.

Source

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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.

A positive association found between autism prevalence and childhood vaccination uptake across the U.S. population.

Delong G.

Source

Department of Economics and Finance, Baruch College/City University of New York, New York, New York, USA. gayle.delong@baruch.cuny.edu

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.

Erythema multiforme following vaccination in an infant.

Kaur S1, Handa S.

Author information

Abstract

Erythema multiforme is a cutaneous reaction pattern precipitated by varied agents, notably herpes simplex and drugs. It predominantly occurs in adolescents and young adults but may be seen at other ages also. While vaccination is rarely a precipitating factor for erythema multiforme, it may occasionally be seen in infants and children. We report here a case of an two-month-old infant with lesions of erythema multiforme minor appearing after two weeks following vaccination for DPT, Hepatitis B and influenza.

Postvaccinal inflammatory neuropathy: peripheral nerve biopsy in 3 cases.


Source
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Abstract
Autoimmune inflammatory polyneuropathy (PN) can be triggered by vaccination. We report 3 such cases. A 36-year-old female nurse presented 15 days after a hepatitis B vaccination (HBV) with acute sensory disturbances in the lower limbs. She had severe ataxia but no weakness. Cerebrospinal fluid (CSF) protein level was 84 mg/100 mL, with 3 lymphocytes. A 66-year-old man presented 21 days after HBV with severe motor and sensory PN involving all 4 limbs. A 66-year-old man presented 15 days after a yellow fever vaccination with progressive motor and sensory PN involving all 4 limbs and bilateral facial paralysis. CSF protein level was 300 mg/100 mL, with 5 lymphocytes. Six weeks later, a tracheostomy was performed. In these 3 patients, the nerve deficits lasted for months. In each case, peripheral nerve biopsy showed KP1-positive histiocytes but no T-lymphocytes in the endoneurium. On ultrastructural examination, there was axonal degeneration in the first 2 cases; in case 2, a few myelinated fibers exhibited an intra-axonal macrophage but the myelin sheath was preserved. There was only 1 example of macrophage-associated demyelination in case 2, but these were numerous in case 3. It is likely that in the first 2 cases, an autoimmune reaction against some axonal or neuronal components was triggered by HBV. It induced an acute sensory ataxic PN in case 1 and an acute motor and sensory axonal neuropathy (AMSAN) in case 2. The third patient had a chronic inflammatory demyelinating PN, likely triggered by yellow fever vaccination.

Stevens-Johnson syndrome and toxic epidermal necrolysis after vaccination: reports to the vaccine adverse event reporting system.

Ball R¹, Ball LK, Wise RP, Braun MM, Beeler JA, Salive ME.

Author information

Abstract
We conducted a telephone survey of reports of Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) to the Vaccine Adverse Event Reporting System. We identified six cases of SJS or TEN after vaccination without other obvious triggers, suggesting that SJS and TEN might very rarely be caused by vaccination. Confirmation of this hypothesis will likely require controlled studies.
Genotoxicity


[Genotoxicity of vaccines: an unresolved problem of ecological genetics].
[Article in Russian]

Volgareva GM.

Abstract

The problem of potential remote consequences of vaccinations still remains to be solved. Data on the effects of immunobiological preparations, including vaccines, employed for preventive mass immunization on certain hereditary structures are reviewed. Many of these preparations are genotoxic. Prospects for diminishing the genetic risks of vaccinations are discussed.


See also: Determination of genotoxicity of classical swine flu vaccine
**Ingredients**

**Adjuvants (General)**


**Systemic immunotoxicity reactions induced by adjuvanted vaccines.**

Batista-Duharte A¹, Portuondo D², Carlos IZ².

**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.

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**KEYWORDS:**

Action mechanisms, Adjuvant, Immunotoxicity, Systemic reactions, Vaccine

Autoimmune/inflammatory syndrome induced by adjuvants (ASI A) 2013: Unveiling the pathogenic, clinical and diagnostic aspects.

Perricone C¹, Colafrancesco S, Mazor RD, Soriano A, Agmon-Levin N, Shoenfeld Y.

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.

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KEYWORDS:
Adjuvant, Autoantibodies, Autoimmune/Inflammatory syndrome induced by adjuvants, Autoimmunity, Saccharomyces cerevisiae, Vaccine

A review on the association between inflammatory myopathies and vaccination.

Stübben JP.

Source

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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 myofasiositis 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.

A literature review on optic neuritis following vaccination against virus infections.
Stübgen JP.

Source
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Abstract
Optic neuritis (ON) is a primary inflammation of the optic nerve. ON is mostly idiopathic, and infrequently occurs on the background of systemic autoimmune disease, recent infectious disease or inoculation with mostly adjuvanted vaccines. Published case histories, retrospective reviews and analyses of epidemiological data report on the onset of immune-mediated ON (and other autoimmune disorders) within a defined period (days to weeks) after immunization of patients with probable genetic predisposition. After vaccination, there exists no long-term increased risk to develop ON. The risk for these vaccine-induced adverse events may be enhanced by adjuvants. Patient age distribution reflected immunization schedules and advisories, or patient age groups studied. Vaccination is one of the most important prevention tools in modern medicine, and a discussion on risk-benefit or cost-benefit analysis, and advisory on individual vaccines or vaccination programs falls outside the scope of this review. Despite a great deal of scientific uncertainty, the existence of a possible causal link between vaccines and acute ON should not be totally disregarded.

Adverse events following immunization with vaccines containing adjuvants.

Cerpa-Cruz S1, Paredes-Casillas P, Landeros Navarro E, Bernard-Medina AG, Martínez-Bonilla G, Gutiérrez-Ureña S.

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.

‘ASIA’ – Autoimmune/inflammatory syndrome induced by adjuvants

Yehuda Shoenfeld† ‡, Nancy Agmon-Levin

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”.

Keywords

- Autoimmunity; Adjuvant; Vaccine; Gulf war syndrome (GWS); Macrophagic myofasciitis syndrome (MMF); Silicone

Aluminium


Administration of aluminium to neonatal mice in vaccine-relevant amounts is associated with adverse long term neurological outcomes.

Shaw CA, Li Y, Tomljenovic L.

Source

Dept. of Ophthalmology and Visual Sciences, University of British Columbia, Vancouver, British Columbia, Canada; Program in Experimental Medicine, University of British Columbia, Vancouver, British Columbia, Canada; Program in Neuroscience, University of British Columbia, Vancouver, British Columbia, Canada. Electronic address: cashawlab@gmail.com.

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.

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KEYWORDS:

Adjuvants, Aluminium, Autism, Neurodevelopmental disorders, Neurotoxicity, Vaccines

Aluminium in the central nervous system (CNS): toxicity in humans and animals, vaccine adjuvants, and autoimmunity.

Shaw CA, Tomljenovic L.

Source
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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.

A child with a long-standing, intensely itching subcutaneous nodule on a thigh: an uncommon (?) reaction to commonly used vaccines.

Bergfors E, Lundmark K, Nyström Kronander U.

Source

Research and Development Unit in Local Health Care, County of Östergötland, Linköping, Sweden. elisabet.bergfors@lio.se

Abstract

A 2-year-old girl presented with an intensely itching subcutaneous nodule on the front of a thigh. The nodule persisted for 10 months until it was excised. Subsequent investigation for malignancy and systemic disease showed no pathological findings. The diagnosis, persistent itching vaccination granuloma, was revealed by hazard almost 2 years after the onset of symptoms. Persistent itching subcutaneous nodules at the injection site for aluminium containing vaccines (mostly diphtheria-tetanus-pertussis combination vaccines for primary immunisation of infants) may appear with a long delay after the vaccination (months), cause prolonged itching (years) and are often associated with contact allergy to aluminium. The condition is poorly recognised in Health Care which may lead to prolonged symptoms and unnecessary investigations.

Effect of Routine Vaccination on Aluminum and Essential Element Levels in Preterm Infants

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Parenteral feedings containing more than 4 to 5 µg/kg/d of aluminum have been shown to result in neurodevelopmental delay in preterm infants.¹ However, an infant at the 2-month checkup receives multiple aluminum-containing vaccines that in combination may have as high as 1225 µg of intramuscular aluminum; this is a much higher intramuscular aluminum dose than the safely recommended intravenous aluminum dose.² Our first objective was to measure prevaccine and postvaccine levels of aluminum in preterm infants, a population at higher risk of aluminum neurotoxic effects. Our second objective was to measure prevaccine and postvaccine levels of essential elements (EE). Inflammation from trauma can cause declines in serum levels of specific EE such as zinc and selenium³ ⁵; there may be similar EE perturbations secondary to vaccination-induced inflammation.

http://archpedi.jamanetwork.com/article.aspx?articleid=1712578#pld130004r2
Mechanisms of aluminum adjuvant toxicity and autoimmunity in pediatric populations.

Tomljenovic L, Shaw CA.

Source

Neural Dynamics Research Group, Department of Ophthalmology and Visual Sciences, University of British Columbia, Vancouver, BC, Canada. lucija77@gmail.com

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.

Review

Empirical Data Confirm Autism Symptoms Related to Aluminum and Acetaminophen Exposure†

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† This paper attracts great attention. Please refer to our policy regarding possibly controversial articles.

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Received: 24 September 2012; in revised form: 16 October 2012 / Accepted: 5 November 2012 / Published: 7 November 2012

(This article belongs to the Special Issue Biosemiotic Entropy: Disorder, Disease, and Mortality)

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.

Keywords: autism; vaccines; MMR; HEP-B; glutathione; sulfate; cholesterol sulfate; aluminum; mercury; acetaminophen

http://www.mdpi.com/1099-4300/14/11/2227
Do aluminum vaccine adjuvants contribute to the rising prevalence of autism?

Tomljenovic L, Shaw CA.

Source

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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 disorder. 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.

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http://www.ncbi.nlm.nih.gov/pubmed/?term=Do+aluminum+vaccine+adjuvants+contribute+to+the+rising+prevalence+of+autism%3F
Aluminum vaccine adjuvants: are they safe?

Tomljenovic L, Shaw CA.

Source

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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.

Aluminum hydroxide injections lead to motor deficits and motor neuron degeneration.

Shaw CA¹, Petrik MS.

Author information

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.

Vaccines as a trigger for myopathies.

Orbach H, Tanay A.

Source

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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.

Aluminum adjuvant linked to Gulf War illness induces motor neuron death in mice.

Petrik MS, Wong MC, Tabata RC, Garry RF, Shaw CA.

Source

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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.

Vaccine adjuvants: Current state and future trends

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Received 18 May 2004; Accepted 19 May 2004; Published online 28 September 2004.

Abstract

The problem with pure recombinant or synthetic antigens used in modern day vaccines is that they are generally far less immunogenic than older style live or killed whole organism vaccines. This has created a major need for improved and more powerful adjuvants for use in these vaccines. With few exceptions, alum remains the sole adjuvant approved for human use in the majority of countries worldwide. Although alum is able to induce a good antibody (Th2) response, it has little capacity to stimulate cellular (Th1) immune responses which are so important for protection against many pathogens. In addition, alum has the potential to cause severe local and systemic side-effects including sterile abscesses, eosinophilia and myofascitis, although fortunately most of the more serious side-effects are relatively rare. There is also community concern regarding the possible role of aluminium in neurodegenerative diseases such as Alzheimer’s disease. Consequently, there is a major unmet need for safer and more effective adjuvants suitable for human use. In particular, there is demand for safe and non-toxic adjuvants able to stimulate cellular (Th1) immunity. Other needs in light of new vaccine technologies are adjuvants suitable for use with mucosally-delivered vaccines, DNA vaccines, cancer and autoimmunity vaccines. Each of these areas are highly specialized with their own unique needs in respect of suitable adjuvant technology. This paper reviews the state of the art in the adjuvant field, explores future directions of adjuvant development and finally examines some of the impediments and barriers to development and registration of new human adjuvants.

Keywords:

adjuvants, immune response, mucosal immunity, vaccines

Hypothesis: is Alzheimer's disease a metal-induced immune disorder?

Armstrong RA¹, Winsper SJ, Blair JA.

Author information

Abstract

A hypothesis that a metal-induced immune disorder may be involved in the pathogenesis of some forms of Alzheimer's disease (AD) is presented. The classical complement pathway is activated in AD and T cells and reactive microglial appear in the brain. Studies of metal induced autoimmunity and the use of compounds containing aluminium as vaccine adjuvants suggest that metals can activate complement and can be taken up by antigen presenting cells. The consequent immune response could contribute to neuronal damage, beta-amyloid deposition and cell death. The strengths and weaknesses of this hypothesis are discussed and tests of some aspects are proposed.

Formaldehyde (Formalin)

J Lab Autom. 2013 Oct 2. [Epub ahead of print]


Stallings KD, Kitchener RL, Hentz NG.

Source

1Department of Food, Bioprocessing and Nutrition Sciences, North Carolina State University, Raleigh, NC, USA.

Abstract

Formaldehyde has long been used in the chemical inactivation of viral material during vaccine production. Viral inactivation is required so that the vaccine does not infect the patient. Formaldehyde is diluted during the vaccine manufacturing process, but residual quantities of formaldehyde are still present in some current vaccines. Although formaldehyde is considered safe for use in vaccines by the Food and Drug Administration, excessive exposure to this chemical may lead to cancer or other health-related issues. An assay was developed that is capable of detecting levels of residual formaldehyde in influenza vaccine samples. The assay employs incubation of dosage formulation suspensions with hydralazine hydrochloride under mildly acidic conditions and elevated temperatures, where formaldehyde is derivatized to yield fluorescent s-triazolo-[3,4-a]-phthalazine. The assay has been traditionally run by high-performance liquid chromatography, where runtimes of 15 minutes per sample can be expected. Our laboratory has developed a plate-based version that drastically improved the throughput to a runtime of 96 samples per minute. The assay was characterized and validated with respect to reaction temperature, evaporation, stability, and selectivity to monitor residual formaldehyde in various influenza vaccine samples, including in-process samples. Heat transfer and evaporation will be especially considered in this work. Since the assay is plate based, it is automation friendly. The new assay format has attained detection limits of 0.01 µg/mL residual formaldehyde, which is easily able to detect and quantify formaldehyde at levels used in many current vaccine formulations (<5 µg/0.5-mL dose).

KEYWORDS:

formaldehyde assay, high-temperature assay, residual formaldehyde, vaccine

Mercury (Thimerosal)


Methodological issues and evidence of malfeasance in research purporting to show thimerosal in vaccines is safe.

Hooker B1, Kern J2, Geier D3, Haley B4, Sykes L5, King P5, Geier M3.

Author information

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 [Thimerosal]-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.

Effect of thimerosal on the neurodevelopment of premature rats.

Chen YN¹, Wang J, Zhang J, Li SJ, He L, Shao DD, Du HY.

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 thimerosal containing vaccines to infants.

Thimerosal exposure and the role of sulfation chemistry and thiol availability in autism.

Kern JK, Haley BE, Geier DA, Sykes LK, King PG, Geier MR.

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.

Toxicological status of children with autism vs. neurotypical children and the association with autism severity.


Source
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Abstract
This study investigates both the level of toxic metals in children with autism and the possible association of those toxic metals with autism severity. This study involved 55 children with autism ages 5-16 years compared to 44 controls with similar age and gender. The study included measurements of toxic metals in whole blood, red blood cells (RBC), and urine. The autism group had higher levels of lead in RBC (+41%, p = 0.002) and higher urinary levels of lead (+74%, p = 0.02), thallium (+77%, p = 0.0001), tin (+115%, p = 0.01), and tungsten (+44%, p = 0.00005). However, the autism group had slightly lower levels of cadmium in whole blood (-19%, p = 0.003). A stepwise, multiple linear regression analysis found a strong association of levels of toxic metals with variation in the degree of severity of autism for all the severity scales (adjusted R(2) of 0.38-0.47, p < 0.0003). Cadmium (whole blood) and mercury (whole blood and RBC) were the most consistently significant variables. Overall, children with autism have higher average levels of several toxic metals, and levels of several toxic metals are strongly associated with variations in the severity of autism for all three of the autism severity scales investigated.

B-lymphocytes from a population of children with autism spectrum disorder and their unaffected siblings exhibit hypersensitivity to thimerosal.

Sharpe MA, Gist TL, Baskin DS.

Source
Department of Neurosurgery, The Methodist Neurological Institute, 6560 Fannin Street, Scurlock Tower No. 944, Houston, TX 77030, USA.

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.

Translational Neurodegeneration 2013, 2:25
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

David A Geier, Brian S Hooker, Janet K Kern, Paul G King, Lisa K Sykes and Mark R Geier

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.

Keywords:
Autism; Ethylmercury; Merthiolate; Thimerosal; Thiomersal; Vaccine
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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The results of this study suggest that ethylmercury is a mitochondrial toxin in human astrocytes. We believe that this finding is important, particularly since the number of diseases in which mitochondrial dysfunction has been implicated are rapidly increasing.

http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3395253/
Administration of thimerosal to infant rats increases overflow of glutamate and aspartate in the prefrontal cortex: protective role of dehydroepiandrosterone sulfate.

Duszczyk-Budhathoki M, Olczak M, Lehner M, Majewska MD.

Source
Marie Curie Chairs Program, Department of Pharmacology and Physiology of Nervous System, Institute of Psychiatry and Neurology, 02-957, Warsaw, Poland.

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.

Persistent behavioral impairments and alterations of brain dopamine system after early postnatal administration of thimerosal in rats.

Olczak M, Duszczyk M, Mierzejewski P, Meyza K, Majewska MD.

Source

Department of Pharmacology and Physiology of the Nervous System, Institute of Psychiatry and Neurology, 02-957 Warsaw, Poland.

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 to neurodevelopmental disorders.


Integrating experimental (in vitro and in vivo) neurotoxicity studies of low-dose thimerosal relevant to vaccines.

Dórea JG.

Source
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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.


Lasting neuropathological changes in rat brain after intermittent neonatal administration of thimerosal.

Olczak M, Duszczyk M, Mierzejewski P, Wierzba-Bobrowicz T, Majewska MD.

Source

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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 astrogia in the hippocampus and cerebellum, and positive caspase-3 reaction in Bergmann astrogia. 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.

Thimerosal exposure in infants and neurodevelopmental disorders: An assessment of computerized medical records in the Vaccine Safety Datalink

Heather A. Young, David A. Geier, Mark R. Geier

http://dx.doi.org/10.1016/j.jns.2008.04.002

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.

Thimerosal induces micronuclei in the cytochalasin B block micronucleus test with human lymphocytes.

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Source
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Abstract
Thimerosal is a widely used preservative in health care products, especially in vaccines. Due to possible adverse health effects, investigations on its metabolism and toxicity are urgently needed. An in vivo study on chronic toxicity of thimerosal in rats was inconclusive and reports on genotoxic effects in various in vitro systems were contradictory. Therefore, we reinvestigated thimerosal in the cytochalasin B block micronucleus test. Glutathione S-transferases were proposed to be involved in the detoxification of thimerosal or its decomposition products. Since the outcome of genotoxicity studies can be dependent on the metabolic competence of the cells used, we were additionally interested whether polymorphisms of glutathione S-transferases (GSTM1, GSTT1, or GSTP1) may influence the results of the micronucleus test with primary human lymphocytes. Blood samples of six healthy donors of different glutathione S-transferase genotypes were included in the study. At least two independent experiments were performed for each blood donor. Significant induction of micronuclei was seen at concentrations between 0.05-0.5 micro g/ml in 14 out of 16 experiments. Thus, genotoxic effects were seen even at concentrations which can occur at the injection site. Toxicity and toxicity-related elevation of micronuclei was seen at and above 0.6 micro g/ml thimerosal. Marked individual and intraindividual variations in the in vitro response to thimerosal among the different blood donors occurred. However, there was no association observed with any of the glutathione S-transferase polymorphism investigated. In conclusion, thimerosal is genotoxic in the cytochalasin B block micronucleus test with human lymphocytes. These data raise some concern on the widespread use of thimerosal.


Bernard S, Enayati A, Redwood L, Roger H, Binstock T.

Source

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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.

Childhood infectious diseases and risk of leukaemia in an adult population.


Author information

Abstract

Our study is aimed at investigating the association between common childhood infectious diseases (measles, chickenpox, rubella, mumps and pertussis) and the risk of developing leukaemia in an adult population. A reanalysis of a large population-based case-control study was carried out. Original data included 1,771 controls and 649 leukaemia cases from 11 Italian areas. To contain recall bias, the analysis was restricted to subjects directly interviewed and with a good quality interview (1,165 controls and 312 cases). Odds ratios (ORs) and their related 95% confidence intervals (95% CIs) were estimated by unconditional polychotomous logistic regression model adjusting for age, gender and occupational and lifestyle exposures. A protective effect of at least one infection (OR = 0.66, 95% CI: 0.45-0.97), measles (OR = 0.57, 95% CI: 0.39-0.82) and pertussis (OR = 0.66, 95% CI: 0.45-0.98) was observed for chronic lymphoid leukaemia (CLL). The number of infections was strongly inversely associated with the risk of CLL (p = 0.002, test for trend). With regard to the other types of leukaemia, only a protective effect of pertussis was observed for AML (OR = 0.52, 95% CI: 0.32-0.87). Our results pointed out a protective role of childhood infectious diseases on the risk of CLL in adults. Although a specific antioncogenic effect of some infectious disease, especially measles, cannot be ruled out, the observed decrease of risk with increasing number of infections suggests that a more general "hygiene hypothesis" could be the most likely explanation of the detected association. The protective role of pertussis remains to be elucidated.

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KEYWORDS:

case-control study, infectious diseases, leukaemia, measles, pertussis

DTaP Vaccination

Arch Dis Child 2012;97:685-691 doi:10.1136/archdischild-2011-300646

Early diphtheria-tetanus-pertussis vaccination associated with higher female mortality and no difference in male mortality in a cohort of low birthweight children: an observational study within a randomised trial


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• Published Online First 13 February 2012

Abstract

Background Studies from low-income countries have suggested that diphtheria-tetanus-pertussis (DTP) vaccine provided after Bacille Calmette-Guerin (BCG) vaccination may have a negative effect on female survival. The authors examined the effect of DTP in a cohort of low birthweight (LBW) infants.

Methods 2320 LBW newborns were visited at 2, 6 and 12 months of age to assess nutritional and vaccination status. The authors examined survival until the 6-month visit for children who were DTP vaccinated and DTP unvaccinated at the 2-month visit.

Results Two-thirds of the children had received DTP at 2 months and 50 deaths occurred between the 2-month and 6-month visits. DTP vaccinated children had a better anthropometric status for all indices than DTP unvaccinated children. Small mid-upper arm circumference (MUAC) was the strongest predictor of mortality. The death rate ratio (DRR) for DTP vaccinated versus DTP unvaccinated children differed significantly for girls (DRR 2.45; 95% CI 0.93 to 6.45) and boys (DRR 0.53; 95% CI 0.23 to 1.20) (p=0.018, homogeneity test). Adjusting for MUAC, the overall effect for DTP vaccinated children was 2.62 (95% CI 1.34 to 5.09); DRR was 5.68 (95% CI 1.83 to 17.7) for girls and 1.29 (95% CI 0.56 to 2.97) for boys (p=0.023, homogeneity test). While anthropometric indices were a strong predictor of mortality among boys, there was little or no association for girls.
Conclusion Surprisingly, even though the children with the best nutritional status were vaccinated early, early DTP vaccination was associated with increased mortality for girls.
Diphtheria-tetanus-pertussis vaccination administered after measles vaccine: increased female mortality?

Benn CS, Aaby P.

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Abstract
In low-income countries, children should receive 3 doses of diphtheria-tetanus-pertussis vaccine (DTP) at 6, 10 and 14 weeks of age, and measles vaccine at 9 months of age. However, there is often a delay in administering the vaccines, and DTP is often given after measles vaccine. Previous observations suggest that this practice is associated with increased mortality for female, but not for male children. Within a vitamin A trial in Guinea-Bissau, vaccination status was registered at the time of measles vaccination at 9 months; 141 (31%) of 455 children were missing 1 or more DTP vaccines and were likely to receive them afterward. We examined whether missing DTP vaccine at this time point was associated with sex-differential effects on mortality. In female children, missing DTP was associated with 3.55 (95% confidence interval: 1.23-10.26) times higher risk of dying before 36 months of age, whereas it made no difference in male children (0.97 [0.34-2.80]). The result supports that receiving DTP after measles vaccine affects female children negatively.

Delay in diphtheria, pertussis, tetanus vaccination is associated with a reduced risk of childhood asthma.

McDonald KL, Huq SI, Lix LM, Becker AB, Kozyrskyj AL.

Source
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Abstract

BACKGROUND:
Early childhood immunizations have been viewed as promoters of asthma development by stimulating a T(H)2-type immune response or decreasing microbial pressure, which shifts the balance between T(H)1 and T(H)2 immunity.

OBJECTIVE:
Differing time schedules for childhood immunizations may explain the discrepant findings of an association with asthma reported in observational studies. This research was undertaken to determine whether timing of diphtheria, pertussis, tetanus (DPT) immunization has an effect on the development of childhood asthma by age 7 years.

METHODS:
This was a retrospective longitudinal study of a cohort of children born in Manitoba in 1995. The complete immunization and health care records of cohort children from birth until age 7 years were available for analysis. The adjusted odds ratio for asthma at age 7 years according to timing of DPT immunization was computed from multivariable logistic regression.

RESULTS:
Among 11,531 children who received at least 4 doses of DPT, the risk of asthma was reduced to (1/2) in children whose first dose of DPT was delayed by more than 2 months. The likelihood of asthma in children with delays in all 3 doses was 0.39 (95% CI, 0.18-0.86).

CONCLUSION:
We found a negative association between delay in administration of the first dose of whole-cell DPT immunization in childhood and the development of asthma; the association was greater with delays in all of the first 3 doses. The mechanism for this phenomenon requires further research.

Effects of diphtheria-tetanus-pertussis or tetanus vaccination on allergies and allergy-related respiratory symptoms among children and adolescents in the United States

Eric L. Hurwitz, DC, PhD

Hal Morgenstern, PhD

http://dx.doi.org/10.1016/S0161-4754(00)90072-1

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.sciencedirect.com/science/article/pii/S0161475400900721#
Diphtheria [DTaP]

Diphtheria is now more commonly seen in adults than in children in industrialised countries for several reasons. Firstly, improved living conditions impacted on the incidence of childhood diphtheria even before vaccines became available. Smaller families and less overcrowding meant that preschool children were not exposed to the same intensity of infection as previously. As a result, many reached adulthood without having been exposed to diphtheria. Secondly, the implementation of mass childhood vaccination programs further reduced both the incidence of diphtheria and the circulation of toxigenic \textit{C. diphtheriae}, so there was less opportunity to acquire natural immunity or to boost waning vaccine-induced immunity.


1939: Tetanus toxoid vaccine introduced – used mainly to vaccinate Armed Forces

1932-1936: School-based diphtheria vaccination programs commenced

1929: Diphtheria toxoid vaccine introduced

1924: Mass immunisation commenced in Australia with the use of diphtheria antitoxin in Victoria

**H1N1 (Swine Flu)**

Evidence suggests a link between narcolepsy and swine flu vaccination.

http://www.thelancet.com/journals/laninf/article/PIIS1473-3099(13)70117-8/fulltext
Risk factors associated with anaphylaxis and other allergic-like events following receipt of 2009 monovalent AS03-adjuvanted pandemic influenza vaccine in Quebec, Canada

Isabelle Rouleau, Gaston De Serres, Danuta M. Skowronski, Jean Philippe Drolet, Chantal Lemire, Eveline Toth, Monique Landry

http://dx.doi.org/10.1016/j.vaccine.2014.04.059

Abstract

Introduction
In Quebec, Canada, receipt of the 2009 AS03-adjuvanted pandemic H1N1 vaccine was associated with increased risk of anaphylaxis and other allergic-like events (ALE), especially among women of childbearing age. In response to this safety signal, a case-control study was conducted to identify potential risk factors.

Methods
A total of 435 ALE (50 anaphylaxis) occurring <24 h following pandemic vaccination were compared to 849 age-gender matched controls randomly selected from the provincial Pandemic Influenza Vaccination Registry. More than 60 potential risk factors were evaluated through phone interviews and included demographic information, medical history, medication use or acute respiratory illnesses (ARI) concurrent with vaccination and other risk factors associated with general allergy. Odds ratios (ORs) with 95% confidence intervals were estimated with unconditional logistic regression.
Results

Factors associated with increased risk of anaphylaxis included concurrent ARI (18% cases vs. 4% controls, ORadj 7.67, 95%CI: 3.04–13.37), food allergy (26% cases vs. 4% controls, ORadj 3.84, 95%CI: 1.51–9.74) and vaccination during the first four weeks of the campaign (66% cases vs. 50% controls, ORadj 2.16, 95%CI: 1.10–4.25) whereas alcohol exposure (≥1 drink/week) was associated with reduced risk (29% cases vs. 42% controls, ORadj 0.26, 95%CI: 0.13–0.57). These factors were also significantly associated with any ALE but the strength of association was weaker. Allergy to components found in the vaccine (e.g., egg, thimerosal) was infrequent and did not significantly differ between cases and controls.

Conclusion

Increased anaphylaxis and other allergic-like events observed in association with AS03-adjuvanted pandemic H1N1 vaccine remain mostly unexplained despite extensive risk factor review. However, prior to mass vaccination with similar formulations this safety signal warrants further consideration and better understanding. In particular, the predominance among women of childbearing age may be a clue to underlying biological or hormonal influences on adverse immunological responses to vaccine.

Randomized Controlled Ferret Study to Assess the Direct Impact of 2008-09 Trivalent Inactivated Influenza Vaccine on A(H1N1)pdm09 Disease Risk.

Skowronski DM¹, Hamelin ME², De Serres G³, Janjua NZ¹, Li G¹, Sabaiduc S¹, Bouhy X¹, Couture C⁶, Leung A¹, Kobasa D⁴, Embury-Hyatt G⁵, de Bruin E¹⁰, Balshaw R¹¹, Lavigne S⁴, Petric M¹, Koopmans M¹², Boivin G².

Abstract

During spring-summer 2009, several observational studies from Canada showed increased risk of medically-attended, laboratory-confirmed A(H1N1)pdm09 illness among prior recipients of 2008-09 trivalent inactivated influenza vaccine (TIV). Explanatory hypotheses included direct and indirect vaccine effects. In a randomized placebo-controlled ferret study, we tested whether prior receipt of 2008-09 TIV may have directly influenced A(H1N1)pdm09 illness. Thirty-two ferrets (16/group) received 0.5 mL intra-muscular injections of the Canadian-manufactured, commercially-available, non-adjuvanted, split 2008-09 Fluviral or PBS placebo on days 0 and 28. On day 49 all animals were challenged (Ch0) with A(H1N1)pdm09. Four ferrets per group were randomly selected for sacrifice at day 5 post-challenge (Ch+5) and the rest followed until Ch+14. Sera were tested for antibody to vaccine antigens and A(H1N1)pdm09 by hemagglutination inhibition (HI), microneutralization (MN), nucleoprotein-based ELISA and HA1-based microarray assays. Clinical characteristics and nasal virus titers were recorded pre-challenge then post-challenge until sacrifice when lung virus titers, cytokines and inflammatory scores were determined. Baseline characteristics were similar between the two groups of influenza-naïve animals. Antibody rise to vaccine antigens was evident by ELISA and HA1-based microarray but not by HI or MN assays; virus challenge raised antibody to A(H1N1)pdm09 by all assays in both groups. Beginning at Ch+2, vaccinated animals experienced greater loss of appetite and weight than placebo animals, reaching the greatest between-group difference in weight loss relative to baseline at Ch+5 (7.4% vs. 5.2%; p=0.01). At Ch+5 vaccinated animals had higher lung virus titers (log-mean 4.96 vs. 4.23pfu/mL, respectively;
p=0.01), lung inflammatory scores (5.8 vs. 2.1, respectively; p=0.051) and cytokine levels (p>0.05). At Ch+14, both groups had recovered. Findings in influenza-naïve, systematically-infected ferrets may not replicate the human experience. While they cannot be considered conclusive to explain human observations, these ferret findings are consistent with direct, adverse effect of prior 2008-09 TIV receipt on A(H1N1)pdm09 illness. As such, they warrant further in-depth investigation and search for possible mechanistic explanations.

**Narcolepsy and H1N1 vaccination: a link?**

**Thebault S, Vincent A, Gringras P.**

**Abstract**

**PURPOSE OF REVIEW:**

A number of European countries have reported a dramatic increase in the rates of childhood narcolepsy with cataplexy in children immunized with a split-virion adjuvanted swine flu vaccine. Here, we review the strengths and weaknesses of these epidemiological studies and possible neuroimmunological mechanisms.

**RECENT FINDINGS:**

Initial concerns of a 13-fold increased relative risk of narcolepsy were raised by the Scandinavian health protection agencies in 2010. Subsequent retrospective studies support these findings in Canada, France, Ireland, England and Denmark. The cases are predominantly young children who present with severe and rapid onset of cataplexy as well as narcolepsy often within a few weeks of vaccination. The proposed mechanism for postvaccination narcolepsy is one in which an environmental trigger causes or enhances an antibody-mediated autoimmune response in patients with a preexisting genetic susceptibility. However, there have not yet been any reports of specific autoimmunity, either antibody or T-cell-mediated.

**SUMMARY:**

There is a strong association between narcolepsy and H1N1 vaccination. However, whether this reflects a true increase in affected individuals or a hastening of disease onset in individuals who would otherwise have developed narcolepsy later will become clear in the coming years. The pathological explanation of this association and narcolepsy is likely to be autoimmune, although supportive evidence is lacking. Video abstract available: See the Video Supplementary Digital Content 1 (http://links.lww.com/COPM/A9).

Neurologic adverse events following influenza A (H1N1) vaccinations in children.

Lee SJ, Kim YO, Woo YJ, Kim MK, Nam TS, Cho YK.

Source
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Abstract
BACKGROUND:
Since the monovalent pandemic influenza A (H1N1) vaccine was recommended worldwide in October 2009, there has been a shortage of pediatric clinical data for post-vaccine neurologic adverse events (NAE), including Guillain-Barré syndrome. We reviewed pediatric NAE data following H1N1 vaccinations and for patients with peripheral neuropathy, we followed their progress.

METHODS:
In our single-center study, we retrospectively reviewed 14 cases of children who visited the Division of Pediatric Neurology in the Department of Pediatrics of Chonnam National University Hospital due to NAE following monovalent influenza A (H1N1) vaccination between November 2009 and March 2010.

RESULTS:
Clinical diagnoses for major NAE included: polyneuropathy in the extremities (11/14, 78.6%), sensory mononeuropathy with numbness in the left fibula area (1/14, 7.1%), Bell's palsy (1/14, 7.1%) and recent-onset acute headache only (1/14, 7.1%). Therefore, most patients were diagnosed as having peripheral neuropathy (13/14, 92.9%), and two met the Brighton Collaboration Guillain-Barré syndrome definition criteria for level 3 (the lowest level of diagnostic certainty).

CONCLUSIONS:
Post-vaccine NAE were mainly motor weakness due to polyneuropathy, which had a good prognosis of complete improvement within a few months without sequelae.

Complex regional pain syndrome by vaccination: A case of complex regional pain syndrome after vaccination of influenza A(H1N1)

Bum Sun Kwan,1 Jin Woo Park,1 Ho Jun Lee,1 Ae Suk Kim2 and Gi Hyeong Ryu1

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Key words complex regional pain syndrome, influenza A(H1N1), vaccination.

Complex regional pain syndrome (CRPS), a clinical disease characterized by hyperalgesia or allodynia, edema, weakness, and vasomotor malfunction, can be divided into types 1 and 2, according to the inducing cause. The pathologic mechanism is not well known. It is mainly reported to occur after the patient has experienced an external wound and nerve injury, or spontaneously.

Many cases of CRPS in children and adolescents occur in girls, usually later in childhood.1,2 However, the inducing cause cannot be determined in at least 50% of cases.3 Reports of CRPS generated after a vaccination are rare; thus, the authors report on a case of CRPS generated in a 17-year-old girl following influenza A (H1N1) vaccination.


Comment [A11]: The girls had edema and a pain rating of 7/10 with peripheral nerve damage. She was prescribed several medications including corticosteroids and pain medication and after a year she was still suffering pain.
AS03 adjuvanted AH1N1 vaccine associated with an abrupt increase in the incidence of childhood narcolepsy in Finland.


Author information

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.

Erythema multiforme secondary to H1N1 vaccine.
Samad I, Chong VH, Lim SS.

To the Editor:

Since the development of the H1N1 pandemic vaccines, the World Health Organization (WHO) and Centers for Disease Control and Prevention (CDC) have recommended vaccination to reduce the impact of the current H1N1 influenza pandemic.1,2 These vaccines have been developed and tested within a short period and are now distributed for mass vaccination; however, full profiles of the vaccines' adverse effects are still largely unknown. We report a potentially serious adverse effect of one of the vaccines available.

http://sma.org/southern-medical-journal/article/erythema-multiforme-secondary-to-h1n1-vaccine/
Association between the 2008–09 Seasonal Influenza Vaccine and Pandemic H1N1 Illness during Spring–Summer 2009: Four Observational Studies from Canada

Danuta M. Skowronski, Gaston De Serres, Natasha S. Crowcroft, Naveed Z. Janjua, Nicole Boulainne, Travis S. Hottes, Laura C. Rosella, James A. Dickinson, Rodica Gilca, Pam Sethi, Najwa Ouhoummane, Donald J. Willison, Isabelle Rouleau,
[ ... ], for the Canadian SAVOIR Team

Abstract

Background

In late spring 2009, concern was raised in Canada that prior vaccination with the 2008–09 trivalent inactivated influenza vaccine (TIV) was associated with increased risk of pandemic influenza A (H1N1) (pH1N1) illness. Several epidemiologic investigations were conducted through the summer to assess this putative association.

Methods and Findings

Studies included: (1) test-negative case-control design based on Canada’s sentinel vaccine effectiveness monitoring system in British Columbia, Alberta, Ontario, and Quebec; (2) conventional case-control design using population controls in Quebec; (3) test-negative case-control design in Ontario; and (4) prospective household transmission (cohort) study in Quebec. Logistic regression was used to estimate odds ratios for TIV effect on community- or hospital-based laboratory-confirmed seasonal or pH1N1 influenza cases compared to controls with restriction, stratification, and adjustment for covariates including combinations of age, sex, comorbidity, timeliness of medical visit, prior physician visits, and/or health care worker (HCW) status. For the prospective study risk ratios were computed. Based on the sentinel study of 672 cases and 857 controls, 2008–09 TIV was associated with statistically significant protection
against seasonal influenza (odds ratio 0.44, 95% CI 0.33–0.59). In contrast, estimates from the sentinel and three other observational studies, involving a total of 1,226 laboratory-confirmed pH1N1 cases and 1,505 controls, indicated that prior receipt of 2008–09 TIV was associated with increased risk of medically attended pH1N1 illness during the spring–summer 2009, with estimated risk or odds ratios ranging from 1.4 to 2.5. Risk of pH1N1 hospitalization was not further increased among vaccinated people when comparing hospitalized to community cases.

Conclusions

Prior receipt of 2008–09 TIV was associated with increased risk of medically attended pH1N1 illness during the spring–summer 2009 in Canada. The occurrence of bias (selection, information) or confounding cannot be ruled out. Further experimental and epidemiological assessment is warranted. Possible biological mechanisms and immunoepidemiologic implications are considered.

http://www.plosmedicine.org/article/info%3Adoi%2F10.1371%2Fjournal.pmed.1000258
Determination of genotoxicity of classical swine fever vaccine in vitro by cytogenetic and comet tests.

Genghini R, Tiranti I, Bressán E, Zamorano-Ponce E, Fernández J, Dulout F.

Source
GENETICA, Facultad de Agronomía y Veterinaria, Universidad Nacional de Río Cuarto Argentina.

Abstract
Chromosome damage in lymphocyte cultures induced by live virus vaccine against classical swine fever (CSF) has been observed in previous studies. In vivo cytogenetic tests were made with several doses of vaccines used in Argentina to control the disease. These studies have shown that genotoxic effects increased with dose. In the present study, two different in vitro assays were performed by recording the frequency of cells with chromosome alterations and by assessing the ability of the vaccine to damage DNA, using the single cell gel microelectrophoretic assay (comet test). Frequencies of cells with chromosomal alterations increased significantly when compared with controls and were dose (microl/ml) dependent: 0 = 1.23, 5 = 2.29, 10 = 5.42 and 20 = 11.71%. In the comet assay the variables measured, tail length (TL) and tail moment (TM), also increased. For control cultures TL was 2.32 microm, whereas with concentrations of 20 and 100 microl/ml TL were 12.47 and 42.3 microm, respectively. TM of control cultures was 0.18, whereas with vaccine concentrations of 20 and 100 microl/ml TM were 5.52 and 24.52, respectively. Comet frequency distributions differed significantly among treatments. These results agree with previous in vivo observations.

Regarding CSF pathogeny, our results support a direct effect of CSF vaccinal virus on lymphocyte DNA. Genotoxicity of CSF vaccine was corroborated in vitro at the cytogenetic and molecular levels.

Hepatitis A

Natural Immunity

People who have hepatitis A infection become immune to HAV for the rest of their lives once they recover. They cannot get hepatitis A twice. The blood test for immunity to hepatitis A is called the "Hepatitis A Total Antibody test." People who have had hepatitis A and those who have received hepatitis A vaccine show positive antibodies to hepatitis A on this test for the rest of their life.

What are the Symptoms of Hepatitis A?

Children who become infected with hepatitis A before age 6 usually have no symptoms (70%) or mild illness, and if they do become ill, they usually get better in under 2 months. Adults and older children who become infected with hepatitis A can have no symptoms or very mild illness (30%), but most develop jaundice and other symptoms (70%). Mild illness can resolve in 1-2 weeks, but more severe illness can last for months. Common symptoms of HAV infection include:

- Jaundice
- Dark-colored urine, light-colored stools
- Fatigue
- Abdominal pain
- Loss of appetite
- Nausea
- Diarrhea
- Fever

The blood test for hepatitis A infection is called the "Hepatitis A IgM Antibody test." People who have hepatitis A infection right now will show positive IgM antibodies on this test. While most people heal completely from hepatitis A infection, a small number, usually those with pre-existing liver disease, suffer major liver damage which can result in death (0.3-1.3%).

http://www.sfcdc.org/hepatitisa.html
Pancreatitis following hepatitis A vaccination.

Haviv YS¹, Sharkia M, Galun E, Safadi R.

Author information

Abstract

We describe a 23-year-old male patient who presented with epigastric abdominal pain, 8 days following vaccination with inactivated hepatitis A virus (Haverix(R)). Clinical and laboratory data confirmed the diagnosis of pancreatitis. Repeat polymerase chain reaction (PCR) for hepatitis A replication was negative. A comprehensive evaluation ruled out other etiologies for pancreatitis. IgM Hepatitis A antibodies did not develop even after 3 months. Pancreatitis following Hepatitis A is a well-known complication of the viremia, but the exact mechanism is controversial. We suggest that the pancreatitis may have been a cellular immunological reaction to one of the antigens of hepatitis A virus vaccine, or it might have been caused by the release of mediators of anaphylaxis such as histamine and leukotriens, induced by HAV antigens, resulting in pancreatitis without development of humoral immunization.

Erythema multiforme (EM) is an acute, self-limited, sometimes recurring mucocutaneous condition characterized by distinctive target lesions, and it has been associated with infections, accounting for up to 90% of cases, as well as with drugs, and other triggers. Most cases of EM occur in children, adolescents, and young adults, but rarely occur in neonates and infants. Here, we report three infants in whom EM developed following hepatitis B vaccination.


[Acute encephalopathy induced by vaccination in an infant with methylmalonic aciduria cblA].

[Article in Chinese]


Author information

Abstract

OBJECTIVE:
We report the first case of acute encephalopathy induced by vaccination in an infant with methylmalonic aciduria cblA in China.

METHOD:
The clinical presentation, blood acylcarnitines analysis, urine organic acids analysis and gene studies of the patient were summarized.

RESULT:
The proband, a boy, was admitted at the age of 15 months because of recurrent vomiting, acidosis and development delay for 8 months. The previously healthy boy presented vomiting and coma just one hour after hepatitis B vaccination at the age of seven months. Moderate dehydration, electrolyte disturbance and metabolic acidosis had been found. Although his acute metabolic crisis had been corrected soon after intravenous transfusion, psychomotor retardation and recurrent vomiting had been observed. When he was 15 months old, vomiting and lethargy occurred again 3 hours after DTaP vaccination. He was weakened as the illness became worse and got coma with dyspnea 7 days later. He was hospitalized with the suspected diagnosis of viral encephalitis. Blood acylcarnitines analysis, urine organic acids analysis and gene study had been performed for the etiologic investigation. His blood propionylcarnitine (16.3 µmol/L vs. normal range 1.0-5.0 µmol/L) and propionylcarnitine/free carnitine ratio (0.27 vs. normal range 0.03 to 0.25) increased. Markedly elevated urinary methylmalonic acid (388.21 mmol/mol creatinine vs. normal range 0.2 to 3.6 mmol/mol creatinine) and normal plasma total homocysteine supported the diagnosis of isolated methylmalonic aciduria. Two mutations, c.650 T>A (p.L217X) and c.742 C>T (p.Q248X), were identified in his MMAA gene, confirmed the diagnosis of cblA. Each parent carried one of the two mutations. Progressive clinical and biochemical improvement has been observed after hydroxylcobalamin injection, protein-restricted diet with the supplements of special formula and L-carnitine. He is currently 2 years and 7 months old with normal development and general condition.
CONCLUSION:
A boy with cblA was firstly detected after the acute encephalopathy induced by vaccination in China. It is important to pay more attention to the patients with metabolic crisis or organ damage after vaccination. Metabolic studies are keys to the diagnosis of potential diseases and improve the outcome.

Immunization with hepatitis B vaccine accelerates SLE-like disease in a murine model.

Agmon-Levin N\textsuperscript{1}, Arango MT\textsuperscript{2}, Kivity S\textsuperscript{3}, Katzav A\textsuperscript{4}, Gilburd B\textsuperscript{5}, Blank M\textsuperscript{5}, Tomer N\textsuperscript{5}, Volkov A\textsuperscript{6}, Barshack I\textsuperscript{6}, Chapman J\textsuperscript{4}, Shoenfeld Y\textsuperscript{7}.

Author information

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.

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KEYWORDS:
Autoimmune/autoinflammatory syndrome induced by adjuvant (ASIA); Autoimmunity; Hepatitis B vaccine; Neuro-cognitive tests; SLE; Vaccination

Necrolytic acral erythema following hepatitis B vaccination.

Pernet C¹, Guillot B, Araka O, Dereure O, Bessis D.

First described in 1996, necrolytic acral erythema (NAE) is a rare entity characterized by well-demarcated hyperkeratotic scaly plaques involving predominantly acral sites.¹ NAE is almost exclusively associated with hepatitis C virus (HCV) infection, and is often considered an early cutaneous marker of this infection.² Nevertheless, a few cases of NAE have been reported in the absence of HCV infection.³ We report the first case of NAE following hepatitis B virus (HBV) vaccination in a patient without associated HCV infection.

A 50-year-old man from Cameroon presented with scaly lichenified acral lesions. The skin lesions had developed 6 months earlier, a week after the first injection of HBV vaccine (Engerix-B®; GlaxoSmithKline, Brentford, U.K.), and had worsened after the second and third injections administered 1 and 6 months later. Past medical history was unremarkable. Clinical examination revealed well-defined hyperpigmented hyperkeratotic scaly plaques on the fingers, toes (Fig. 1a) and Achilles tendons; keratotic papules on the outer sides of the lower legs; and crusty cheilitis of the lower lip, with warty lesions of the eyelids and around the nostrils (Fig. 1b). Four skin biopsies all showed hyperplasia and acanthosis of the epidermis with parakeratotic hyperkeratosis and hypogranulosis, with focal necrosis of keratinocytes within a very superficial epidermis (Fig. 2). Blood investigations, including complete blood count; liver function tests; serum levels of glucose, albumin, glucagon and zinc; and essential fatty acid chromatography, were normal. Hepatitis C antibody was negative. HBV serology revealed a high level of HBs antibodies (> 1000 mUI mL⁻¹) related to vaccination, and the presence of HBc antibodies from a healed HBV infection unknown to the patient. HBs antigen and HB viral DNA investigations were negative. An abdominal computed tomography scan showed no evidence of pancreatic or hepatic tumour. Oral zinc therapy was proposed but refused by the patient. The lesions spontaneously and gradually improved after the last injection of the vaccine, with complete healing at 6 months.

Necrolytic acral erythema is a particular form of necrolytic erythema characterized by predominantly acral distribution, predilection for the dorsa of the feet and toes, lack of periorificial involvement and strong association with HCV infection.² In our observation, facial periorificial (orbital, nasal and labial) involvement, which is a classical feature of necrolytic migratory erythema (NME), is described here for the first time in NAE, supporting the hypothesis that NAE is part of the spectrum of NME.⁴ NAE without HCV infection has been reported in
rare cases but other nonviral aetiologies could not be ruled out as, for example, glucagon and serum-free fatty acid levels were not measured.[3]
In our observation, the active role of the hepatitis B vaccine was suggested by the delay in onset of NAE after the first injection of vaccine, worsening of symptoms after the following injections, and progressive regression after the last injection. We hypothesize that transient circulation of HBs antigen induced by the hepatitis B vaccine may have caused the NAE, as firstly, transient HBV surface antigen circulation has been observed after vaccination against HBV; and secondly, a previous case of NAE associated with HBV infection has been reported.

Hepatitis B vaccination and associated oral manifestations: a non-systematic review of literature and case reports.
Tarakji B¹, Ashok N¹, Alakeel R², Azzeghaibi S¹, Umair A¹, Darwish S¹, Mahmoud R³, Elkhatat E⁴.

Author information

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, vasculitis optic neuritis, anaphylaxis, systemic lupus erythematosus, 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.

KEYWORDS:
Complications; Hepatitis B vaccine; Oral; Vaccination

Prevalence of systemic lupus erythematosus and risk factors in rural areas of Anhui Province.


Author information

Abstract

Systemic lupus erythematosus (SLE) is a severe complex rheumatic disease, but good estimate of its prevalence and risk factors is lacking in China. The aim of the study was to explore the prevalence of SLE and risk factors in rural areas of Anhui Province of China. Eleven counties were randomly selected in Anhui Province, and then, 15% of the villages in selected counties were randomly sampled as study sites. Patients with SLE were identified through two phases. Based on the cases identified, a population-based case-control study was designed to examine risk factors associated with SLE. A total of 1,253,832 individuals and identified 471 SLE cases were surveyed. Crude and age-standardized prevalence were estimated at 37.56 and 36.03 per 100,000 persons, respectively. Gender difference in the prevalence of SLE was significant (P = 4.62 × 10(-76)), and the age-standardized prevalence was 6.17 for males and 67.78 for females per 100,000 persons. The distribution of SLE prevalence was significant by age group (P = 1.78 × 10(-53)), and the peak prevalence was observed at 40-50 years.

Multiple environmental factors were associated with SLE, including birth conditions, sweet food, cooking oil, taste, fruit consumption, sunlight exposure, quality of sleep, physical activities, drinking water, residence, negative life events, hepatitis B vaccine, age of menarche, and age at birth of first child (P < 0.05). Our large population-based epidemiological survey estimated the prevalence of SLE at 37.56 per 100,000 persons. Multiple environmental factors were associated with the development of SLE.

Connective tissue disease following hepatitis B vaccination.

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The authors declare no conflict of interest.

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Hepatitis B vaccination became available in 1980, and in the following years, subjects at high risk of hepatitis B virus (HBV) infection have been vaccinated. Hepatitis B virus vaccine has been produced with DNA-recombinant technology, and it contains as adjuvant aluminum and, as preservative, thimerosal. In recent years, several cases of autoimmune disorders related to HBV vaccination have been reported in the literature.\textsuperscript{1–4} The majority of these reports deal with rheumatologic complications, such as rheumatoid arthritis, arthralgias, and myalgias.\textsuperscript{5–7} However, neuropsychiatric disorders represent the most frequent HBV vaccine–related complications in some series.\textsuperscript{8} Hereby, we report a complex case of connective tissue disease developed following HBV vaccination.

**CASE REPORT**

A 43-year-old woman—without any familial or personal history of autoimmune disorders—got the first and second doses of HBV vaccine in March and April 2011. A few days following the last dose, she started to complain of paresthesias at the left arm and hand, as well as arthralgias in the upper extremities. A localized area of alopecia in the scalp appeared in November 2011, whereas a severe episode of arthritis localized at the hands with mild pitting edema of the fingers was diagnosed in January 2012. At this time, the patient also presented with progressive asthenia, as well as with an itchy pretibial rash. Biochemistry revealed positivity for antinuclear antibodies (1:1320), whereas anti-dsDNA, ENA profile, anticitrullin, antiphospholipid, and rheumatoid factor were all negative, and also a complete blood count and C-reactive protein were within reference ranges. Chest x-ray and radiological study of the hands did not reveal any alterations. Electromyography revealed a sensory-type peripheral neuropathy of the median nerve of the left arm. Based on these findings, a diagnosis of undifferentiated connective tissue disease (UCTD) related to HBV vaccination was made in March 2012, and therapy with prednisone (25 mg/d) and hydroxychloroquine (200 mg/d) was initiated. A prompt remission of
all the neurological, dermatologic, and rheumatologic symptoms/signs occurred. Two months following the initiation of therapy, the antinuclear antibody became negative. Prednisone therapy has been discontinued, while the patient remains on hydroxychloroquine.

**DISCUSSION**

We have presented a complex case of connective tissue disease that appeared a short time after HBV vaccination. Such case was appropriately diagnosed as UCTD, because the symptoms failed to satisfy the 1997 American College of Rheumatology (ACR) criteria required for the diagnosis of systemic lupus erythematosus (SLE) at that time.9 Although some symptoms presented by our patient—that is, alopecia, neuropathy, and asthenia—were compatible with SLE, they failed to fulfill the 1997 ACR SLE-classifying criteria.9 Indeed, only arthritis and antinuclear antibody positivity were among the ACR SLE-classifying criteria. On the other hand, if we retrospectively reclassify our patient according to a recent revision of the ACR that was available only after our case diagnosis,10 the postvaccination symptoms would fulfill the criteria required for SLE diagnosis, because nonscarring alopecia and neuropathy have been upgraded as SLE-specific criteria.10 This was not unexpected, because the new criteria have been shown to be more sensitive, but less specific, in the validation process. Because no new SLE symptom/sign appeared in the 18 months of follow-up, some uncertainty between UCTD and SLE remains.

Vaccine safety is a critical problem when dealing with population campaigns of vaccination, and the issue of adverse events, especially autoimmune disorders, has become relevant in the medical literature. In a systematic review of the literature, several autoimmune diseases have been described following HBV vaccination, such as demyelinating syndromes—including multiple sclerosis, rheumatoid arthritis, SLE, autoimmune glomerular nephritis, panarteritis nodosa, type I diabetes, Graves disease, lichen planus, and Guillain-Barré syndrome.11–13 Similarly, connective diseases, as well as vasculitis, have also been described following influenza vaccination.14,15

Recently, a syndrome named as “ASIA” (autoimmune syndrome induced by adjuvants) has been proposed. The symptoms of this syndrome have been reported to appear after exposure to silicone, tetramethylpentadecane, pristaine, aluminum, and other adjuvants.8,16 The classification criteria of the syndrome include exposure to external stimuli (vaccines, silicone adjuvant) and the subsequent onset of clinical manifestations (myalgias, arthralgias, chronic fatigue, neurological manifestations, cognitive deficits, fever, dry mouth). Our patient appeared to be within the ASIA classification criteria. Of note, HBV vaccine contains aluminum adjuvant, and clinical symptoms appeared after about 1 month after first dose.
Observational study of vaccine efficacy 24 years after the start of hepatitis B vaccination in two Gambian villages: no need for a booster dose.


Source

Medical Research Council Laboratories, The Gambia, Banjul, the Gambia, West Africa. mendym@iarc.fr

Abstract

OBJECTIVES:

To determine the duration of protection from hepatitis B vaccine given in infancy and early childhood and assess risk factors for HBV infection and chronic infection.

METHODS:

In 1984 infant HBV vaccination was started in two Gambian villages. Cross sectional serological surveys have been undertaken every 4 years to determine vaccine efficacy. In the current survey 84.6% of 1508 eligible participants aged 1-28 years were tested. A spouse study was conducted in females (aged 14 years and above) and their male partners.

RESULTS:

Vaccine efficacy against chronic infection with hepatitis B virus was 95.1% (95% confidence interval 91.5% to 97.1%), which did not vary significantly between age groups or village. Efficacy against infection was 85.4% (82.7% to 87.7%), falling significantly with age. Concentrations of hepatitis B antibody fell exponentially with age varying according to peak response: 20 years after vaccination only 17.8% (95% CI 10.1-25.6) of persons with a low peak response (10-99 mIU/ml) had detectable HBs antibody compared to 27% (21.9% to 32.2%) of those with a high peak response (>999 mIU/ml). Time since vaccination and a low peak response were the strongest risk factors for HBV infections; males were more susceptible, marriage was not a significant risk for females. Hepatitis B DNA was not detected after infection, which tested solely core antibody positive. An undetectable peak antibody response of <10 mIU/ml and a mother who was hepatitis B e antigen positive were powerful risk factors for chronic infection.

CONCLUSIONS:

Adolescents and young adults vaccinated in infancy are at increased risk of hepatitis B infection, but not chronic infection. Married women were not at increased risk. There is no compelling evidence for the use of a booster dose of HBV vaccine in The Gambia.

Autoimmunity following hepatitis B vaccine as part of the spectrum of ‘Autoimmune (Auto-inflammatory) Syndrome induced by Adjuvants’ (ASIA): analysis of 93 cases.

Zafir Y, Agmon-Levin N, Paz Z, Shilton T, Shoenfeld Y.

Author information

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.

Neonatal erythema multiforme: a case report.
Cho YJ1, Huh SY, Hong JS, Jung JY, Suh DH.

Abstract
Erythema multiforme (EM) is an extremely rare condition in infancy. To the best of our knowledge, there have been only three cases of neonatal EM described in the literature, and no such cases have been reported in Korea. A preterm neonate born at 35 weeks and six days of gestation presented with multiple annular erythematous patches with a targetoid shape over his entire body at 36 days of age (corrected age of 7 days). He had no systemic symptoms except for transient mild fever. No triggering factor except for hepatitis B and BCG vaccination was found. Neutropenia was noted upon laboratory analysis. Skin biopsy specimens showed findings suggestive of erythema multiforme. The skin lesions improved rapidly upon administration of intravenous methylprednisolone; however, neutropenia continued for a much longer period. The significance of neutropenia with respect to the development of EM was not clarified. There has been no recurrence of skin lesions over a one-year follow-up period.


Gallagher CM, Goodman MS.

Source
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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.

Ten cases of systemic lupus erythematosus related to hepatitis B vaccine.


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.

Severe thrombocytopenia after hepatitis B vaccine in an infant from Turkey.

Polat A', Akca H, Dagdeviren E.

Author information

Abstract

Recombinant hepatitis B vaccine has been used widely in the world since 1991. The side effects of hepatitis B vaccine are seen rarely. In this paper, we present clinical and laboratory progress of an infant who gets severe thrombocytopenia after the second dosage hepatitis B vaccine. Our case is different from other cases because our patient is very young, the number of platelet is the lowest in the literature, and intravenous immunoglobulin (IVIG) are used in the treatment. Although it is a severe thrombocytopenia, the patient has recovered without any bleeding.

Case report

Severe necrotizing pancreatitis following combined hepatitis A and B vaccination

Eran Shlomovitz, Ward Davies, Ewa Cairns, William C. Brintnell, Mark Goldszmidt, and George K. Dresser

Abstract

The causes of acute pancreatitis are well documented, with alcohol and gallstones among the most common. Viruses such as mumps, Coxsackie B, measles, Epstein–Barr and hepatitis A, B and E can also cause acute pancreatitis. Furthermore, the pancreas is a target organ for the hepatitis B virus. An autoimmune trigger may be the cause of some cases of pancreatitis; however, accurately diagnosing autoimmune pancreatitis can be challenging because of its variable characteristics and clinical presentations. Vaccine-induced pancreatitis may be a subset of this immunologically driven phenomenon, as is suggested by several reports of pancreatitis following vaccination against hepatitis A and other viruses. Necrotizing pancreatitis accounts for 5% of all cases of acute pancreatitis and is far more severe than the more common interstitial pancreatitis. Necrotizing pancreatitis can be distinguished by extensive necrosis of peripancreatic fat in the omentum and retroperitoneum. We report a case of necrotizing pancreatitis that occurred after combined hepatitis A and B vaccination.
Multiple sclerosis and hepatitis B vaccination: Could minute contamination of the vaccine by partial Hepatitis B virus polymerase play a role through molecular mimicry?

E. Faure

Summary
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.

Vaccination-induced cutaneous pseudolymphoma.


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.

Autoimmune hazards of hepatitis B vaccine.

Girard M.

Author information

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.


Comment [AJ13]: Very good read, explores corruption of pharmaceutical industry and the selective publication of studies.
Guillain-Barré syndrome following hepatitis B vaccination.
Khamaisi M1, Shoenfeld Y, Orbach H.

Abstract
A 52-year-old woman developed Guillain-Barré syndrome 10 weeks after immunization with recombinant hepatitis B vaccine. Common infectious causes of GBS were ruled out. The temporal relationship between GBS and hepatitis B virus (HBV) vaccination was suggestive of a vaccine-induced cause. The possible mechanisms of this very, rare complication are discussed.


Hernán MA*, Jick SS, Olek MJ, Jick H

Author information

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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.

Two case reports of cutaneous adverse reactions following hepatitis B vaccine: lichen planus and granuloma annulare.

Criado PR\(^1\), de Oliveira Ramos R, Vasconcellos C, Jardim Criado RF, Valente NY.

**Author information**

**Abstract**

We report two cases of adverse cutaneous reactions following hepatitis B vaccination. The first case occurred 3 weeks after the first dose of hepatitis B vaccine in a 16-year-old white girl with the onset of lichen planus lesions on her thighs and abdomen. After the second dose a disseminated lichen planus developed within 2 weeks. The second case concerns the development of papular and patch granuloma annulare in a 58-year-old white woman 2 months after the second dose of hepatitis B vaccine. To the best of our knowledge, only a few paediatric and adult cases of lichen planus as a complication of hepatitis B vaccination have been reported in medical literature so far. This is the second case of granuloma annulare following hepatitis B vaccine. Our report, similar to earlier papers, appears to support the onset of lichen planus and granuloma annulare as a possible rare complication of hepatitis B immunization.

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Duration of hepatitis B immunity in low risk children receiving hepatitis B vaccinations from birth.

Petersen KM1, Bulkow LR, McMahon BJ, Zanis C, Getty M, Peters H, Parkinson AJ.

Author information

1 Arctic Investigations Program, National Center for Infectious Diseases, Centers for Disease Control and Prevention, Alaska Native Tribal Health Consortium, Anchorage, AK 99508, USA.

Abstract

BACKGROUND:

The duration of protection after hepatitis B vaccination of infants is unknown.

METHODS:

We determined antibody to hepatitis B surface antigen (anti-HBs) at 4-13 years of age in 363 low risk children who had been vaccinated starting at birth with hepatitis B vaccine. Those with nonprotective titers (<10 mIU/mL) received a booster dose. We similarly followed 16 children of hepatitis B surface antigen (HBsAg)-positive mothers.

RESULTS:

Of low risk infants receiving a plasma-derived vaccine, 41% (42 of 102) of those whose primary response was unknown and 24% (4 of 17) who had initially responded retained protective titers (> or = 10 mIU/mL) of anti-HBs at 9 and 13 years, respectively. Of those who did not have protective antibody titers, 61% (33 of 54) and 67% (8 of 12), respectively, responded to a booster dose. In children of HBsAg-positive mothers, 31% retained protective anti-HBs at 12 years, and 90% (9 of 10) with nonprotective titers responded to a booster. In low risk children initially receiving a recombinant vaccine, 12.5% (26 of 208) and none (0 of 36) retained protective anti-HBs titers at 5 and 7 years of age, respectively. Of those who did not have protective titers, 90% (120 of 134) and 91% (32 of 35), respectively, responded to a booster.

CONCLUSIONS:

Anti-HBs disappeared by 5 years of age in most children who were vaccinated with hepatitis B vaccine from birth. Although most children showed immunologic memory, one-third failed to demonstrate an anamnestic response to a booster dose. Additional long term studies of low risk infants are needed to determine duration of protection and the necessity for or timing of booster doses.


Comment [A15]: Challenges need to vaccinate low risk children at birth as their ‘immunity’ wanes quickly, meaning they need a booster dose against an illness they have little chance of catching.
Hepatitis B vaccination and adult associated gastrointestinal reactions: a follow-up analysis.

Geier DA¹, Geier MR.

Author information

Abstract

BACKGROUND/AIMS:
Hepatitis B is the most important infectious cause of acute and chronic liver disease. Hepatitis B vaccine, a highly purified, genetically engineered, single antigen vaccine, has generally been accepted as a safe vaccine. In 2000, the Institute of Medicine noted that few vaccines for any disease have been actively monitored for adverse effects over long periods and encouraged evaluation of active long-term monitoring studies of large populations to further evaluate the relative safety of vaccines. The aim of this study was to accept the charge of the 2000 Institute of Medicine Report and extend our own work to determine the frequency of gastrointestinal adverse reactions after hepatitis B vaccination and determine if this frequency was increased over the background rate of gastrointestinal conditions in the U.S. adult population.

METHODOLOGY:
A retrospective examination of the Vaccine Adverse Events Reporting System (VAERS) database from July 1990 through August 1999 for hepatitis B vaccination and associated gastrointestinal reactions was made. Additionally, as controls, hepatitis A and rubella vaccination associated gastrointestinal adverse reactions reported to the Vaccine Adverse Events Reporting System in adults were analyzed.

RESULTS:
Our analysis shows that the 40-year-old female population between four to eight days after hepatitis B vaccination was at increased risk for developing gastrointestinal reactions.

CONCLUSIONS:
Hepatitis B vaccination was statistically associated by chi 2 analysis with gastrointestinal reactions including: hepatitis, gastrointestinal disease and liver function test abnormalities in comparison to our vaccine control groups. The reaction rate observed is outweighed by the benefits of the vaccine. Further analysis is needed to determine the mechanisms by which hepatitis B vaccine is associated with gastrointestinal reactions.

http://www.ncbi.nlm.nih.gov/pubmed/?term=Hepatitis+B+vaccination+and+adult+associated+gastrointestinal+reactions%3A+a+follow-up+analysis
Lichen planus occurring after hepatitis B vaccination: a new case.
Al-Khenaizan S1.

Author information
Abstract
Lichen planus is a pruritic inflammatory dermatosis of unknown origin. An increased prevalence of a wide range of liver disease in lichen planus has been observed by many authors. Most recently, many reports appeared of the occurrence of lichen planus after administration of different types of hepatitis B vaccines. We report one case and briefly review this intriguing observation.

Large artery vasculitis following recombinant hepatitis B vaccination: 2 cases.

Zaas A1, Scheel P, Venbrux A, Hellmann DB.

Author information

Abstract

We describe 2 women who developed large artery vasculitis shortly after receiving recombinant hepatitis B vaccination. One patient developed Takayasu's arteritis, the other a vasculitis involving subclavian and renal arteries. Both developed renal failure. Whether the vasculitis was caused by the vaccination is not known. Although small vessel vasculitis following hepatitis B vaccination has been reported a number of times, large vessel vasculitis associated with hepatitis B vaccination has been reported only once. These cases suggest that large artery vasculitis should be added to the list of possible side effects of hepatitis B vaccination.

Adverse events associated with hepatitis B vaccine in U.S. children less than six years of age, 1993 and 1994.

Fisher MA¹, Eklund SA, James SA, Lin X.

Author information

¹Department of Community Medicine, School of Medicine, West Virginia University, Morgantown, USA.

Abstract

PURPOSE:
This study evaluated infrequent adverse reactions to hepatitis B vaccine by investigating the association of this vaccine with adverse health outcomes for U.S. children less than six years of age. The evaluation of the association between hepatitis B vaccine and chronic arthritis provides needed data, relevant to the Institute of Medicine's Report that there are inadequate data available to assess the causal relationship of hepatitis B vaccine to arthritis risk.

METHODS:
The 1993 (n = 5505 children) and 1994 (n = 6515 children) National Health Interview Survey (NHIS) datasets were analyzed to provide post-marketing surveillance data from probability samples of the U.S. population. Incident cases of adverse events were determined from the temporal association between the hepatitis B vaccination and the adverse events. Logistic regression modeling was used to adjust for potential confounding.

RESULTS:
Controlling for age, race, and gender simultaneously in the 1994 NHIS, hepatitis B vaccine was found to be associated with prevalent arthritis (odds ratio [OR] = 5.91, 95% confidence interval [CI] = 1.05–33.14), incident acute ear infections (OR = 1.60, 95% CI = 1.00–2.58), and incident pharyngitis/nasopharyngitis (OR = 1.41, 95% CI = 0.95–2.09).

CONCLUSIONS:
Evidence from this study suggests that hepatitis B vaccine is positively associated with adverse health outcomes in the general population of US children.


Comment [A17]: The purpose of this study was to evaluate HB vaccination and associated adverse health outcomes, as reported by a representative sample of the U.S. population of children under 6 years of age. This study addresses the lack of long-term follow-up after HB vaccination, and the unknown external validity of results from high risk populations in clinical trials. This epidemiologic approach also addresses the issue of rare adverse reactions (included in IOM report or a minimum of 20 incident cases) which are not found in clinical trials.

Comment [A18]: The risk of chronic arthritis was 6.20 (1.08–35.46) times greater among those children 0–5 years of age who received the HB vaccine than among those children without HB vaccination. The risk of incident cases of acute ear infections was 1.58 (0.98–2.56) times greater among those children who were HB vaccinated than among those children who did not receive the HB vaccine. The risk of incident cases of acute ear infections was 2.56 (1.34–4.45) times greater among those children 0–5 years of age who received the HB vaccine than among those children without HB vaccination.

Comment [A19]: The risk of chronic arthritis was 6.20 (1.08–35.46) times greater among those children 0–5 years of age who received the HB vaccine than among those children without HB vaccination. The risk of incident cases of acute ear infections was 1.58 (0.98–2.56) times greater among those children 0–5 years of age who received the HB vaccine than among those children who did not receive the HB vaccine. The risk of incident cases of acute ear infections was 3.02 (1.67–5.50) times greater among those children who were HB vaccinated than among those children who did not receive the HB vaccine.

Comment [A20]: The risk of incident cases of pharyngitis/nasopharyngitis was 1.19 (0.65–1.67) times greater among those children 0–5 years of age who received the HB vaccine than among those children without HB vaccination.

Comment [A21]: The IOM report also concluded that the data established a causal relation for the association of HB vaccine with anaphylaxis. Other investigators state...
Lichen planus after HBV vaccination in a child: a case report from Nepal.

Agrawal S¹, Garg VK, Joshi A, Agarwalla A, Sah SP.

Author information

Abstract

Vaccination against hepatitis B virus has rarely been associated with lichen planus. We report a case of this kind in a child from Nepal. A 12-year-old boy had developed generalized itchy violaceous papules and plaques six weeks after the second dose of hepatitis B virus vaccine. Serum HBsAg and HBeAb were negative, but HBsAb was positive. New crops of generalized, similar eruptions developed after the booster dose of vaccine. All the lesions resolved within three months of systemic steroid therapy. There was no recurrence after one year of follow up. Awareness of such an association is necessary, especially in children, because vaccination campaigns are increasing.

BACKGROUND: Central nervous system (CNS) demyelinating episodes have been described following numerous vaccines but there is no definite conclusion about a causal relationship. Recently, in France, in the context of an Expanded Program on Immunization, several cases of CNS demyelination have been observed following injection of recombinant hepatitis B (HB) vaccine, leading to great concern.

METHODS: We performed a hospital-based case-control study of 121 patients with a first episode of CNS demyelination occurring between July 1993 and December 1995 and 121 age and sex matched controls seen in the same period. Data on vaccinations history of cases and controls were collected by a postal questionnaire and confirmed by a phone interview.

RESULTS: Adjusted odds ratio (OR) obtained from conditional logistic regression between a first episode of CNS demyelination and any vaccination were equal to 1.4 (95 p. 100 CI 0.5-4.3) for an exposure within the 60 previous days and 2.1 (95 p. 100 CI 0.7-6.0) for an exposure within the 61-180 previous days. Similar results were found for HB vaccine exposure within the 60 previous days (adjusted OR=1.7, 95 p. 100 CI 0.5-6.3) or within the 61 to 180 previous days (adjusted OR= 1.5, 95 p. 100 CI 0.5-5.3).

CONCLUSION: These findings did not permit to exclude confidently an association between HB vaccine and the occurrence of a first CNS demyelinating episode.

http://www.ncbi.nlm.nih.gov/pubmed/?term=The+first+episode+of+central+nervous+system+demyelinization+and+hepatitis+B+virus+vaccination
Suspected hepatitis B vaccination related vasculitis.

Le Hello C', Cohen P, Bousser MG, Letellier P, Guillevin L.

Author information

Abstract

Recombinant hepatitis B vaccination is widely used and severe side effects are rare. We describe 3 cases of vasculitis occurring after such immunization that are thought to have been vaccine induced. Vasculitides are now recognized as possible severe adverse side effects of immunization.


Thrombocytopenic purpura as adverse reaction to recombinant hepatitis B vaccine.

Ronchi F¹, Cecchi P, Falcioni F, Marsciani A, Minak G, Muratori G, Tazzari PL, Beverini S.

Author information

Abstract

Three cases of immune thrombocytopenic purpura after the first dose of recombinant hepatitis B vaccine occurred in infants under 6 months of age. Other possible causes of this condition were excluded. Antiplatelet antibodies were present. A defect in platelet production was excluded in two children. Corticosteroid treatment was effective. Subsequent administration of other vaccines (against polio, diphtheria, and tetanus) did not cause relapse of thrombocytopenia.

Immune thrombocytopenic purpura after recombinant hepatitis B vaccine: retrospective study of seven cases.

Neau D¹, Bonnet F, Michaud M, Perel Y, Longy-Boursier M, Ragnaud JM, Guillard JM.

Abstract
Recombinant hepatitis B vaccine is usually well tolerated. Clinical and laboratory test manifestations with immunologic mechanisms have nonetheless been described following use of this vaccine. We retrospectively report 7 cases of thrombocytopenia occurring within 3 months (7 weeks on the average) of 1 or following injections of recombinant hepatitis B vaccine. Four boys and 3 girls, average age 12 y, were involved. Three had a history of immune thrombocytopenic purpura. Four had haemorrhagic manifestations. The haemogram showed thrombocytopenia (24 x 10⁹/L on the average) without alterations of the other lines. Infectious and immune aetiologies were excluded in all cases. The course varied after treatment by corticosteroids, high-dose intravenous immunoglobulin, or both. After describing the different manifestations subsequent to recombinant hepatitis B vaccination, we discuss post-vaccinal thrombocytopenias (vaccines in question, mechanisms) and the reality of this entity.

**Haemophilus influenzae type B (HiB)**

Around 500 cases annually in Australia prior to vaccination with 10-15 deaths. Post vaccination there are 20 cases annually.


**Risk Factors**

**Host and environmental factors associated with Hib in England, 1998–2002**

J McVernon, N Andrews, M Slack, R Moxon, M Ramsay

Results: Increased disease risk was noted among children with frequent antibiotic use (adjusted OR (AOR) (trend) 1.51 (95% CI 1.06 to 2.13); p = 0.02) and from sole-parent households (AOR 2.56 (95% CI 1.24 to 5.29); p = 0.01)

Clinical and Molecular Epidemiology of Haemophilus influenzae Causing Invasive Disease in Adult Patients.


Abstract

OBJECTIVES:
The epidemiology of invasive Haemophilus influenzae (Hi) has changed since the introduction of the Hi type b (Hib) vaccine. The aim of this study was to analyze the clinical and molecular epidemiology of Hi invasive disease in adults.

METHODS:
Clinical data of the 82 patients with Hi invasive infections were analyzed. Antimicrobial susceptibility, serotyping, and genotyping were studied (2008-2013).

RESULTS:
Men accounted for 63.4% of patients (whose mean age was 64.3 years). The most frequent comorbidities were immunosuppressive therapy (34.1%), malignancy (31.7%), diabetes, and COPD (both 22%). The 30-day mortality rate was 20.7%. The majority of the strains (84.3%) were nontypeable (NTHi) and serotype f was the most prevalent serotype in the capsulated strains. The highest antimicrobial resistance was for cotrimoxazole (27.1%) and ampicillin (14.3%). Twenty-three isolates (32.9%) had amino acid changes in the PBP3 involved in resistance. Capsulated strains were clonal and belonged to clonal complexes 6 (serotype b), 124 (serotype f), and 18 (serotype e), whereas NTHi were genetically diverse.

CONCLUSIONS:
Invasive Hi disease occurred mainly in elderly and those with underlying conditions, and it was associated with a high mortality rate. NTHi were the most common cause of invasive disease and showed high genetic diversity.


Ladhani S, Slack MP, Heath PT, von Gottberg A, Chandra M, Ramsay ME; European Union Invasive Bacterial Infection Surveillance participants.

Collaborators (64)

Author information

Abstract

An international collaboration was established in 1996 to monitor the impact of routine Haemophilus influenzae type b (Hib) vaccination on invasive H. influenzae disease; 14 countries routinely serotype all clinical isolates. Of the 10,081 invasive H. influenzae infections reported during 1996-2006, 4,466 (44%, incidence 0.28 infections/100,000 population) were due to noncapsulated H. influenzae (ncHi); 2,836 (28%, 0.15/100,000), to Hib; and 690 (7%, 0.036/100,000), to non-b encapsulated H. influenzae. Invasive ncHi infections occurred in older persons more often than Hib (median age 58 years vs. 5 years, p<0.0001) and were associated with higher case-fatality ratios (12% vs. 4%, p<0.0001), particularly in infants (17% vs. 3%, p<0.0001). Among non-b encapsulated H. influenzae, types f (72%) and e (21%) were responsible for almost all cases; the overall case-fatality rate was 9%. Thus, the incidence of invasive non-type b H. influenzae is now higher than that of Hib and is associated with higher case fatality.


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A CASE-CONTROL STUDY OF RISK FACTORS FOR HAEMOPHILUS INFLUENZAE TYPE B DISEASE IN NAVAJO CHILDREN

MARK C. WOLFF, LAWRENCE H. MOULTON, WENDY NEWCOMER, RAYMOND REID, AND MATHURAM SANTOSHAM

Departments of International Health and Biostatistics, School of Hygiene and Public Health, and the Department of Pediatrics, School of Medicine, The Johns Hopkins University, Baltimore, Maryland

Abstract.

To understand the potential risk factors and protective factors for invasive Haemophilus influenzae type b (Hib) disease, we conducted a case-control study among Navajo children less than two years of age resident on the Navajo Nation. We analyzed household interview data for 60 cases that occurred between August 1988 and February 1991, and for 116 controls matched by age, gender, and geographic location. The Hib vaccine recipients were excluded from the analyses. Conditional logistic regression models were fit to examine many variables relating to social and environmental conditions. Risk factors determined to be important were never breast fed (odds ratio [OR] 5 3.55, 95% confidence interval [CI] 5 1.52, 8.26), shared care with more than one child less than two years of age (OR 5 2.32, 95% CI 5 0.91, 5.96); wood heating (OR 5 2.14, 95% CI 5 0.91, 5.05); rodents in the home (OR 5 8.18, 95% CI 5 0.83, 80.7); and any livestock near the home (OR 5 2.18, 95% CI 5 0.94, 5.04).

http://www.ajtmh.org/content/60/2/263.full.pdf
Socioeconomic risk factors for invasive Haemophilus influenzae type b disease.

Takala AK¹, Clements DA.

Author information

Abstract

Socioeconomic risk factors for primary invasive Haemophilus influenzae type b (Hib) disease include factors that increase exposure to Hib (day care attendance, presence of siblings, and crowded households) and factors that increase an individual's susceptibility to Hib infections (short duration of breast feeding, parental smoking, and frequent infections in general). These factors are consistently found to be associated with risk of Hib disease in studies conducted in populations that differ in their Hib disease epidemiology. However, there are large differences in the prevalence of these risk factors among populations. According to present knowledge, variations in the prevalence of socioeconomic risk factors may explain most of the differences in the epidemiology of Hib disease and may also contribute to the differences in Hib vaccine efficacy in different populations.

**Hib and Vaccination**


**Acute bacterial meningitis in infants and children: epidemiology and management.**

Agrawal S¹, Nadel S.

**Abstract**

Acute bacterial meningitis (ABM) continues to be associated with high mortality and morbidity, despite advances in antimicrobial therapy. The causative organism varies with age, immune function, immunization status, and geographic region, and empiric therapy for meningitis is based on these factors. Haemophilus influenzae type b (Hib), Streptococcus pneumoniae, and Neisseria meningitidis cause the majority of cases of ABM. Disease epidemiology is changing rapidly due to immunization practices and changing bacterial resistance patterns. Hib was the leading cause of meningitis in children prior to the introduction of an effective vaccination. In those countries where Hib vaccine is a part of the routine infant immunization schedule, Hib has now been virtually eradicated as a cause of childhood meningitis. Vaccines have also been introduced for pneumococcal and meningococcal diseases, which have significantly changed the disease profile. Where routine pneumococcal immunization has been introduced there has been a reported increase in invasive pneumococcal disease due to non-vaccine serotypes. In those parts of the world that have introduced conjugate meningococcal vaccines, there has been a significant change in the epidemiology of meningococcal meningitis. As a part of the United Nations Millennium Development Goal 4, the WHO has introduced a new vaccine policy to improve vaccine availability in resource poor countries. In addition, antibiotic resistance is an increasing problem, especially with pneumococcal infection. Effective treatment focuses on early recognition and use of effective antibiotics. This review will attempt to focus on the changing epidemiology of ABM in pediatric patients due to vaccination, the changing patterns of infecting bacterial serotypes due to vaccination, and on antibiotic resistance and its impact on current management strategies.

Correspondence

Sir,

We congratulate the authors of this meticulous study. The authors found the incidence of Hib meningitis only 0.007 per cent and they speculate that the population may have ‘natural immunity’ to invasive Hib disease.

This paper is published 10 years after the data were obtained. Three years ago an editorial published in the ‘Expert Review Pharmacoeconomics Outcomes Research’, cited this study as an instance of selective non-publication of research. To understand the interest in this paper it is useful to remember the context in which the study was done. *Hib disease in Asia is very low – six in 100,000 compared with 109 in 100,000 in the Western Pacific.* The thrust of Hib research in Asia is to convince health planners that Hib was a major problem that had gone unrecognized due to poor microbiologic facilities and the technical inability to culture the organism. An Invasive Bacterial Infections Surveillance Group (IBIS) study performed over 4 years, in six large referral hospitals in India, employed sophisticated culture techniques to isolate the organism. This study also revealed a remarkably low incidence of Hib disease. Not convinced, the World Health Organization (WHO) undertook this large population-based study in Tamil Nadu, assuming that hospital-based study like the IBIS study would miss cases of meningitis that die in the community, before they reach the hospital. The very low incidence in this community based study, is therefore of great interest to epidemiologists and health planners.

Unfortunately, because of this delay in publication, the data could not inform the debate prior to decision of the WHO to recommend Hib vaccine to all infants. We have previously suggested that ‘natural immunity’ (due to infections with bacteria with cross-reacting antigens) was the WHO study suggests low incidence of Hib in India is due to natural immunity reason for the low incidence of invasive Hib disease in India, and the reason why this population does not need vaccination with Hib. It is gratifying that this is now borne out in a study supported by the WHO.

We hope the government and public health planners will take note of this latest evidence against the need for Hib vaccine in India.

Neeraj Gupta & Jacob Puliyel

Naturally Acquired Immunity to Haemophilus influenzae Type B in Healthy Cuban Children

Gilda Toraño Peraza+, Ibis Hernández Vadell, María Eugenia Toledo Román,
Alberto Baly Gil, Isis Tamargo Martínez, Annia Carmenate García

National Reference Center for Haemophilus, Instituto de Medicina Tropical “Pedro Kouri”, Havana, Cuba

We have evaluated the prevalence of antibody to immunogenicity of Haemophilus influenzae type b (Hib) in a group of 4 to 5 years old healthy children, who were too old to be included in the first vaccinated cohort when Hib vaccination begun in Cuba in 1999. Serum capsular polysaccharide specific IgG antibody concentrations were measured in 974 healthy children, between February and May 2002. The prevalence of Hib nasopharyngeal carriage was also estimated. The majority of children (99.7%) had more than 1 µg/ml of antibody. The preliminary report of the nasopharyngeal cultures was positive for H. influenzae in 16 children, but in only one was confirmed as Hib after serotyping (0.1% Hib nasopharyngeal carrier). These results provide evidence that in Cuba the natural active immunity to Hib can be acquired at an early age.

Key words: Haemophilus influenzae type b - natural immunity - pre-vaccination antibody titres – Cuba

http://www.bioline.org.br/pdf?oc04140
Natural immunity to Haemophilus influenzae type B in children of Ankara, Turkey.

Ocaktan E, Ozyurda F, Akar N.

Abstract

BACKGROUND: Haemophilus influenzae type b (Hib) infection has a high morbidity and mortality rate especially in children under 5 years of age. The incidence of Hib disease in Turkey is not known, and Hib vaccine is not included in the National Immunization Program. The aim of this study was to determine the natural immunity to Hib of children 6-60 months of age living in the Park Health Center region of Ankara, Turkey.

METHODS: A total of 270 children were selected by layered random sampling method, and 242 of them (89.6%) participated in the study. A questionnaire was given to the parents of the children who were included in the study and blood samples were taken from those children. Anti-Hib IgG antibody (anti-PRP) level was determined in the serum by using anti-Haemophilus influenzae IgG EIA kit and anti-PRP antibody levels of 0.15 microg/mL and over were accepted as the natural immunity.

RESULTS: Natural immunity was determined in 65.3% of the children. A relationship was determined statistically between the history of disease with possible Hib agent and with natural immunity.

CONCLUSIONS: The exposure rate of children with Hib was higher than expected, even in children who were just a few months old. Our data revealed that multicentric, national studies should be done to define the burden of Hib disease before making a decision for Hib vaccine to be included in the National Immunization Program.

**Human Papillomavirus (HPV)**

Human papillomavirus vaccine in boys: background rates of potential adverse events

- Most common cancer in developing countries


Cancer resources for patients and healthcare professionals

It usually takes a very long time for pre-cancerous lesions to progress to invasive cancers and we have effective screening methods that can detect pre-cancerous lesions that can generally be cured without serious side effects. Effective screening programs in the United States have led to the drastic decline in the numbers of cervical cancer deaths in the last 50 years. For women who do end up with cervical cancer in developed nations, 60% of them either have never been screened or haven't been screened in the last five years. The importance of regular cervical cancer screening cannot be overstated.

Women who have received the HPV vaccine should follow the same guidelines as unvaccinated women, as the vaccine does not prevent infection with all strains of HPV.

[http://www.oncolink.org/types/article.cfm?c=179&id=8226](http://www.oncolink.org/types/article.cfm?c=179&id=8226)
On the relationship between human papilloma virus vaccine and autoimmune diseases.


Author information

Abstract
The human papilloma virus (HPV) vaccines were introduced to reduce the incidence of cervical cancer. The bivalent vaccine is effective against HPV-16, -18, -31, -33 and -45 while the quadrivalent vaccine is effective against HPV-16, 18, 31, 6 and 11 types. The immunisation, recommended for adolescent females, has led to high vaccine coverage in many countries. Along with the introduction of the HPV vaccines, several cases of onset or exacerbations of autoimmune diseases following the vaccine shot have been reported in the literature and pharmacovigilance databases, triggering concerns about its safety. This vaccination programme, however, has been introduced in a population that is at high risk for the onset of autoimmune diseases, making it difficult to assess the role of HPV vaccine in these cases and no conclusive studies have been reported thus far. We have thus analysed and reviewed comprehensively all case reports and studies dealing with either the onset of an autoimmune disease in vaccinated subject or the safety in patients with autoimmune diseases to define the role of the HPV vaccines in these diseases and hence its safety. A solid evidence of causal relationship was provided in few cases in the examined studies, and the risk vs. benefit of vaccination is still to be solved. The on-going vigilance for the safety of this vaccine remains thus of paramount importance.

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KEYWORDS:
Acute disseminated encephalomyelitis, Autoimmunity diseases, Human papilloma virus vaccine, Juvenile idiopathic arthritis, Multiple sclerosis, Rheumatoid arthritis

Human papilloma virus vaccine and primary ovarian failure: another facet of the autoimmune/inflammatory syndrome induced by adjuvants.

Colafrancesco S, Perricone C, Tomljenovic L, Shoenfeld Y.

Source
Zabludowicz Center for Autoimmune Diseases Sheba Medical Center, Tel-Hashomer, Israel; Rheumatology Unit, Department of Internal Medicine and Medical Specialties, Sapienza University of Rome, Rome, Italy.

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.


**HPV vaccines and cancer prevention, science versus activism.**

Tomljenovic L, Wilyman J, Vanamee E, Bark T, Shaw CA.

**Source**

Neural Dynamics Research Group, Vancouver General Hospital Research Pavilion, University of British Columbia, 828 W, 10th Ave, Vancouver, BC, V5Z 1L8, Canada. lucijat77@gmail.com.

**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.

Human papillomavirus (HPV) vaccines as an option for preventing cervical malignancies: (how) effective and safe?

Tomljenovic L, Spinosa JP, Shaw CA.

Source

Neural Dynamics Research Group, Department of Ophthalmology and Visual Sciences, University of British Columbia, 828 W. 10th Ave, Vancouver, BC, V5Z 1L8, Canada. lucijat77@gmail.com

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.

Premature ovarian failure 3 years after menarche in a 16-year-old girl following human papillomavirus vaccination.

Little DT¹, Ward HR.

Author information

Abstract

Premature ovarian failure in a well adolescent is a rare event. 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.

Vaccine-type human papillomavirus and evidence of herd protection after vaccine introduction.

Kahn JA, Brown DR, Ding L, Widdice LE, Shew ML, Glynn S, Bernstein DI.

Source
Division of Adolescent Medicine, MLC 4000, Cincinnati Children's Hospital Medical Center, 3333 Burnet Ave, Cincinnati, OH 45229, USA. jessica.kahn@cchmc.org

Abstract

OBJECTIVES:
The aims of this study were to compare prevalence rates of human papillomavirus (HPV) in young women before and after HPV vaccine introduction to determine the following: (1) whether vaccine-type HPV infection decreased, (2) whether there was evidence of herd protection, and (3) whether there was evidence for type-replacement (increased prevalence of nonvaccine-type HPV).

METHODS:
Young women 13 to 26 years of age who had had sexual contact were recruited from 2 primary care clinics in 2006-2007 for a prevaccination surveillance study (N = 368, none were vaccinated) and 2009-2010 for a postvaccination surveillance study (N = 409, 59% were vaccinated). Participants completed a questionnaire and were tested for cervicovaginal HPV DNA. HPV prevalence rates were compared in the pre- versus postsurveillance studies by using χ² tests. Propensity score weighting was used to balance differences in covariates between the 2 surveillance studies.

RESULTS:
The mean age was ~19 years for both groups of participants and most were African American and non-Hispanic. After propensity score weighting, the prevalence rate for vaccine-type HPV decreased substantially (31.7%-13.4%, P < .0001). The decrease in vaccine-type HPV not only occurred among vaccinated (31.8%-9.9%, P < .0001) but also among unvaccinated (30.2%-15.4%, P < .0001) postsurveillance study participants. Nonvaccine-type HPV increased (60.7%-75.9%, P < .0001) for vaccinated postsurveillance study participants.

CONCLUSIONS:
Four years after licensing of the quadrivalent HPV vaccine, there was a substantial decrease in vaccine-type HPV prevalence and evidence of herd protection in this community. The increase in nonvaccine-type HPV in vaccinated participants should be interpreted with caution but warrants further study.

Telogen effluvium following bivalent human papillomavirus vaccine administration: a report of two cases.

Tuccori M¹, Pisani C, Bachini L, Pardini M, Mantarro S, Antonioli L, Fornai M, Rubinelli M, Cirinei C, Blandizzi C.

Abstract

We describe two cases of telogen effluvium occurring in two 11-year-old children following bivalent human papillomavirus (HPV) vaccine administration. The two children began to lose their hair following the second HPV vaccine dose. Alopecia worsened following the third vaccine dose and then resolved spontaneously within a few months. In both cases, laboratory analysis and psychiatric evaluation excluded causes other than anti-HPV vaccine. Social discomfort and isolation were associated with alopecia in the two children. The clinical presentation was consistent with a pattern of telogen effluvium. The identification of specific vaccine components responsible for triggering the adverse event remains difficult. In similar cases, suspension of immunization is not recommended, as it provides health benefits that overcome the possible adverse effect of transient telogen effluvium. Caregivers should ensure psychiatric support to their patients to manage the social and emotional distress that might be associated with hair loss.

http://www.ncbi.nlm.nih.gov/pubmed/?term=Telogen+Effluvium+following+Bivalent+Human+Papillomavirus+Vaccine+Administration%3A+A+Report+of+Two+Cases
Clinical perspectives on the role of the human papillomavirus vaccine in the prevention of cancer.

Julius JM, Ramondeta L, Tipton KA, Lal LS, Schneider K, Smith JA.

Although both HPV vaccines were greater than 90% effective in the prevention of cervical cancer precursors in an according-to-protocol cohort, both vaccines were significantly less effective in the intent-to-treat population. In patients who achieved seroconversion, the geometric mean titers decrease dramatically within the first 2 years after vaccination, and then continue to decline at a slower rate. No effective antibody titer has been defined for either vaccine, and no studies have been conducted with documented HPV exposure after vaccination. With low efficacy rates in an intent-to-treat population and the potential for waning immunity, it is imperative for women to continue to receive regular Pap tests and gynecologic examinations. Although vaccine administration was shown to be cost-effective when administered to adolescent girls, many of these simulations underestimated the durability of protection, efficacy rates in sexually active women, impact of incomplete vaccination, or necessity of boosters in the future. Whereas the introduction of the HPV vaccine was an enormous advancement in the cancer prevention research arena, optimization of its clinical use is still needed.


Souayah N', Michas-Martin PA, Nasar A, Krivitskaya N, Yacoub HA, Khan H, Qureshi AI.

Author information

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.sciencedirect.com/science/article/pii/S0264410X10013307#
The quadrivalent human papillomavirus vaccine: erythema multiforme and cutaneous side effects after administration.

Pérez-Carmona L, Aguayo-Leiva I, González-García C, Jaén-Olasolo P.

Author information

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.


Comment [A27]: Very selective view of the literature as many studies report the opposite.
Erythema multiforme following vaccination for human papillomavirus.

Katoulis AC, Liakou A, Bozi E, Theodorakis M, Alevizou A, Zafeiraki A, Mistidou M, Stavrianeas NG.

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 HPVvaccination.

Quadrivalent Human Papillomavirus recombinant vaccine associated lipoatrophy.

Ojaimi S, Buttery JP, Korman TM.

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 DiptheriaPertussis Tetanus (DPT) vaccine. We report on two cases of lipoatrophy associated with the new Quadrivalent Human Papillomavirus (HPV) recombinant vaccine (Gardasil).


Marsee DK, Williams JM, Velazquez EF.

Abstract

We report the case of a young woman who developed a subcutaneous granulomatous response after administration of the quadrivalent human papillomavirus vaccine. The inciting agent was most likely an aluminum adjuvant, which previously has been reported to be associated with a granulomatous response after administration of other vaccines. Histologically, the lesion consisted of a necrotic/necrobiotic center surrounded by palisading epithelioid histiocytes closely resembling deep granuloma annulare or rheumatoid nodule. The histiocytes contained abundant intracytoplasmic violaceous/gray granular material. An ammonium aurintricarboxylate (Aluminon) stain demonstrated the presence of aluminum in the granular material. Aluminum granulomas should be included in the differential diagnosis of deep granulomatous reaction in young women, due to the high frequency of vaccination in this population.

Anaphylaxis following quadrivalent human papillomavirus vaccination.

Brotherton JM¹, Gold MS, Kemp AS, McIntyre PB, Burgess MA, Campbell-Lloyd S; New South Wales Health HPV Adverse Events Panel.

Abstract

BACKGROUND:
In 2007, Australia implemented the National human papillomavirus (HPV) Vaccination Program, which provides quadrivalent HPV vaccine free to all women aged 12-26 years. Following notification of 7 presumptive cases of anaphylaxis in the state of New South Wales, Australia, we verified cases and compared the incidence of anaphylaxis following HPV vaccination to other vaccines in comparable settings.

METHODS:
We contacted all patients with suspected anaphylaxis and obtained detailed histories from telephone interviews and a review of medical records. A multidisciplinary team determined whether each suspected case met the standardized Brighton definition. Some participants also received skin-prick allergy testing for common antigens and components of the HPV vaccine.

RESULTS:
Of 12 suspected cases, 8 were classified as anaphylaxis. Of these, 4 participants had negative skin-prick test results for intradermal Gardasil. From the 269,680 HPV vaccine doses administered in schools, 7 cases of anaphylaxis were identified, which represents an incidence rate of 2.6 per 100,000 doses (95% CI 1.0-5.3 per 100,000). In comparison, the rate of identified anaphylaxis was 0.1 per 100,000 doses (95% CI 0.003-0.7) for conjugated meningococcal C vaccination in a 2003 school-based program.

INTERPRETATION:
Based on the number of confirmed cases, the estimated rate of anaphylaxis following quadrivalent HPV vaccine was significantly higher than identified in comparable school-based delivery of other vaccines. However, overall rates were very low and managed appropriately with no serious sequelae.
Influenza


Does Influenza Vaccination Modify Influenza Severity? Data on Older Adults Hospitalized With Influenza During the 2012-2013 Season in the United States.

Arriola CS¹, Anderson EJ², Baumbach J³, Bennett N⁴, Bohn S⁵, Hill M⁶, Lindegren ML⁷, Lung K⁸, Meek J⁹, Mermel E¹⁰, Miller L¹¹, Monroe ML¹², Morin C¹³, Oni O¹⁴, Reingold A¹⁵, Schaffner W¹⁶, Thomas A¹⁶, Zansky SM¹⁷, Finelli L¹⁸, Chaves SS¹⁸.

Author information

Abstract

BACKGROUND:

Some studies suggest that influenza vaccination might be protective against severe influenza outcomes in vaccinated persons who become infected. We used data from a large surveillance network to further investigate the effect of influenza vaccination on influenza severity in adults aged ≥50 years who were hospitalized with laboratory-confirmed influenza.

METHODS:

We analyzed influenza vaccination and influenza severity using Influenza Hospitalization Surveillance Network (FluSurv-NET) data for the 2012-2013 influenza season. Intensive care unit (ICU) admission, death, diagnosis of pneumonia, and hospital and ICU lengths of stay served as measures of disease severity. Data were analyzed by multivariable logistic regression, parametric survival models, and propensity score matching (PSM).

RESULTS:

Overall, no differences in severity were observed in the multivariable logistic regression model. Using PSM, adults aged 50-64 years (but not other age groups) who were vaccinated against influenza had a shorter length of ICU stay than those who were unvaccinated (hazard ratio for discharge, 1.84; 95% confidence interval, 1.12-3.01).

CONCLUSIONS:

Our findings show a modest effect of influenza vaccination on disease severity. Analysis of data from seasons with different predominant strains and higher estimates of vaccine effectiveness are needed.

The impact of vaccination on influenza-related respiratory failure and mortality in hospitalized elderly patients over the 2013-2014 season.

Joshi M¹, Chandra D², Mittadodla P¹, Bartter T¹.

Author information

Abstract

BACKGROUND:
Seasonal Influenza ("the flu") is a respiratory illness caused by influenza viruses. Yearly influenza vaccination is considered to be protective against illness and/or severity of illness and is recommended by CDC for all individuals > 6 months of age. However, the effectiveness of influenza vaccine in older individuals has come under question.

OBJECTIVES:
To describe the clinical characteristics and treatment outcomes of patients admitted to an academic tertiary care Veterans Administration hospital with influenza during the 2013-2014 influenza season and determine the impact, if any, of prior influenza vaccination upon patient outcomes.

METHODS:
Medical electronic records were searched for all patients admitted to the Little Rock Veterans Administration Hospital with proven influenza during the 2013-2014 influenza season. Cohorts of vaccinated and non-vaccinated patients were then compared to determine the impact of prior influenza vaccination upon respiratory-failure and mortality.

RESULTS:
Seventy patients met selection criteria. Mean age was 66 years. Sixty-four (91%) patients had at least one underlying co-morbid condition; these conditions included COPD, congestive heart failure, diabetes, and cancer. 60/70 (85%) tested positive for Influenza A, and 43 tested positive for H1N1. Oseltamivir was initiated in 55 (78%) patients. Forty-four percent of the patients had been vaccinated. When separated by vaccination status, those who had been vaccinated had higher rates of ICU admission, need for mechanical or non-invasive ventilation, and mortality. All but mortality reached statistical significance.

CONCLUSION:
The data suggest that there was no protective effect from prior vaccination in preventing hospital admission, respiratory failure, and mortality in this population of older men admitted to the hospital with influenza.

Are influenza-associated morbidity and mortality estimates for those ≥ 65 in statistical databases accurate, and an appropriate test of influenza vaccine effectiveness?

**Author information**

**Abstract**

**PURPOSES:**
To assess the accuracy of estimates using statistical databases of influenza-associated morbidity and mortality, and precisely measure influenza vaccine effectiveness.

**PRINCIPAL RESULTS:**
Laboratory testing of influenza is incomplete. Death certificates under-report influenza. Statistical database models are used as an alternative to randomised controlled trials (RCTs) to assess influenza vaccine effectiveness. Evidence of the accuracy of influenza morbidity and mortality estimates was sought from: (1) Studies comparing statistical models. For four studies Poisson and ARIMA models produced higher estimates than Serfling, and Serfling higher than GLM. Which model is more accurate is unknown. (2) Studies controlling confounders. Fourteen studies mostly controlled one confounder (one controlled comorbidities), and limited control of confounders limits accuracy.

**EVIDENCE FOR VACCINE EFFECTIVENESS WAS SOUGHT FROM:**
(1) Studies of regions with increasing vaccination rates. Of five studies two controlled for confounders and one found a positive vaccination effect. Three studies did not control confounders and two found no effect of vaccination. (2) Studies controlling multiple confounders. Of thirteen studies only two found a positive vaccine effect and no mortality differences between vaccinees and non-vaccinees in non-influenza seasons, showing confounders were controlled.

Key problems are insufficient testing for influenza, using influenza-like illness, heterogeneity of seasonal and pandemic influenza, population aging, and incomplete confounder control (comorbidities, frailty, vaccination history) and failure to demonstrate control of confounders by proving no mortality differences between vaccinees and non-vaccinees in non-influenza seasons.

**MAJOR CONCLUSIONS:**
Improving model accuracy requires proof of no mortality differences in pre-influenza periods between the vaccinated and non-vaccinated groups, and reduction in influenza morbidity and mortality in seasons with a good vaccine match, more virulent strains, in the younger elderly with less immune senescence, and specific outcomes (laboratory-confirmed outcomes, pneumonia deaths). Proving influenza vaccine effectiveness requires appropriately powered RCTs, testing participants with RT-PCR tests, and comprehensively monitoring morbidity and mortality.


**Comment [A30]:** This is a literature review finding that:

"Of thirteen studies only two found a positive vaccine effect and no mortality differences between vaccinees and non-vaccinees in non-influenza seasons, showing confounders were controlled"
A structured avian influenza model with imperfect vaccination and vaccine-induced asymptomatic infection.

Gulbudak H¹, Martcheva M.

Author information

¹Department of Mathematics, University of Florida, 358, Little Hall, PO Box 118105, Gainesville, FL, 32611-8105, USA, hgulbudak@ufl.edu.

Abstract

We introduce a model of avian influenza in domestic birds with imperfect vaccination and age-since-vaccination structure. The model has four components: susceptible birds, vaccinated birds (stratified by vaccination age), asymptomatically infected birds, and infected birds. The model includes reduction in the probability of infection, decreasing severity of disease of vaccinated birds and vaccine waning. The basic reproduction number, $R_0$, is calculated. The disease-free equilibrium is found to be globally stable under certain conditions when $R_0 < 1$. When $R_0 > 1$, existence of an endemic equilibrium is proved (with uniqueness for the ODE case and local stability under stricter conditions) and uniform persistence of the disease is established. The inclusion of reduction in susceptibility of vaccinated birds, reduction in infectiousness of asymptomatically infected birds and vaccine waning can have important implications for disease control. We analytically and numerically demonstrate that vaccination can paradoxically increase the total number of infected, resulting in the "silent spread" of the disease. We also study the effects of vaccine efficacy on disease prevalence and the minimum critical vaccination coverage, a threshold value for vaccination coverage to avoid an increase in total disease prevalence due to asymptomatic infection.

Acute renal failure after influenza vaccination: a case report.
Novati R, Nebiolo PE, Galotto C, Mastaglia M, Manes M.

Abstract
A fifty-three years old surgeon had acute renal failure consisting with acute tubulo-interstitial nephropathy twelve days after influenza vaccination; he was on statin therapy since one month. He was given steroidal therapy and fully recovered two weeks apart. This is the fourth case report of acute renal failure after influenza vaccination in patients on statins therapy. The case we describe could account for a underestimated, even if very rare, phenomenon.

Glossopharyngeal nerve and vagus nerve palsies associated with influenza vaccination.

Ishii K', Kanazawa T, Tomidokoro Y, Tamaoka A.

Abstract

We herein report the first case of glossopharyngeal nerve and vagus nerve palsies that appeared after an influenza vaccination. A 15-year-old boy developed dysphagia and dysarthria seven days after receiving an inoculation of the inactivated influenza vaccine. Massive intravenous immunoglobulin (IVIg) treatment was applied, as the patient's symptoms were considered to be immunological adverse effects of the influenza vaccine. He responded well to IVIg, and the symptoms immediately diminished. The mechanisms underlying the development of neurologic symptoms following vaccination are difficult to determine; however, providing immediate immunological treatment, such as IVIg, is effective and beneficial in countering these symptoms.

Available online 26 November 2013

Influenza vaccination and risk of hospitalization among adults with laboratory confirmed influenza illness

Huong Q. McLean, Jennifer K. Meece, Edward A. Belongia

Marshfield Clinic Research Foundation, Marshfield, WI, USA

Abstract

Background

Influenza vaccine is moderately effective for preventing influenza illness. It is not known if vaccination reduces the risk of subsequent hospital admission among patients with vaccine failure and laboratory confirmed influenza illness.

Methods

Patients in a community cohort presenting with acute respiratory illness were prospectively enrolled and tested for influenza during 8 seasons to estimate seasonal vaccine effectiveness. Hospital admissions within 14 days after illness onset were identified for all participants aged ≥20 years with laboratory confirmed influenza. The association between vaccination and hospital admission was examined in a propensity score adjusted logistic regression model. The model was validated by examining the association between vaccination and hospital admission in participants without influenza.

Results

Influenza was identified in 1393 (28%) of 4996 participants. Sixty-two (6%) of 1020 with influenza A and 17 (5%) of 369 with influenza B were hospitalized. Vaccination was not associated with a reduced risk of hospital admission among all participants with influenza [adjusted odds ratio (aOR) = 1.08; 95% CI: 0.62, 1.88]; or among those with influenza A (aOR = 1.35; 95% CI: 0.71, 2.57) or influenza B (aOR = 0.67; 95% CI: 0.21, 2.15). Influenza vaccination was not associated with hospitalization after non-influenza respiratory illness (aOR = 1.14; 95% CI: 0.84, 1.54).

Conclusions

Influenza vaccination did not reduce the risk of subsequent hospital admission among patients with vaccine failure. These findings do not support the hypothesis that vaccination mitigates influenza illness severity.

Keywords, Influenza vaccine; Severity; Hospitalization; Effectiveness
Acknowledgements

We thank the following individuals for their contribution to this work: Burney Kieke, Sarah Kopitzke, Pam Squires, Jim Donahue, Stephanie Irving, David Shay, and Alicia Fry.

Conflicts of interest: HQM, JKM, and EAB receive research funding from MedImmune, LLC.

Funding: Centers for Disease Control and Prevention (cooperative agreement U18 IP000183).

Increased risk of noninfluenza respiratory virus infections associated with receipt of inactivated influenza vaccine.

Cowling BJ1, Fang VJ, Nishiura H, Chan KH, Ng S, Ip DK, Chiu SS, Leung GM, Peiris JS.

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.

Efficacy and effectiveness of influenza vaccines: a systematic review and meta-analysis

• Prof Michael T Osterholm, PhD
• Nicholas S Kelley, PhD
• Prof Alfred Sommer, MD
• Edward A Belongia, MD

Summary

Background

No published meta-analyses have assessed efficacy and effectiveness of licensed influenza vaccines in the USA with sensitive and highly specific diagnostic tests to confirm influenza.

Methods

We searched Medline for randomised controlled trials assessing a relative reduction in influenza risk of all circulating influenza viruses during individual seasons after vaccination (efficacy) and observational studies meeting inclusion criteria (effectiveness). Eligible articles were published between Jan 1, 1967, and Feb 15, 2011, and used RT-PCR or culture for confirmation of influenza. We excluded some studies on the basis of study design and vaccine characteristics. We estimated random-effects pooled efficacy for trivalent inactivated vaccine (TIV) and live attenuated influenza vaccine (LAIV) when data were available for statistical analysis (eg, at least three studies that assessed comparable age groups).

Findings
We screened 5707 articles and identified 31 eligible studies (17 randomised controlled trials and 14 observational studies). Efficacy of TIV was shown in eight (67%) of the 12 seasons analysed in ten randomised controlled trials (pooled efficacy 59% [95% CI 51–67] in adults aged 18–65 years). No such trials met inclusion criteria for children aged 2–17 years or adults aged 65 years or older. Efficacy of LAIV was shown in nine (75%) of the 12 seasons analysed in ten randomised controlled trials (pooled efficacy 83% [69–91]) in children aged 6 months to 7 years. No such trials met inclusion criteria for children aged 8–17 years. Vaccine effectiveness was variable for seasonal influenza: six (35%) of 17 analyses in nine studies showed significant protection against medically attended influenza in the outpatient or inpatient setting. Median monovalent pandemic H1N1 vaccine effectiveness in five observational studies was 69% (range 60–93).

Interpretation

Influenza vaccines can provide moderate protection against virologically confirmed influenza, but such protection is greatly reduced or absent in some seasons. Evidence for protection in adults aged 65 years or older is lacking. LAIVs consistently show highest efficacy in young children (aged 6 months to 7 years). New vaccines with improved clinical efficacy and effectiveness are needed to further reduce influenza-related morbidity and mortality.

Funding

Alfred P Show more information

Lichen planus occurring after influenza vaccination: report of three cases and review of the literature.

Sato NA, Kano Y, Shiohara T.

Author information

Abstract

Although influenza vaccine is thought to be effective and safe, it occasionally causes systemic reactions such as toxic epidermal necrolysis, bullous pemphigoid, lichen planus (LP), etc. The period of increased risk of developing these events was different depending on the immune responses induced by the vaccination. We report 3 cases of LP which appeared after an influenza vaccination. Our cases indicate that the period of increased risk of developing vaccine-related LP was concentrated within 2 weeks after vaccination, and that the vaccine alone represents a triggering factor necessary for immune alteration sufficient for the development of LP. Because these adverse events tend to develop over a predictable time course, the time of onset may give an important clue to the diagnosis of vaccine-related diseases. We suggest that a history of recent vaccination should be sought in all patients presenting with linear LP.

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Vaccines for preventing influenza in healthy adults.

Abstract

BACKGROUND:
Different types of influenza vaccines are currently produced worldwide. Healthy adults are presently targeted mainly in North America.

OBJECTIVES:
Identify, retrieve and assess all studies evaluating the effects of vaccines against influenza in healthy adults.

SEARCH STRATEGY:
We searched the Cochrane Central Register of Controlled Trials (CENTRAL) (The Cochrane Library, 2010, issue 2), MEDLINE (January 1966 to June 2010) and EMBASE (1990 to June 2010).

SELECTION CRITERIA:
Randomised controlled trials (RCTs) or quasi-RCTs comparing influenza vaccines with placebo or no intervention in naturally-occurring influenza in healthy individuals aged 16 to 65 years. We also included comparative studies assessing serious and rare harms.

DATA COLLECTION AND ANALYSIS:
Two review authors independently assessed trial quality and extracted data.

MAIN RESULTS:
We included 50 reports. Forty (59 sub-studies) were clinical trials of over 70,000 people. Eight were comparative non-RCTs and assessed serious harms. Two were reports of harms which could not be introduced in the data analysis. In the relatively uncommon circumstance of vaccine matching the viral circulating strain and high circulation, 4% of unvaccinated people versus 1% of vaccinated people developed influenza symptoms (risk difference (RD) 3%, 95% confidence interval (CI) 2% to 5%). The corresponding figures for poor vaccine matching were 2% and 1% (RD 1, 95% CI 0% to 3%). These differences were not likely to be due to chance. Vaccination had a modest effect on time off work and had no effect on hospital admissions or complication rates. Inactivated
vaccines caused local harms and an estimated 1.6 additional cases of Guillain-Barre Syndrome per million vaccinations. The harms evidence base is limited.

**AUTHORS’ CONCLUSIONS:**
Influenza vaccines have a modest effect in reducing influenza symptoms and working days lost. There is no evidence that they affect complications, such as pneumonia, or transmission. WARNING: This review includes 15 out of 36 trials funded by industry (four had no funding declaration). An earlier systematic review of 274 influenza vaccine studies published up to 2007 found industry funded studies were published in more prestigious journals and cited more than other studies independently from methodological quality and size. Studies funded from public sources were significantly less likely to report conclusions favorable to the vaccines. The review showed that reliable evidence on influenza vaccines is thin but there is evidence of widespread manipulation of conclusions and spurious notoriety of the studies. The content and conclusions of this review should be interpreted in light of this finding.

ANCA-associated vasculitis following influenza vaccination: causal association or mere coincidence?

Birck R, Kaelsch I, Schnuelle P, Flores-Suárez LF, Nowack R.

Source
Fifth Department of Medicine, University Hospital Mannheim, Germany. rainer.birck@med5.ma.uni-heidelberg.de

Abstract
Whether autoimmune or rheumatic disease may be precipitated after vaccination is controversially discussed among experts. Here we describe 4 cases of new onset or relapsing antineutrophil cytoplasmic antibodies associated vasculitis occurring in timely association with influenza vaccination. In the literature different subtypes of vasculitis have been repeatedly reported after influenza vaccination. Several trials in patients with preexisting autoimmune disease failed to indicate an increased risk for disease recurrence after influenza vaccination but these investigations might be underpowered to detect this very rare but relevant side effect. Although our report does not prove a causal association between vaccination and vasculitis, it seems possible that in rare cases vaccination might induce vasculitic disease.


Lasky T, Terracciano GJ, Magder L, Koski CL, Ballesteros M, Nash D, Clark S, Haber P, Stolley PD, Schonberger LB, Chen RT.

Source
Department of Epidemiology and Preventive Medicine, School of Medicine, University of Maryland, Baltimore 21201, USA.

Abstract
BACKGROUND:
The number of reports of influenza-vaccine-associated Guillain-Barré syndrome to the national Vaccine Adverse Event Reporting System increased from 37 in 1992-1993 to 74 in 1993-1994, arousing concern about a possible increase in vaccine-associated risk.

METHODS:
Patients given a diagnosis of the Guillain-Barré syndrome in the 1992-1993 and 1993-1994 influenza-vaccination seasons were identified in the hospital-discharge data bases of four states. Vaccination histories were obtained by telephone interviews during 1995-1996 and were confirmed by the vaccine providers. Disease with an onset within six weeks after vaccination was defined as vaccine-associated. Vaccine coverage in the population was measured through a random-digit-dialing telephone survey.

RESULTS:
We interviewed 180 of 273 adults with the Guillain-Barré syndrome; 15 declined to participate, and the remaining 78 could not be contacted. The vaccine providers confirmed influenza vaccination in the six weeks before the onset of Guillain-Barré syndrome for 19 patients. The relative risk of the Guillain-Barré syndrome associated with vaccination, adjusted for age, sex, and vaccine season, was 1.7 (95 percent confidence interval, 1.0 to 2.8; P=0.04). The adjusted relative risks were 2.0 for the 1992-1993 season (95 percent confidence interval, 1.0 to 4.3) and 1.5 for the 1993-1994 season (95 percent confidence interval, 0.8 to 2.9). In 9 of the 19 vaccine-associated cases, the onset was in the second week after vaccination, all between day 9 and day 12.

CONCLUSIONS:
There was no increase in the risk of vaccine-associated Guillain-Barré syndrome from 1992-1993 to 1993-1994. For the two seasons combined, the adjusted relative risk of 1.7 suggests slightly more than one additional case of Guillain-Barré syndrome per million persons vaccinated against influenza.

Microscopic polyangiitis after influenza vaccination.

Kelsall JT, Chalmers A, Sherlock CH, Tron VA, Kelsall AC.

Source

University of British Columbia (UBC), Division of Rheumatology, Vancouver, Canada.

Abstract

We describe a case of microscopic polyangiitis involving skin and joints after influenza vaccination. Titers of antiinfluenza A antibody were markedly elevated in synovial fluid (SF) relative to those in serum. Antiinfluenza B antibodies were not present in SF but were present in serum, suggesting a reaction specifically involving antiinfluenza A antibodies localized to the affected joint. A review identified 16 other cases of vasculitis after influenza vaccination. The cases reclassified according to the Chapel Hill diagnostic criteria identified multiple forms of vasculitis including 7 other cases of microscopic polyangiitis. Three patients had similar illnesses after previous influenza vaccination or influenza-like illness. As in our case 11 cases resolved without recurrence. While this does not provide conclusive evidence that the vaccination caused the vasculitis, together with the serologic data we present it supports this hypothesis.

Systemic vasculitis following influenza vaccination--report of 3 cases and literature review.


Source
University of Toronto Rheumatic Disease Unit, Wellesley Hospital, Ontario, Canada.

Abstract
Influenza vaccination is a widely accepted practice particularly among the elderly and high risk individuals. Minor and transitory side effects following the vaccination are common while systemic complications are infrequently reported. We describe 3 patients who developed systemic vasculitis following influenza vaccination. With increasing use of influenza vaccination, attention should be drawn to the possible expression of systemic adverse effects such as vasculitis.

Measles

A letter from Andrew Wakefield’s co-author. The work was criticised but not disproven and it was through epidemiological studies that it was challenged.

“In such highly selected children, Uhlmann and colleagues have now provided new evidence that measles might be involved, by use of molecular techniques to show the presence of measles virus genomes in 75 of 91 children with ileal-lymphoid-nodular hyperplasia, enterocolitis, and developmental disorder, compared with five of 70 control children.”

http://www.thelancet.com/journals/lancet/article/PIIS0140-6736(02)07783-8/fulltext
Local public health response to vaccine-associated measles: case report.


Abstract

BACKGROUND: The most appropriate public health approach to vaccine-associated measles in immunocompromised patients is unknown, mainly because these cases are rare and transmission of vaccine-associated measles has not been previously documented. In this case report, we describe Peel Public Health's response to a vaccine-associated measles case in an immunocompromised child in Ontario, Canada.

CASE PRESENTATION: A five-year-old Canadian-born boy with a history of a hematopoetic stem cell transplant three years previously received live attenuated measles, mumps, and rubella (MMR) vaccine. Over the subsequent 7 to 14 days, he developed an illness clinically consistent with measles. There was no travel history or other measles exposure. Serology and polymerase chain reaction (PCR) testing confirmed acute measles infection. Following discussion with pediatric infectious diseases specialists, but prior to the availability of virus sequencing, it was felt that this case was most likely due to vaccine strain. Although no microbiologically confirmed secondary cases of vaccine-associated measles have been previously described, we sent notification letters to advise all contacts of measles symptoms since the likelihood of transmission from an immunocompromised patient was low, but theoretically possible. We decided to stratify contacts into immune competent and compromised and to deal with the latter group conservatively by excluding them as if they were exposed to wild-type measles because the risk of transmission of disease in this population, while presumably very low, is unknown. However, no contacts self-identified as immunocompromised and there were no secondary cases. Subsequent genotyping confirmed that this case was caused by vaccine strain measles virus.

CONCLUSION: The public health approach to contact tracing and exclusions for vaccine-associated measles in immunocompromised patients is unclear. The rarity of secondary cases provides further evidence that the risk to the general public is likely extremely low. Although the risk appears negligible, exclusion and administration of immune globulin may be considered for susceptible, immunocompromised contacts of cases of vaccine-associated measles in immunocompromised patients.
Abnormal Measles-Mumps-Rubella Antibodies and CNS Autoimmunity in Children with Autism

Vijendra K. Singh Sheren X. Lin Elizabeth Newell Courtney Nelson
Department of Biology and Biotechnology Center, Utah State University, Logan, Utah, USA
Vijendra Singh, PhD
Biotechnology Center
Utah State University

Key Words
Autoantibodies W Autism W Autoimmunity W Measles virus W Measles-mumps-rubella antibodies W Vaccines

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 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.

Abnormal measles-mumps-rubella antibodies and CNS autoimmunity in children with autism.

Singh VK, Lin SX, Newell E, Nelson C.

Source

Department of Biology and Biotechnology Center, Utah State University, Logan, Utah 84322, USA. singhvk@cc.usu.edu

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.

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Serological association of measles virus and human herpesvirus-6 with brain autoantibodies in autism.

Singh VK, Lin SX, Yang VC.

Source

College of Pharmacy, University of Michigan, Ann Arbor, Michigan, 48109-1065, USA.

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.

Incidence of subacute sclerosing panencephalitis following measles and measles vaccination in Japan.


Source

Research Institute for Microbial Diseases, Osaka University, Japan.

Abstract

The Japanese Committee for the National Registry of Subacute Sclerosing Panencephalitis (SSPE) confirmed that 215 cases of SSPE occurred in the 20 years from 1966 to 1985, as discovered in the 10-year surveillance from April 1976 through March 1986. The annual incidence in recent years has been between 10 and 23 cases. Among cases with a certain history of measles illness or measles vaccination, 184 (90.2%) had a history of measles illness without receiving measles vaccine. There were 11 probable measles vaccine-associated cases (5.4%), three (1.5%) being vaccinated with a combined use of killed and live vaccine and eight (3.9%) with further attenuated live vaccine. There were nine cases (4.4%) without a history of either measles illness or measles vaccination. Intervals between measles illness and the onset of SSPE varied from 1 to 16 years (mean, 7.0 years). The periods following measles vaccination with further attenuated live vaccine were 2 to 11 years (mean, 4.6 years). Annual incidence rates of SSPE per million cases of measles ranged between 6.1 and 40.9 (mean, 16.1) in the 10 measles epidemic years 1968-1977, and those following vaccination with further attenuated live vaccine were zero in most years and at the highest 3.08 (mean, 0.9) per million doses of distributed vaccine.

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.

Weibel RE, Caserta V, Benor DE, Evans G.

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 (Mumpsivax, 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.

Meningococcal Conjugate Vaccine


**Erythema multiforme after meningitis vaccine: patient safety concerns with repeat immunization.**

Studdiford J¹, Oppenheim L, McCann E, Altshuler M.

**Author information**

**Abstract**

A 20-year-old college student developed an immunologic hypersensitivity reaction, erythema multiforme minor, 1-2 weeks after receiving a meningococcal conjugate vaccine. He had no history of erythema multiforme, nor had he received any other vaccine or drug therapy. The temporal relationship between the development of erythema multiforme and the vaccination suggests that the meningitis vaccine probably was the causal agent. The occurrence of this distinct cutaneous reaction, with the potential for a serious complication such as erythema multiforme major or Stevens-Johnson syndrome on rechallenge, should serve as a warning against repeated booster vaccinations in patients who develop reactions such as this one.


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Comment [A32]: Recommends suspension of booster doses in patients with these reactions, yet many doctors continue to recommend vaccinations even when serious side effects develop.
An unusual occurrence of Kleine-Levin syndrome in a man with refractory immune thrombocytopenic purpura: a case report.

Amirifard H1, Barzkar F2, Fazeli SA3, Hashemi SM4,5.

Abstract

INTRODUCTION:
Kleine-Levin syndrome is an extremely rare neurological entity characterized by recurrent episodes of hypersomnia which are sometimes associated with compulsive hyperphagia and behavioral changes. Autoimmunity has recently been proposed as a factor contributing to its pathogenesis. Immune thrombocytopenic purpura is a relatively common autoimmune disease showing a lot of complexity and uncertainty regarding its treatment regimens and its refractory nature in some cases.

CASE PRESENTATION:
A 32-year-old Persian White man visited his private hematologist complaining of recent episodes of epistaxis and appearance of petechial lesions 24 hours after receiving a meningococcal vaccine. He had a history of immune thrombocytopenic purpura 13 years before his presentation. Based on his history and laboratory findings, his condition was diagnosed as a relapse of immune thrombocytopenic purpura and was managed accordingly. He did not respond to first-line corticosteroid regimens and later developed neurological symptoms as recurrent episodes of hypersomnia and hyperphagia. After a complete clinical and paraclinical evaluation and ruling out other possible conditions, he was given a diagnosis of Kleine-Levin syndrome. He was followed up for his immune thrombocytopenic purpura and received different treatment regimens none of which were adequately successful except intravenous immunoglobulin that was only temporarily effective. He has had 4 documented self-limited episodes of Kleine-Levin syndrome since his initial presentation.

CONCLUSIONS:

Immune thrombocytopenic purpura may be associated with meningococcal vaccination in adulthood. Responses to treatment in immune thrombocytopenic purpura vary among patients. Our patient only had a transient acceptable response to intravenous immunoglobulin while all other options failed to improve his platelet count. Concurrence of immune thrombocytopenic purpura and Kleine-Levin syndrome supports the role of autoimmunity as the proposed pathophysiologica mechnism of Kleine-Levin syndrome.
Meningococcal Serogroup B

"serogroup B disease notifications decreased by 27% from a peak in 2002 of 294 to 213 cases in 2007 (1.5 to 1.1 per 100,000 population)" before the vaccine was introduced.

https://www.health.gov.au/.../cda-cdi34suppl.htm~cda...

"Bexsero is not expected to provide protection against all circulating meningococcal group B strains"

Additionally, Kawasaki disease is listed as a complication which occurs in 1/1000<1/10,000. So a risk of 0.11/10,000 for men b, but in a best case scenario 1/10,000 for kawasaki disease and at least 1/10 risk for eating disorders, diarrhea, vomiting etc etc and the decision was easy to make for me. http://ec.europa.eu/.../20130114125155/anx_125155_en.pdf
**Immunogenicity and safety of an investigational multicomponent, recombinant, meningococcal serogroup B vaccine (4CMenB) administered concomitantly with routine infant and child vaccinations: results of two randomised trials.**


Source
University of Tampere Medical School, Tampere, Finland. timo.vesikari@uta.fi

Erratum in

Abstract

**BACKGROUND:**

Meningococcal serogroup B disease disproportionately affects infants. We assessed lot-to-lot consistency, safety and immunogenicity, and the effect of concomitant vaccination on responses to routine vaccines of an investigational multicomponent vaccine (4CMenB) in this population.

**METHODS:**

We did primary and booster phase 3 studies between March 31, 2008, and Aug 16, 2010, in 70 sites in Europe. We used two series of sponsor-supplied, computer-generated randomisation envelopes to allocate healthy 2 month-old infants to receive routine vaccinations (diphtheria-tetanus-acellular pertussis, inactivated poliovirus, hepatitis B plus Haemophilus influenzae type b, and seven-valent pneumococcal vaccine) at 2, 4, and 6 months of age alone, or concomitantly with 4CMenB or serogroup C conjugate vaccine (MenC) in: 1) an open-label, lot-to-lot immunogenicity and safety substudy of three 4CMenB lots compared with routine vaccines alone (1:1:1:1, block size eight); or 2) an observer-blind, lot-to-lot safety substudy of three 4CMenB lots compared with MenC (1:1:1:3, block size six). At 12 months, 4CMenB-primed children from either substudy were randomised (1:1, block size two) to receive 4CMenB booster, with or without measles-mumps-rubella-varicella (MMRV) vaccine. Immunogenicity was assessed by serum bactericidal assay with human complement (hSBA) against serogroup B test strains, and on randomly selected subsets of serum samples for routine vaccines; laboratory personnel were masked to assignment. The first coprimary outcome was lot-to-lot consistency (hSBA geometric mean ratio of all lots between 0.5 and 2.0), and the second was an immune response (hSBA titre ≥5) for each of the three strains. The primary outcome for the booster study was immune response to booster dose. Immunogenicity data for 4CMenB were for the modified intention-to-treat population, including all infants from the open-label substudy who provided serum samples. The safety population included all participants who contributed safety data after at least one dose of study vaccine. These trials are registered with ClinicalTrials.gov, numbers NCT00657709 and NCT00847145.
FINDINGS:

We enrolled 2627 infants in the open-label phase, 1003 in the observer-blind phase, and 1555 in the booster study. Lot-to-lot consistency was shown for the three 4CMenB lots, with the lowest 95% lower confidence limit being 0.74 and the highest upper limit being 1.33. Of 1181–1184 infants tested 1 month after three 4CMenB doses (all lots pooled), 100% (95% CI 99–100) had hSBA titres of 5 or more against strains selective for factor H binding protein and neisserial adhesin A, and 84% (82–86) for New Zealand outer-membrane vesicle. In a subset (n=100), 84% (75–91) of infants had hSBA titres of 5 or more against neisseria heparin binding antigen. At 12 months of age, waning titres were boosted by a fourth dose, such that 95–100% of children had hSBA titres of 5 or more for all antigens, with or without concomitant MMRV. Immune responses to routine vaccines were much the same with or without concomitant 4CMenB, but concomitant vaccination was associated with increased reactogenicity. 77% (1912 of 2478) of infants had fever of 38.5°C or higher after any 4CMenB dose, compared with 45% (295 of 659) after routine vaccines alone and 47% (228 of 490) with MenC, but only two febrile seizures were deemed probably related to 4CMenB.

INTERPRETATION:

4CMenB is immunogenic in infants and children aged 12 months with no clinically relevant interference with routine vaccines, but increases reactogenicity when administered concomitantly with routine vaccines. This breakthrough vaccine offers an innovative solution to the major remaining cause of bacterial meningitis in infant and toddlers.

FUNDING:

Novartis Vaccines and Diagnostics.

Measles-mumps-rubella vaccination induced thrombocytopenia: a case report and review of the literature.

Owatanapanich S, Wanlapakorn N, Tangsiri R, Poovorawan Y.

Abstract

Immune thrombocytopenia (ITP) is a disease with autoimmune destruction of platelets. ITP among children has been associated with viral infections and some vaccinations. We report a case of ITP after measles-mumps-rubella (MMR) vaccination in a 10-month-old male infant who presented with purpura and acute gastrointestinal bleeding. This case was successfully treated with corticosteroids and intravenous immunoglobulin. ITP is a rare complication of the MMR vaccine that physicians should be aware of.

Immune thrombocytopenic purpura: an autoimmune cross-link between infections and vaccines.

Rinaldi M¹, Perricone C, Ortega-Hernandez OD, Perricone R, Shoenfeld Y.

Author information

Abstract

Immune thrombocytopenic purpura (ITP) is an autoimmune systemic disease detectable by the presence of low blood platelets count (<10⁵/µl) and the production of autoantibodies against glycoproteins expressed on the platelet surface. The clinical course is often acute, and life-threatening events may occur especially in children, with 52% of paediatric patients recovering either spontaneously or after treatment. A chronic ITP evolution is observed in 64% of adults, of whom 12% will develop an overlapping autoimmune disease. Several microbial agents such as CagA-positive Helicobacter pylori or Candida albicans and a number of viruses including CMV, EBV or HIV can potentially trigger ITP through molecular mimicry. Moreover, ITP improves after treatment of the underlying infection.

Similarly, vaccines such as MMR may prompt ITP (IRR 5.48, 1.61-18.64, p < 0.006). Early recognition of the underlying microbial trigger and the removal of modifiable aetiopathogenetic factors should be integrated as a complementary treatment strategy in all patients who do not readily improve with standard ITP care.

KEYWORDS:

ASIA; Helicobacter pylori; Immune thrombocytopenic purpura; autoantibodies; autoimmune diseases; infections; vaccines

The risk of immune thrombocytopenic purpura after vaccination in children and adolescents.

O'Leary ST, Glanz JM, McClure DL, Akhtar A, Daley MF, Nakasato C, Baxter R, Davis RL, Izurieta HS, Lieu TA, Ball R.

Abstract

BACKGROUND:
The risk of immune thrombocytopenic purpura (ITP) after childhood vaccines other than measles-mumps-rubella vaccine (MMR) is unknown.

METHODS:
Using data from 5 managed care organizations for 2000 to 2009, we identified a cohort of 1.8 million children ages 6 weeks to 17 years. Potential ITP cases were identified by using diagnostic codes and platelet counts. All cases were verified by chart review. Incidence rate ratios were calculated comparing the risk of ITP in risk (1 to 42 days after vaccination) and control periods.

RESULTS:
There were 197 chart-confirmed ITP cases out of 1.8 million children in the cohort. There was no elevated risk of ITP after any vaccine in early childhood other than MMR in the 12- to 19-month age group. There was a significantly elevated risk of ITP after hepatitis A vaccine at 7 to 17 years of age, and for varicella vaccine and tetanus-diphtheria-acellular pertussis vaccine at 11 to 17 years of age. For hepatitis A, varicella, and tetanus-diphtheria-acellular pertussis vaccines, elevated risks were based on one to two vaccine-exposed cases. Most cases were acute and mild with no long-term sequelae.

CONCLUSIONS:
ITP is unlikely after early childhood vaccines other than MMR. Because of the small number of exposed cases and potential confounding, the possible association of ITP with hepatitis A, varicella, and tetanus-diphtheria-acellular pertussis vaccines in older children requires further investigation.

Thrombocytopenic purpura after measles-mumps-rubella vaccination: a systematic review of the literature and guidance for management.

Mantadakis E1, Farmaki E, Buchanan GR.

Abstract

OBJECTIVE: To determine the incidence of immune thrombocytopenic purpura (ITP) after measles-mumps-rubella (MMR) immunization compared with natural measles and rubella, its clinical course and outcome, and the risk of recurrence after repeat MMR vaccination.

STUDY DESIGN: We performed a systematic review of the Ovid MEDLINE (1950 to present) bibliographic database. We selected studies that reported cases of thrombocytopenia in a known number of children who were immunized with MMR vaccine before development of ITP. We also extracted data from the same and other studies regarding bleeding manifestations and the resolution of MMR-associated thrombocytopenia or thrombocytopenic purpura within 6 months. Finally, we studied the risk of ITP recurrence after MMR immunization or reimmunization.

RESULTS: On the basis of 12 studies, the incidence of MMR-associated ITP ranged from 0.087 to 4 (median 2.6) cases per 100,000 vaccine doses. Severe bleeding manifestations were rare, and MMR-associated thrombocytopenia resolved within 6 months from diagnosis in 93% of the children. MMR vaccination of unimmunized patients with ITP and revaccination of patients with prior ITP did not lead to recurrence of thrombocytopenia.

CONCLUSIONS: MMR-associated ITP is rare, self-limited, and non-life threatening, and susceptible children with ITP should be immunized with MMR at the recommended ages.

Vaccination associated thrombocytopenic purpura in children.

Rajantie J, Zeller B, Treutiger I, Rosthøj S; NOPHO ITP working group and five national study groups.

Abstract

Patients who presented with purpura and blood platelets <30x10^9/l within 1 month after vaccination were collected from a population based material of 506 consecutive pediatric patients with newly diagnosed ITP. Of the 35 such patients, 24 had thrombocytopenia after MMR vaccination giving an estimated ITP risk of approximately 1 in 30,000 MMR inoculations. Symptoms of the 35 patients were nearly always acute. Thrombocytopenia disappeared within a month in 74% of the study patients and lasted longer than 6 months in only 10%. Bleeding episodes were uncommon during the follow-up period. We conclude that the incidence of symptomatic thrombocytopenia after vaccinations is much lower than that after respective natural infections and that the outcome in most cases is excellent.

Immune thrombocytopenic purpura in childhood: a Lebanese perspective.

Moussalem M\textsuperscript{1}, Yassine N.

Author information

Abstract

Immune thrombocytopenic purpura (ITP), due to the production of antiplatelet antibodies, is the most prevalent etiology of thrombocytopenia in children and a frequent cause of consultation for the pediatrician. We review here a series of Lebanese pediatric patients presenting with ITP and we discuss the relevant characteristics of the group.

STUDY:

A retrospective chart analysis was performed for 40 hospitalized or outpatient children presenting with ITP between January 1998 and December 2001. All cases except two had a diagnosis confirmed by bone marrow aspirate. Patients were equally distributed between the sexes with a mean age of 56 months. More than half of the patients had an episode of fever 2 days to 8 weeks prior to the diagnosis. For 42\% of them, the disease appeared in the months between January and March. Ten percent presented with epistaxis but all of these had a platelet count less than 12,000. One-third of the patients had received immunization 2-8 weeks before the diagnosis, with one patient having a relapse 4 weeks after mumps-measles-rubella (MMR) immunization, which was 1 year after the initial cure. Initial treatment consisted of either steroids or intravenous polyvalent immunoglobulin in 58 and 36\% of the cases, respectively. None of the patients had life-threatening hemorrhage. Only 10\% of the patients developed chronic ITP (unremitting after 6 months).

CONCLUSION:

ITP is generally a benign disease in infancy and childhood. Certain characteristics of ITP in this series, such as the seasonal variation and the post-vaccine ITP, will need to be better defined in larger prospective studies. Optimal treatment will eventually be targeted towards a better delineation of the disease phenotype.

MMR vaccine and idiopathic thrombocytopenic purpura
Corri Black, 1, 2 James A Kaye, 2 and Hershel Jick 2

Abstract

Aims
To estimate the relationship between idiopathic thrombocytopenic purpura (ITP) and the measles, mumps and rubella (MMR) vaccination in children; calculating the relative risk estimate for ITP within 6 weeks after MMR vaccination and the attributable risk of ITP within 6 weeks after MMR vaccination.

Methods
Using the General Practice Research Database we identified children with a first-time diagnosis of ITP from a base population of children aged less than 6 years between January 1988 and December 1999. After describing the characteristics of all the children identified with ITP, we focused on cases aged 13–24 months to perform a population-based, case–control analysis to estimate the relative risk of developing ITP within 6 weeks after MMR vaccination. We also calculated the risk of ITP attributable to the MMR vaccination.

Results
Sixty-three children with a first time diagnosis of ITP were identified; 23 cases were between 13 and 24 months old. The relative risk estimate for ITP within 6 weeks after MMR vaccination, compared to the combined group of unvaccinated children and children vaccinated with MMR more than 26 weeks previously was 6.3 (95% CI 1.3–30.1). The attributable risk of developing ITP within 6 weeks after MMR vaccination was estimated to be 1 in 25 000 vaccinations (95% confidence interval 21 300, 89 400).

Conclusion
This study confirms the increased risk of ITP within 6 weeks after MMR vaccination. However, the attributable risk of ITP within 6 weeks after MMR vaccination is low.

Keywords: idiopathic thrombocytopenic purpura, MMR vaccine

http://www.ncbi.nlm.nih.gov/pmc/articles/PMC1884189/
Aseptic meningitis in a large MMR vaccine campaign (590,609 people) in Curitiba, Paraná, Brazil, 1998.

Arruda WO, Kondageski C.

Abstract

The aseptic meningitis after Measles-Mumps-Rubella vaccine (MMR) is a well recognized complication, and different incidences have been observed in several studies. We retrospectively analyzed forty cases of aseptic meningitis, during a large public immunization campaign (1998) in Curitiba, Southern Brazil (590,609 people), admitted in our Service. The vaccine utilized was Leningrad-3-Zagreb mumps strain, Edmonston-Zagreb measles strain, and RA 27#3 rubella strain. In all county, a total number of 87 cases were reported, resulting in an incidence of 1.7 cases per 10,000 given doses. The mean age was 23.7 +/- 12.8 years. The female:male ratio was 1.35:1. Severe headache with meningismus (92.5%), fever (87.5%), nausea/vomiting (82.5%) were the most common clinical findings. Three cases (7.5%) developed mild mumps. All patients underwent cerebrospinal fluid (CSF) tap with the following findings: mononuclear pleocytosis from 100 to 500 cells/mm(3) in 17 cases (42.5%; 257.5 +/- 260.6 cells/mm3); increased protein 28 cases (67.5%; 92.1 +/- 76.9 mg/dL); glucose was normal in all cases (56.8 +/- 11.2 mg/dL) except in 4 (10%) cases, which presented less than 44 mg/dL. All serological tests (latex to bacterial meningitis, Cryptococcus, cysticercosis, VDRL) and bacteriological cultures were negative. Virus identification were also negative in 8 samples. None of the patients had neurological deficits or related symptoms after one year of onset. We believe the benefit of vaccination clearly outweighs the incidence of benign vaccine-associated meningitis.


Comment [A34]: Despite the authors being in favour of vaccination, the rate of meningitis is 1.7 cases per 10,000 doses. With multiple doses the risk of meningitis is thus increased per patient. This must be weighed against the risk of catching the disease and the fact that MMR is now given to infants multiple times. In this case this was on fully developed adults and no long-term negative effects were observed. This may be different in infants whose brains are not fully developed.

The number of AM cases as greatly increased following the campaign: "A total number of 87 cases was reported, giving an incidence of vaccine-associated meningitis in our study of 1.7 per 10,000 doses. Forty patients out of the 87 cases of post-vaccination AM were admitted to our Service, giving an annual prevalence rate of 29/1,000 cases, in comparison with an average annual rate of 5/1,000 rate in other years (from 1994 to 1997)."
Idiopathic thrombocytopenic purpura and MMR vaccine


Author Affiliations

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Dr Miller e.miller@phls.co.uk

Accepted 11 April 2000

Abstract

A causal association between measles mumps–rubella (MMR) vaccine and idiopathic thrombocytopenic purpura (ITP) was confirmed using immunisation/hospital admission record linkage. The absolute risk within six weeks of immunisation was 1 in 22,300 doses, with two of every three cases occurring in the six week post-immunisation period being caused by MMR. Children with ITP before MMR had no vaccine associated recurrences.

http://adc.bmj.com.simsrad.net.ocs.mq.edu.au/content/84/3/227.full
Toxic epidermal necrolysis following morbilli-parotitis-rubella vaccination.

Dobrosavljevic D¹, Milinkovic MV, Nikolic MM.

Author information

Abstract

We present the first reported case of toxic epidermal necrolysis (TEN) caused by morbilli-parotitis-rubella (MPR) vaccine. A 13-year-old girl developed TEN 7 days after she received live, attenuated, triple MPR vaccine. The history of drug intake and any illness was negative. At admission the patient was acutely ill with high fever. The whole body was erythematous. The epidermis was wrinkled and the Nikolsky sign was positive. Numerous erosions were present on the lips and genital region. On the seventh day of illness, the eruption involved 80% of the skin. Systemic corticosteroid therapy was not employed. The skin and mucosal defects completely epithelized by the end of the third week of illness. Mild keratoconjunctivitis sicca remained because of permanent cup cell damage.

http://www.ncbi.nlm.nih.gov/pubmed/?term=Toxic+epidermal+necrolysis+following+morbilli-parotitis-rubella+vaccination
Pancreatitis caused by measles, mumps, and rubella vaccine.

Adler JB¹, Mazzotta SA, Barkin JS.

**Author information**

**Abstract**

Acute pancreatitis may result from viral infections, including mumps, coxsackie B, Epstein-Barr, and varicella. However, viral pancreatitis has not been reported after immunization with viral vaccines. We report the occurrence of acute pancreatitis in an adult who had received measles, mumps, and rubella II vaccine (MMR II).

Risk of febrile seizure after measles-mumps-rubella-varicella vaccine: A systematic review and meta-analysis.

Ma SJ¹, Xiong YQ¹, Jiang LN¹, Chen Q².

Abstract

BACKGROUND: Considering the febrile seizure rate, there is no longer a clear preference for use of measles-mumps-rubella-varicella (MMRV) vaccine over separate measles-mumps-rubella (MMR) and varicella (V) vaccine. This work was undertaken to assess the risk of febrile seizure after MMRV vaccine in children.

METHODS: We searched PubMed, Embase, BIOSIS Previews, Scopus, Web of Science, Cochrane Library and other databases through 12 December 2014. Meta-analysis was conducted using R version 3.1.2 and Stata version 12.0.

RESULTS: A total of thirty-nine studies were included. Thirty-one published or unpublished clinical trials involving about 40,000 subjects did not show significant differences in incidence of febrile seizure or vaccine related febrile seizure between MMRV and MMR with or without varicellavaccine after any doses, in the risk windows of 0-28, 0-42 or 0-56 days and 7-10 days. In addition, these studies showed that the receipt of concomitant use of MMRV and other pediatric vaccines was not a significant predictor of febrile seizure. Eight post-marketing observations involving more than 3,200,000 subjects were included. No evidence suggested elevated risk of febrile seizure associated with MMRV vaccine among children aged 4-6 years old during 7-10 days or 0-42 days after vaccination. However, an approximately 2-fold increase in risk of seizure or febrile seizure during 7-10 days or 5-12 days after MMRV vaccination was found among children aged 10-24 months, although the highest incidence of seizure was still lower than 2.95‰.

CONCLUSIONS: First MMRV vaccine dose in children aged 10-24 months was associated with an elevated risk of seizure or febrile seizure. Further post-marketing restudies based on more rigorous study design are needed to confirm the findings.

KEYWORDS: Febrile seizure; Measles–mumps–rubella–varicella vaccine; Meta-analysis; Post-marketing observation; Randomized controlled trial

Analysis of safety data in children after receiving two doses of ProQuad® (MMRV).

**METHODS:**
Safety data from five clinical studies were combined for all children who were scheduled to receive two doses of MMRV ~3-6 months apart. All vaccinated children were followed for safety following each dose of MMRV.

**RESULTS:**
Of 3112 children who received a first dose of MMRV, 2780 (89.3%) received a second dose of MMRV. Overall, 70.5% and 57.7% of children reported ≥1 adverse experiences following first and second doses of MMRV, respectively. Injection-site redness was statistically significantly higher postdose 2 than postdose 1, while injection-site pain/tenderness was statistically significantly higher postdose 1 compared to postdose 2. Rashes were statistically significantly lower postdose 2 compared to postdose 1. Ten febrile seizures (8 postdose 1, 2 postdose 2) were reported following MMRV vaccination. The incidence of febrile seizures postdose 1 of MMRV was 0.26% (8/3019) compared to 0.07% (2/2695) postdose 2 of MMRV.

**CONCLUSIONS:**
Administration of two doses of MMRV has an acceptable safety profile in children 12 to 23 months of age. There is a small increase in the risk of febrile seizures following the first dose of MMRV as compared to the component vaccines, but the risk for any individual child is relatively low.

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**KEYWORDS:**
Integrated analyses; MMRV; NCT00109343; NCT00312858; NCT00326183; NCT00975507; NCT00986232; ProQuad®; Safety; Tolerability
Measles-containing vaccines and febrile seizures in children age 4 to 6 years.


Abstract

BACKGROUND:

In the United States, children receive 2 doses of measles-mumps-rubella vaccine (MMR) and varicella vaccine (V), the first between ages 1 to 2 years and the second between ages 4 to 6 years. Among 1- to 2-year-olds, the risk of febrile seizures 7 to 10 days after MMRV is double that after separate MMR + V. Whether MMRV or MMR + V affects risk for febrile seizure risk among 4- to 6-year-olds has not been reported.

METHODS:

Among 4- to 6-year-old Vaccine Safety Datalink members, we identified seizures in the emergency department and hospital from 2000 to 2008 and outpatient visits for fever from 2006 to 2008 during days 7 to 10 and 0 to 42 after MMRV and MMR + V. Incorporating medical record reviews, we assessed seizure risk after MMRV and MMR + V.

RESULTS:

From 2006 through 2008, 86 750 children received MMRV; from 2000 through 2008, 67 438 received same-day MMR + V. Seizures were rare throughout days 0 to 42 without peaking during days 7 to 10. There was 1 febrile seizure 7 to 10 days after MMRV and 0 after MMR + V. Febrile seizure risk was 1 per 86 750 MMRV doses (95% confidence interval, 1 per 3 426 441, 1 per 15 570) and 0 per 67 438 MMR + V doses (1 per 18 282).

CONCLUSIONS:

This study provides reassurance that MMRV and MMR + V were not associated with increased risk of febrile seizures among 4- to 6-year-olds. We can rule out with 95% confidence a risk greater than 1 febrile seizure per 15 500 MMRV doses and 1 per 18 000 MMR + V doses.

http://www.ncbi.nlm.nih.gov/pubmed/?term=Measles-containing+vaccines+and+febrile+seizures+in+children+age+4+to+6+years

Comment [A41]: Although it is higher amongst younger age groups when the first dose is given.
Mumps


Published online Jun 18, 2010. doi: 10.1007/s10552-010-9546-1

Daniel W. Cramer, Allison F. Vitonis, Simone P. Pinheiro, John R. McKolanis, Raina N. Fichorova, Kevin E. Brown, Todd F. Hatchette, and Olivera J. Finn

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Abstract

Background

Epidemiologic studies found childhood mumps might protect against ovarian cancer. To explain this association, we investigated whether mumps might engender immunity to ovarian cancer through antibodies against the cancer-associated antigen MUC1 abnormally expressed in the inflamed parotid gland.

Methods

Through various health agencies, we obtained sera from 161 cases with mumps parotitis. Sera were obtained from 194 healthy controls. We used an ELISA to measure anti-MUC1 antibodies and electro-chemiluminescence assays to measure MUC1 and CA 125. Log-transformed measurements were analyzed by t-tests, generalized linear models, and Pearson or Spearman correlations. We also conducted a meta-analysis of all published studies regarding mumps and ovarian cancer.

Results

Adjusting for assay batch, age, and sex, the level of anti-MUC1 antibodies was significantly higher in mumps cases compared to controls (p = 0.002). Free circulating levels of CA 125, but not MUC1, were also higher in cases (p = 0.02). From the meta-analysis, the pooled odds ratio estimate (and 95% CI) for the mumps and ovarian cancer association was 0.81 (0.68–0.96) (p = 0.01).

Conclusion
Mumps parotitis may lead to expression and immune recognition of a tumor-associated form of MUC1 and create effective immune surveillance of ovarian cancer cells that express this form of MUC1.

**Keywords:** Ovarian cancer, Mumps parotitis, MUC1, CA125

http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2951028/
Mumps vaccine associated orchitis: Evidence supporting a potential immune-mediated mechanism.

Clifford V1, Wadsley J, Jenner B, Buttery JP.

Author information

Abstract

We report 3 cases of orchitis following vaccination with mumps-measles-rubella (MMR) vaccine, two with an onset within 3 days following vaccination. Orchitis is a common complication of mumps infection, particularly in post-pubertal males, and is also recognized as a very rare complication of mumps vaccination. These cases, discussed together with a comprehensive review of the existing literature regarding post-vaccine orchitis, highlight uncertainty regarding the pathogenesis of post-vaccine orchitis.

A comparative study of the incidence of aseptic meningitis in symptomatic natural mumps patients and monovalent mumps vaccine recipients in Japan.


Abstract
To compare the incidence of aseptic meningitis associated with symptomatic natural mumps infection and in mumps vaccine recipients, we conducted a prospective comparative study. Consecutive samples of 1051 children with mumps were enrolled by 10 pediatricians and 21,465 vaccine recipients by 143 pediatric primary care practitioners, from January 1, 2000 to January 1, 2003. Parents used a daily diary to record symptoms during the period of illness (15 days) or 30-day period following immunization. Mumps infection was confirmed by virus isolation and/or detection of mumps virus genome in salivary and CSF samples. The incidence of aseptic meningitis was 13/1051 (1.24%) in patients with symptomatic natural mumps infection and was estimated to be 0.7-1.1% of overall infection in considering asymptomatic infection, and 10/21,465 (0.05%) in vaccine recipients. Although aseptic meningitis is a clear side effect of the mumps vaccine, the incidence is considerably lower than among those with symptomatic natural infection. Our results provide an informative data for consideration to resume mumps vaccine as a part of routine immunization schedule for Japanese children.

Pancreatitis complicating adult immunisation with a combined mumps measles rubella vaccine. A case report and literature review.

Toovey S¹, Jamieson A²

Abstract

We report a case of pancreatitis and parotitis in an adult male following immunisation with a trivalent mumps-measles-rubella vaccine. Presentation was 21 days after vaccination, with the patient making a full recovery without intervention. A literature review revealed only five other such cases, with the Urabe strain of attenuated mumps virus appearing to be disproportionately represented. The Urabe vaccine strain has been withdrawn in some countries as it has been implicated disproportionately in the genesis of post-vaccination aseptic meningitis. Temporal separation of pancreatitis onset from vaccination raises the possibility that pancreatitis as a complication of mumps vaccination is under reported.

Vaccine, 2001 Jan 8;19(11-12):1353-5.

Mumps vaccine virus genome is present in throat swabs obtained from uncomplicated healthy recipients.

Nagai T, Nakayama T.

Author information

Abstract

Seven children were followed for up to 42 days post-vaccination with live mumps vaccine and 37 throat swabs were obtained serially. Viral genomic RNA was detected by reverse transcription-polymerase chain reaction (RT-PCR) in the phosphoprotein (P) and hemagglutinin-neuraminidase (HN) regions. Virus isolation was also attempted. Genomic differentiation of detected mumps virus genome was performed by sequence analysis and/or restriction fragment length polymorphism (RFLP). No adverse reaction was observed in these children. Although mumps virus was not isolated from any of the samples, viral RNA was detected in four samples from three vaccine recipients, 18, 18 and 26, and 7 days after vaccination, respectively. Detected viral RNA was identified as the vaccine strain. Our data suggests that vaccine virus inoculated replicates in the parotid glands but the incidence of virus transmission from recipients to other susceptible subjects should be low.


Comment [A43]: Mumps virus may be present following vaccination although viral transmission is low.
Infantile acute pancreatitis after mumps vaccination simulating an acute abdomen.

Feldman G\textsuperscript{1}, Zer M.

Author information

Abstract

We describe an extremely rare case of acute pancreatitis presenting as an acute abdomen that appeared as a complication of mumps vaccination in a young child. A laparotomy performed because of suspected perforated appendicitis proved unnecessary in retrospect. No similar case in infancy and early childhood has been reported to date.

Aseptic meningitis as a complication of mumps vaccination.

Sugiura A, Yamada A.

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.


Comment [A44]: Mumps vaccination was suspended in Japan following this.
Pertussis (Whooping Cough) [DTaP]

It is plausible that the recent increase in the incidence of pertussis is at least partly related to the change from whole cell to acellular vaccine. The latter causes fewer adverse events and is well tolerated by adults, but provides less prolonged, narrower spectrum\(^1\) immunity. There is evidence that the current, circulating strains of *Bordetella pertussis* have changed since the introduction of acellular vaccine and they express antigens that differ from those contained in the vaccine\(^1\).

\(^1\) Whole cell vaccines contain numerous poorly defined antigens, in addition to the main "protective" antigens. These additional antigens were responsible for much of the excess reactogenicity, but also probably acted as adjuvants, leading to enhanced immune responses to specific protective antigens (probably including different alleles from those in the vaccine strain, such as those in *Bordetella pertussis* strains that are currently circulating).
Substantial gaps in knowledge of Bordetella pertussis antibody and T cell epitopes relevant for natural immunity and vaccine efficacy.

Vaughan K¹, Seymour E², Peters B², Sette A².

Author information

Abstract

The recent increase in whooping cough in vaccinated populations has been attributed to waning immunity associated with the acellular vaccine. The Immune Epitope Database (IEDB) is a repository of immune epitope data from the published literature and includes T cell and antibody epitopes for human pathogens. The IEDB conducted a review of the epitope literature, which revealed 300 Bordetella pertussis-related epitopes from 39 references. Epitope data are currently available for six virulence factors of B. pertussis: pertussis toxin, pertactin, fimbrial 2, fimbrial 3, adenylate cyclase and filamentous hemagglutinin. The majority of epitopes were defined for antibody reactivity; fewer T cell determinants were reported. Analysis of available protective correlates data revealed a number of candidate epitopes; however few are defined in humans and few have been shown to be protective. Moreover, there are a limited number of studies defining epitopes from natural infection versus whole cell or acellular/subunit vaccines. The relationship between epitope location and structural features, as well as antigenic drift (SNP analysis) was also investigated. We conclude that the cumulative data is yet insufficient to address many fundamental questions related to vaccine failure and this underscores the need for further investigation of B. pertussis immunity at the molecular level.

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Effectiveness and cost-effectiveness of different immunization strategies against whooping cough to reduce child morbidity and mortality.

Rivero-Santana A¹, Cuéllar-Pompa L², Sánchez-Gómez LM³, Perestelo-Pérez L⁴, Serrano-Aguilar P⁵.

Author information

Abstract

INTRODUCTION:
In the last years there has been a significant increase in reported cases of pertussis in developed countries, in spite of high rates of childhood immunization. Health institutions have recommended different vaccination strategies to reduce child morbidity and mortality: vaccination of adolescents and adults, pregnant women, people in contact with the newborn (cocoon strategy) and health care workers. The aim of this paper is to review the scientific evidence supporting these recommendations.

METHODS:
Systematic review on the effectiveness and cost-effectiveness of the above strategies for the reduction of morbidity and mortality from pertussis in infants under 12 months. The electronic databases Medline, PreMedline, Embase, CRD, Cochrane Central, and Trip Database were consulted from 1990 to October 2012. The evidence was assessed using the GRADE system.

RESULTS:
There were eight studies on the efficacy or safety of the strategies analyzed, and 18 economic evaluations. Direct evidence on the efficacy of these strategies is scarce. Economic evaluations suggest that vaccination of adolescents and adults would be cost-effective, although there is major uncertainty over the parameters used.

CONCLUSIONS:
From the perspective of health technology assessment, there is insufficient evidence to recommend the vaccination strategies evaluated.

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KEYWORDS:
Adolescent, Adult, Diphtheria–tetanus–pertussis vaccine, Health personnel, Immunization, Whooping cough

Acellular pertussis vaccines protect against disease but fail to prevent infection and transmission in a nonhuman primate model.

Warfel JM, Zimmerman LI, Merkel TJ.

Author information

Abstract

Pertussis is a highly contagious respiratory illness caused by the bacterial pathogen Bordetella pertussis. Pertussis rates in the United States have been rising and reached a 50-y high of 42,000 cases in 2012. Although pertussis resurgence is not completely understood, we hypothesize that current acellular pertussis (aP) vaccines fail to prevent colonization and transmission. To test our hypothesis, infant baboons were vaccinated at 2, 4, and 6 mo of age with aP or whole-cell pertussis (wP) vaccines and challenged with B. pertussis at 7 mo. Infection was followed by quantifying colonization in nasopharyngeal washes and monitoring leukocytosis and symptoms. Baboons vaccinated with aP were protected from severe pertussis-associated symptoms but not from colonization, did not clear the infection faster than naïve animals, and readily transmitted B. pertussis to unvaccinated contacts. Vaccination with wP induced a more rapid clearance compared with naïve and aP-vaccinated animals. By comparison, previously infected animals were not colonized upon secondary infection. Although all vaccinated and previously infected animals had robust serum antibody responses, we found key differences in T-cell immunity. Previously infected animals and wP-vaccinated animals possess strong B. pertussis-specific T helper 17 (Th17) memory and Th1 memory, whereas aP vaccination induced a Th1/Th2 response instead. The observation that aP, which induces an immune response mismatched to that induced by natural infection, fails to prevent colonization or transmission provides a plausible explanation for the resurgence of pertussis and suggests that optimal control of pertussis will require the development of improved vaccines.

KEYWORDS:

IL-17, T-cell memory, adaptive immunity, animal models, whooping cough

Acellular pertussis vaccination facilitates *Bordetella parapertussis* infection in a rodent model of bordetellosis

Gráinne H. Long, Alexia T. Karanikas, Eric T. Harvill, Andrew F. Read, and Peter J. Hudson

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This article has been cited by other articles in PMC.

Go to: Abstract

Despite over 50 years of population-wide vaccination, whooping cough incidence is on the rise. Although *Bordetella pertussis* is considered the main causative agent of whooping cough in humans, *Bordetella parapertussis* infections are not uncommon. The widely used acellular whooping cough vaccines (aP) are comprised solely of *B. pertussis* antigens that hold little or no efficacy against *B. parapertussis*. Here, we ask how aP vaccination affects competitive interactions between *Bordetella* species within co-infected rodent hosts and thus the aP-driven strength and direction of in-host selection. We show that aP vaccination helped clear *B. pertussis* but resulted in an approximately 40-fold increase in *B. parapertussis* lung colony-forming units (CFUs). Such vaccine-mediated facilitation of *B. parapertussis* did not arise as a result of competitive release; *B. parapertussis* CFUs were higher in aP-relative to sham-vaccinated hosts regardless of whether infections were single or mixed. Further, we show that aP vaccination impedes host immunity against *B. parapertussis*—measured as reduced lung inflammatory and neutrophil responses. Thus, we conclude that aP vaccination interferes with the optimal clearance of *B. parapertussis* and enhances the performance of this pathogen. Our data raise the possibility that widespread aP vaccination can create hosts more susceptible to *B. parapertussis* infection.

Keywords: pathogen evolution, *Bordetella parapertussis*, disease, acellular vaccination, epidemiology, co-infection

http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2880100/
Pertussis epidemic despite high levels of vaccination coverage with acellular pertussis vaccine.

Authors
Sala-Farré MR, et al. Show all

Journal

Affiliation
Unitat de Vigilància Epidemiològica Vallès Occidental i Vallès Oriental, Public Health Agency of Catalonia, Sant Cugat del Vallès, Barcelona, Spain. Electronic address: mrosa.salaf@gencat.cat.

Abstract
INTRODUCTION: We describe the pertussis epidemic, based only on confirmed whooping cough cases. We have analyzed data on the diagnosis, epidemiology and vaccine history in order to understand the factors that might explain the trends of the disease.

METHODS: A descriptive study of the confirmed pertussis cases reported during 2011 in the Vallès region (population 1,283,000). Laboratory criteria for confirmed pertussis cases include isolation of Bordetella pertussis from a clinical specimen or detection of B. pertussis by PCR in nasopharyngeal swabs.

RESULTS: A total of 421 pertussis confirmed cases were reported, which was the highest incidence reported in the last decade (33 cases/100,000 people/year in 2011). The highest incidence rate was among infants less than 1 year old (448/100,000), followed by children 5-9 years old (154/100,000). Pertussis cases aged 2 months-1 year were 90% vaccinated following the current DTaP schedule for their age group in Catalonia, and cases of 5-9 years were 87% fully vaccinated with 5 doses of DTaP vaccine. There were no deaths, although 8% of cases were hospitalized. Pertussis was more severe in infants, 30% required hospitalization despite having received the vaccine doses corresponding to their age. Children of 5-9 years were most often identified as primary cases in households or school clusters.

CONCLUSION: Despite high levels of vaccination coverage, pertussis circulation cannot be controlled at all. The results question the efficacy of the present immunization programmes.

Pertussis Infection in Fully Vaccinated Children in Day-Care Centers, Israel

Isaac Srugo*, Daniel Benilevi*, Ralph Madeb*, Sara Shapiro†, Tamy Shohat‡, Eli Somekh§, Yossi Rimmar*, Vladimir Gershtein†, Rosa Gershtein*, Esther Marva¶, and Nitza Lahat†

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Abstract

We tested 46 fully vaccinated children in two day-care centers in Israel who were exposed to a fatal case of pertussis infection. Only two of five children who tested positive for Bordetella pertussis met the World Health Organization's case definition for pertussis. Vaccinated children may be asymptomatic reservoirs for infection.

Conclusion

The effects of whole-cell pertussis vaccine wane after 5 to 10 years, and infection in a vaccinated person causes nonspecific symptoms (3-7). Vaccinated adolescents and adults may serve as reservoirs for silent infection and become potential transmitters to unprotected infants (3-11). The whole-cell vaccine for pertussis is protective only against clinical disease, not against infection (15-17). Therefore, even young, recently vaccinated children may serve as reservoirs and potential transmitters of infection.

Children who were seropositive and remained both asymptomatic and PCR negative probably had sufficient immunity from vaccines or natural boosters to protect them against persistent colonization and clinical disease. Their seropositivity could not be due to vaccine because the children were tested more than a year after having been vaccinated. Yet not all the children were protected from infection and from colonization with the bacteria. Whether a child who is serologically or PCR positive for pertussis and is clinically asymptomatic is a potential transmitter of infection has not been established. What is certain, however, is that vaccine-induced immunity against infection does not persist throughout adulthood. In France, booster vaccinations have been recommended for adolescents and teenagers (18). We found that immunity does not even persist into early childhood in some cases. We also observed that DPT vaccine does not fully protect children against the level of clinical disease defined by WHO. Our results indicate that children ages 5-6 years and possibly younger, ages 2-3 years, play a role as silent reservoirs in the transmission of pertussis in the community. More studies are needed to find the immunologic basis of protection against infection and colonization and thus an effective way to eradicate pertussis.

http://wwwnc.cdc.gov/eid/article/6/5/00-0512_article.htm
Pneumococcal Disease


Five winters of pneumococcal serotype replacement in UK carriage following PCV introduction.
Gladstone RA1, Jefferies JM2, Tocheva AS1, Beard KR1, Garley D1, Chong WW1, Bentley SD3, Faust SN4, Clarke SC5.

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Abstract

The seven-valent pneumococcal conjugate vaccine (PCV7) was added to the UK national immunisation programme in September 2006. PCV13 replaced PCV7 in April 2010. As carriage precedes disease cases this study collected carried pneumococci from children each winter from 2006/7 to 2010/11 over PCV introduction. Conventional microbiology and whole genome sequencing were utilised to characterise pneumococcal strains. Overall prevalence of pneumococcal carriage remained stable. Vaccine serotypes (VT) decreased (p<0.0001) with concomitant increases in non-vaccine serotypes (NVT). In winter 2010/11 only one isolate of PCV7 VT was observed (6B). PCV13 unique VTs decreased between winters immediately preceding and following PCV13 introduction (p=0.04). Significant decreases for VTs 6B, 19F, 23F (PCV7) and 6A (PCV13) and increases for NVT 21, 23B, 33F and 35F were detected. Serotype replacement was accompanied by parallel changes in genotype prevalence for associated sequence types with clonal expansion contributing to replacement. By winter 2010/11, serotype coverage of PCV7 and PCV13 was 1% and 11% respectively. VT replacement was observed for PCV7 and PCV13 serotypes. Conjugate vaccine design and use requires continuous monitoring and revision.

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KEYWORDS:
Next generation sequencing; Pneumococcal vaccines; Serotype replacement; Streptococcus pneumoniae; Whole genome

A 4-month-old baby presenting with dermal necrotizing granulomatous giant cell reaction at the injection site of 13-valent pneumococcal conjugate vaccine: a case report.

Alsuwaidi AR, Albawardi A, Khan NH, Souid AK.

Author information

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Abstract

**INTRODUCTION:**

Adjuvants (for example, aluminum salts) are frequently incorporated in licensed vaccines to enhance the host immune response. Such vaccines include the pneumococcal conjugate, combinations of diphtheria-tetanus/acellular pertussis, tetanus-diphtheria/acellular pertussis, hepatitis B, some Haemophilus influenzae type b, hepatitis A, and human papillomavirus. These preparations have been associated with complicated local adverse events, especially if administered subcutaneously or intradermally in comparison to deep intramuscular injection. We describe a severe inflammatory reaction at the site of an injection of 13-valent pneumococcal conjugate vaccine.

**CASE PRESENTATION:**

A 4-month-old Arab baby boy developed dermal necrotizing granulomatous giant cell reaction at the injection site (right anterior thigh) of the second dose of 13-valent pneumococcal conjugate vaccine. Ziehl-Neelsen and periodic-acid Schiff were negative. This reaction probably resulted from improper intramuscular administration because the first (at 2 months of age) and third (at 10 months of age) doses were uneventful.

**CONCLUSIONS:**

Dermal necrotizing granulomatous reactions are a serious complication of the 13-valent pneumococcal conjugate vaccine. Health care providers need to administer this preparation deeply into a muscle mass. Completing the vaccine series is an acceptable option. Physicians are encouraged to report their experience with completing vaccine series following adverse events.

**Vaccine**, 2014 May 6. [Epub ahead of print]

**Effects of 7-valent pneumococcal conjugate 1 vaccine on the severity of adult 2 bacteremic pneumococcal pneumonia**

- Amelieke J.H. Cremers,
- Jacques F. Meis,
- Grietje Walraven,
- Christa E. van der Gaast-de Jong,
- Gerben Ferwerda,
- Peter W.M. Hermans

[http://dx.doi.org/10.1016/j.vaccine.2014.04.089](http://dx.doi.org/10.1016/j.vaccine.2014.04.089)

**Highlights**

- Introduction of pediatric PCV7 reduced adult pneumococcal pneumonia prevalence.
- After PCV7 introduction serotypes 1 and 7F occurred more frequent in adult pneumonia.
- After PCV7 introduction pneumonia was more often accompanied with pleural effusion.
- Pediatric PCV7 did also affect disease severity of adult pneumococcal pneumonia.
- PCV10 introduction will further change the clinical manifestation of adult pneumonia.

**Abstract**

*Purpose*

The introduction of a 7-valent conjugate pneumococcal vaccine (PCV7) in children largely affected the prevalence of adult pneumococcal pneumonia. In this study we investigated whether the clinical severity of adult bacteremic pneumococcal pneumonia has also altered following the introduction of pediatric PCV7 vaccination.
**Methods**

Adults hospitalized with bacteremic pneumococcal pneumonia between 2001 and June 2011 at two Dutch hospitals were included retrospectively. Clinical data on patient characteristics, comorbidities and severity of disease were obtained and pneumococcal serotypes were determined.

**Results**

Among 343 patients investigated, those infected with PCV7 serotypes had a higher PSI score ($p = 0.0072$) and mortality rate ($p = 0.0083$) compared with the remainder of the cohort. Since the introduction of PCV7 the proportion of pneumococcal pneumonias caused by serotypes 1 and 7F ($p$-values 0.037 and 0.025) increased, as well as the rate of pleural effusion and empyema ($p$-values 0.011 and 0.049). Whilst the proportion of adults infected with PCV7 serotypes decreased after the introduction of PCV7 ($p = 0.015$), PSI scores in these patients remained higher ($p = 0.030$), although mortality rates between PCV7 and non PCV7 types equalized. After the introduction of PCV7 a marked shortening in hospital stay was observed only among patients infected with non PCV7 serotypes ($p = 0.019$).

**Conclusions**

After pediatric PCV7 vaccination, adult bacteremic pneumococcal pneumonia was more frequently caused by serotype 1 or 7F and pleural effusion occurred more often. Although PSI scores remained higher among adults infected with PCV7 serotypes, mortality rates equalized between PCV7 and non PCV7 types alongside shortening of hospital stay in patients infected with PCV7 serotypes.


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Comment [A345]: “After introduction of PCV7 we observed higher rates of pleural effusion and empyema, which are generally interpreted as more severe manifestations of pneumonia.”

“Exclusively for patients infected with non PCV7 serotypes a marked decrease in length of hospital stay was observed after the introduction of vaccination.”
**Systemic inflammatory reaction after pneumococcal vaccine: a case series.**

*Hum Vaccin Immunother.* 2014 Mar 18;10(6). [Epub ahead of print]

**von Elten KA¹, Duran LL², Banks TA¹, Collins LC².**

**Abstract**

**Background:** Fever, leukocytosis, and large local reactions following the pneumococcal polysaccharide vaccine (PS23) have been described only in isolated case reports in the adult literature. Such atypical reactions can pose difficulty to providers when determining management. Patients experiencing this non infectious reaction may receive unnecessary treatment if the diagnosis of robust inflammatory response to the PS23 vaccine is not considered. **Observations:** This is a clinical case series of five adult patients who received the influenza and PS23 vaccines and experienced a cellulitis-like reaction, fever, and leukocytosis in the days following vaccination. Four of the five patients received the influenza and PS23 vaccines in the same arm. The patient who received the vaccines in opposite arms had the local findings in the arm that received the PS23 vaccine. All five patients sought care and four were admitted to the hospital for observation or treatment with intravenous antibiotics. **Conclusions:** This case series highlights potential side effects of the PS23 vaccine that are not well described in the adult literature. Antibiotics were not helpful in treating these patients' local and systemic symptoms. Patients with histories consistent with that highlighted in this case series may avoid antibiotics and hospitalization if their providers recognize these symptoms as a non-infectious reaction to the PS23 vaccine.

**KEYWORDS:**

Pneumococcal polysaccharide vaccine, local vaccine reaction, systemic inflammatory vaccine reaction

Changes in nasopharyngeal carriage of Streptococcus pneumoniae, Haemophilus influenzae and Moraxella catarrhalis among healthy children attending a day-care centre before and after official financial support for the 7-valent pneumococcal conjugate vaccine and H. influenzae type b vaccine in Japan.

Oikawa J¹, Ishiwada N², Takahashi Y³, Hishiki H³, Nagasawa K³, Takahashi S³, Watanabe M⁴, Chang B⁵, Kohno Y³.

Abstract

The 7-valent pneumococcal conjugate vaccine (PCV7) and Haemophilus influenzae type b (Hib) vaccine reduce nasopharyngeal carriage of vaccine-type bacteria, which may in turn influence the presence of other nasopharyngeal bacterial pathogens. To investigate this possibility, nasopharyngeal carriage of potential pathogens was examined before and after official financial support was provided to offer the PCV7 and Hib vaccines in healthy children attending a day care centre in Japan during 2011-2012. Despite a virtual disappearance of PCV7 serotypes over time, the overall pneumococcal carriage rate remained unchanged. Although others have reported an increase in PCV13 serotypes following PCV7 vaccination, only non-PCV13 serotypes were observed to have increased in this study. The majority of H. influenzae isolates were non-typeable and Hib was not found. Our data identified an unexpected pattern of pneumococcal serotype replacement following PCV7. Continuous monitoring of pneumococcal carriage is important for decisions regarding the future of national vaccination policy in Japan.

http://www.ncbi.nlm.nih.gov/pubmed/?term=Changes+in+nasopharyngeal+carriage+of+Streptococcus+pneumoniae%2C+Haemophilus+influenzae+and+Moraxella+catarrhalis+among+healthy+children+attending+a+day-care+centre+before+and+after+official+financial+support+for+the+7-valent+pneumococcal+conjugate+vaccine+and+H.+influenzae+type+b+vaccine+in+Japan
COMMENTS

Polio programme: let us declare victory and move on

Neetu Vashisht, Jacob Puliye

Abstract
It was hoped that following polio eradication, immunisation could be stopped. However the synthesis of polio virus in 2002, made eradication impossible. It is argued that getting poor countries to expend their scarce resources on an impossible dream over the last 10 years was unethical.

Furthermore, while India has been polio-free for a year, there has been a huge increase in non-polio acute flaccid paralysis (NPAFP). In 2011, there were an extra 47,500 new cases of NPAFP. Clinically indistinguishable from polio paralysis but twice as deadly, the incidence of NPAFP was directly proportional to doses of oral polio received. Though this data was collected within the polio surveillance system, it was not investigated. The principle of primum-non-nocere was violated.

The authors suggest that the huge bill of US$ 8 billion spent on the programme, is a small sum to pay if the world learns to be wary of such vertical programmes in the future.

Respiratory Syncytial Virus (RSV) – Vaccine under-development

A.D.A.M. Medical Encyclopedia.

Respiratory syncytial virus (RSV)

RSV; Palivizumab; Respiratory syncytial virus immune globulin

Last reviewed: February 21, 2013.

Respiratory syncytial virus (RSV) is a very common virus that leads to mild, cold-like symptoms in adults and older healthy children. It can be more serious in young babies, especially those in certain high-risk groups.

Causes, incidence, and risk factors

RSV is the most common germ that causes lung and airway infections in infants and young children. Most infants have had this infection by age 2. Outbreaks of RSV infections most often begin in the fall and run into the spring.

The infection can occur in people of all ages. The virus spreads through tiny droplets that go into the air when a sick person blows their nose, coughs, or sneezes.

You can catch RSV if:

- A person with RSV sneezes, coughs, or blows their nose near you
- You touch, kiss, or shake hands with someone who is infected by the virus
- You touch your nose, eyes, or mouth after you have touched something contaminated by the virus, such as a toy or doorknob.

RSV often spreads very rapidly in crowded households and day care centers. The virus can live for a half an hour or more on hands. The virus can also live for up to 5 hours on countertops and for several hours on used tissues.

The following increase the risk for RSV:

- Attending day care
- Being near tobacco smoke
- Having school-aged brothers or sisters
- Living in crowded conditions

Symptoms

Symptoms vary and differ with age. They usually appear 4 - 6 days after coming in contact with the virus.

Older children usually have only mild, cold-like symptoms, such as cough, stuffy nose, or low-grade fever.
Infants under age 1 may have more severe symptoms and often have the most trouble breathing.

In general, RSV symptoms include:

- Bluish skin color due to a lack of oxygen (cyanosis)
- Breathing difficulty or labored breathing
- Cough
- Croupy cough (often described as a "seal bark" cough)
- Fever
- Nasal flaring
- Rapid breathing (tachypnea)
- Shortness of breath
- Stuffy nose
- Wheezing

**Signs and tests**

Many hospitals and clinics can rapidly test for RSV using a sample of fluid taken from the nose with a cotton swab.

**Treatment**

Antibiotics do not treat RSV.

*Mild infections go away without treatment.*

Infants and children with a severe RSV infection may be admitted to the hospital. Treatment will include:

- Oxygen
- Moist (humidified) air
- Fluids through a vein (by IV)

A breathing machine (ventilator) may be needed.

**Expectations (prognosis)**

Rarely, RSV infection can cause death in infants. However, this is unlikely if the child is seen by a health care provider in the early stages of the disease.

More severe RSV disease may occur in the following infants:

- Premature infants
- Infants with chronic lung disease
- Infants whose immune system does not work well
- Infants with certain forms of heart disease

**Complications**

In young children, RSV can cause:
Children who have had RSV bronchiolitis may be more likely to develop asthma.

Calling your health care provider

Call your health care provider if breathing difficulties or other symptoms of this disorder appear. Any breathing difficulties in an infant are an emergency. Seek medical attention right away.

Prevention

A simple way to help prevent RSV infection is to wash your hands often, especially before touching your baby. It is important to make certain that other people, especially caregivers, take steps to avoid giving RSV to your baby.

The following simple steps can help protect your baby from getting sick:

- Insist that others wash their hands with warm water and soap before touching your baby.
- Have others avoid contact with the baby if they have a cold or fever. If necessary, have them wear a mask.
- Be aware that kissing the baby can spread RSV infection.
- Try to keep young children away from your baby. RSV is very common among young children and easily spreads from child to child.
- Do not smoke inside your house, car, or anywhere near your baby. Exposure to tobacco smoke increases the risk of RSV illness.

Parents of high-risk young infants should avoid crowds during outbreaks of RSV. Moderate-to-large outbreaks are often reported in the local news and newspapers to provide parents with an opportunity to avoid exposure.

The drug Synagis (palivizumab) is approved for the prevention of RSV disease in children younger than 24 months who are at high risk for serious RSV disease. Ask your doctor if your child should receive this medicine.

References

3. Cincinnati Children's Hospital Medical Center. Evidence based clinical practice guideline for medical management of bronchiolitis in infants less than 1 year of age presenting with a first time episode. Cincinnati (OH): Cincinnati Children's Hospital Medical Center; 2006 May. 13 p.
The role of non-viral antigens in the cotton rat model of respiratory syncytial virus vaccine-enhanced disease.

Shaw CA, Galarneau JR, Bowenkamp KE, Swanson KA, Palmer GA, Palladino G, Markovits JE, Valiante NM, Dormitzer PR, Otten GR.

Source

Novartis Vaccines and Diagnostics, Cambridge, MA 02139, USA.

Abstract

In the 1960s, infant immunization with a formalin-inactivated respiratory syncytial virus (FI-RSV) vaccine candidate caused enhanced respiratory disease (ERD) following natural RSV infection. Because of this tragedy, intensive effort has been made to understand the root causes of how the FI-RSV vaccine induced a pathogenic response to subsequent RSV infection in vaccinees. A well-established cotton rat model of FI-RSV vaccine-enhanced disease has been used by numerous researchers to study the mechanisms of ERD. Here, we have dissected the model and found it to have significant limitations for understanding FI-RSV ERD. This view is shaped by our finding that a major driver of lung pathology is cell-culture contaminants, although FI-RSV immunization and RSV challenge serve as co-factors to exacerbate disease. Specifically, non-viral products from the vaccine and challenge preparations that are devoid of RSV give rise to alveolitis, which is considered a hallmark of FI-RSV ERD in the cotton rat model. Although FI-RSV immunization and RSV challenge promote more severe alveolitis, they also drive stronger cellular immune responses to non-viral antigens. The severity of alveolitis is associated with T cells specific for non-viral antigens more than with T cells specific for RSV. These results highlight the limitations of the cotton rat ERD model and the need for an improved animal model to evaluate the safety of RSV vaccine candidates.
A Case of Immune Thrombocytopenic Purpura After Rabies Vaccination

Fulbright JM, Williams SE, Pahud BA.

Abstract
We describe a case of immune thrombocytopenic purpura (ITP) occurring 15 days after the first dose of a 4-dose rabies vaccination series. ITP is thought to be an immune-mediated process triggered by an infection or toxin. There is little evidence in the literature beyond case reports of an association of ITP with vaccines other than with the measles, mumps, and rubella vaccine. This is the third reported case of ITP associated with rabies vaccination. Because of the rare occurrence of this adverse event relative to the severity of rabies infection, the benefits of rabies vaccination, when indicated, outweigh the low and possible risk of ITP.

Rotavirus


Intussusception risk after rotavirus vaccination in U.S. infants.


Author information

Abstract

BACKGROUND: International postlicensure studies have identified an increased risk of intussusception after vaccination with the second-generation rotavirus vaccines RotaTeq (RV5, a pentavalent vaccine) and Rotarix (RV1, a monovalent vaccine). We studied this association among infants in the United States.

METHODS: The study included data from infants 5.0 to 36.9 weeks of age who were enrolled in three U.S. health plans that participate in the Mini-Sentinel program sponsored by the Food and Drug Administration. Potential cases of intussusception and vaccine exposures from 2004 through mid-2011 were identified through procedural and diagnostic codes. Medical records were reviewed to confirm the occurrence of intussusception and the status with respect to rotavirus vaccination. The primary analysis used a self-controlled risk-interval design that included only vaccinated children. The secondary analysis used a cohort design that included exposed and unexposed person-time.

RESULTS: The analyses included 507,874 first doses and 1,277,556 total doses of RV5 and 53,638 first doses and 103,098 total doses of RV1. The statistical power for the analysis of RV1 was lower than that for the analysis of RV5. The number of excess cases of intussusception per 100,000 recipients of the first dose of RV5 was significantly elevated, both in the primary analysis (attributable risk, 1.1 [95% confidence interval, 0.3 to 2.7] for the 7-day risk window and 1.5 [95% CI, 0.2 to 3.2] for the 21-day risk window) and in the secondary analysis (attributable risk, 1.2 [95% CI, 0.2 to 3.2] for the 21-day risk window). No significant increase in risk was seen after dose 2 or 3. The results with respect to the primary analysis of RV1 were not significant, but the secondary analysis showed a significant risk after dose 2.

CONCLUSIONS: RV5 was associated with approximately 1.5 (95% CI, 0.2 to 3.2) excess cases of intussusception per 100,000 recipients of the first dose. The secondary analysis of RV1 suggested a potential risk, although the study of RV1 was underpowered. These risks must be considered in light of the demonstrated benefits of rotavirus vaccination. (Funded by the Food and Drug Administration.).

Intussusception after rotavirus vaccines reported to US VAERS, 2006-2012.


Abstract

BACKGROUND:

In 2006 and 2008, 2 new rotavirus vaccines (RotaTeq [RV5] and Rotarix [RV1]) were introduced in the United States.

METHODS:

We assessed intussusception events reported to the Vaccine Adverse Event Reporting System from February 2006 through April 2012 for RV5 and from April 2008 through April 2012 for RV1. For RV5, we conducted a self-controlled risk interval analysis using Poisson regression to estimate the daily reporting ratio (DRR) of intussusception comparing average daily reports 3 to 6 versus 0 to 2 days after vaccination. We calculated reporting rate differences based on DRRs and background rates of intussusception. Sensitivity analyses were conducted to assess effects of differential reporting completeness and inaccuracy of baseline rates. Few reports were submitted after RV1, allowing only a descriptive analysis.

RESULTS:

The Vaccine Adverse Event Reporting System received 584 confirmed intussusception reports after RV5 and 52 after RV1, with clustering 3 to 6 days after both vaccines. The DRR comparing the 3- to 6-day and the 0- to 2-day periods after RV5 dose 1 was 3.75 (95% confidence interval = 1.90 to 7.39). There was no significant increase in reporting after dose 2 or dose 3. Over all 3 doses, the excess risk of intussusception was 0.79 events (95% confidence interval = -0.04 to 1.62) per 100,000 vaccinations. From the sensitivity analyses, we conclude that under a worst-case scenario, the DRR could be 5.00 and excess risk per 100,000 doses could be 1.36.

CONCLUSIONS:

We observed a persistent clustering of reported intussusception events 3 to 6 days after the first dose of RV5 vaccination. This clustering could translate to a small increased risk of intussusception, which is outweighed by the benefits of rotavirus vaccination.

KEYWORDS:

VAERS, adverse event, intussusception, rotavirus vaccines, safety monitoring

The temporal relationship between RotaTeq immunization and intussusception adverse events in the Vaccine Adverse Event Reporting System (VAERS).

Geier DA, King PG, Sykes LK, Geier MR.

Abstract

BACKGROUND:
In August of 2006, the Advisory Committee on Immunization Practices (ACIP) recommended RotaTeq for routine vaccination of US infants. The hypothesis tested in the present study is that rotavirus vaccines are associated with an increased risk of intussusception adverse events (AEs) characterized by an onset in a biologically plausible a priori identified temporal period post-vaccination (days 3 to 7).

MATERIAL/METHODS:
The Vaccine Adverse Event Reporting System (VAERS) updated as of December 28, 2010 was analyzed.

RESULTS:
Following RotaTeq vaccination, a significantly (p<0.001) higher percentage of AEs were classified as serious, permanently disabling, resulted in hospitalizations, or were life-threatening among intussusception AEs in comparison to the total AE reports (removing intussusception AE reports) submitted to VAERS. A significantly greater portion of intussusception AEs in comparison to the portion of total AE reports (removing intussusception AE reports) were reported to VAERS in the onset interval from 3 to 7 days post-RotaTeq vaccination than within the onset interval from 1 to 2 days post-RotaTeq vaccination (78.7% vs. 29.1%, risk ratio=2.7, 95% CI=2.4-3.0, p<0.0001). It was assumed in our onset time-trend analyses of the distribution of AEs following RotaTeq vaccination that the AE's should be equally likely to be reported with an onset time for each day, from 1 to 9 days post-vaccination or, alternatively, should follow similar daily proportions as observed for total AEs reports (removing intussusception AE reports). Results of this onset time-trend analyses of the distribution of intussusception AEs reported to VAERS following RotaTeq vaccination revealed significant differences (p<0.001) from our expectations. Consistent and similarly remarkable trends were observed for intussusception AE reports associated with RotaShield vaccine.

CONCLUSIONS:
The present study significantly associates RotaTeq vaccination with intussusception AEs.

Detection of fecal shedding of rotavirus vaccine in infants following their first dose of pentavalent rotavirus vaccine.


Author information

Abstract

Studies on rotavirus vaccine shedding and its potential transmission within households including immunocompromised individuals are needed to better define the potential risks and benefits of vaccination. We examined fecal shedding of pentavalent rotavirus vaccine (RV5) for 9 days following the first dose of vaccine in infants between 6 and 12 weeks of age. Rotavirus antigen was detected by enzyme immunoassay (EIA), and vaccine-type rotavirus was identified by nucleotide sequencing based on genetic relatedness to the RV5 VP6 gene. Stool from 22 (21.4%) of 103 children contained rotavirus antigen-positive specimens on ≥ 1 post-vaccination days. Rotavirus antigen was detected as early as post-vaccination day 3 and as late as day 9, with peak numbers of shedding on post-vaccination days 6 through 8. Vaccine-type rotavirus was detected in all 50 antigen-positive specimens and 8 of 8 antigen-negative specimens. Nine (75%) of 12 EIA-positive and 1 EIA-negative samples tested culture-positive for vaccine-type rotavirus. Fecal shedding of rotavirus vaccine virus after the first dose of RV5 occurred over a wide range of post-vaccination days not previously studied. These findings will help better define the potential for horizontal transmission of vaccine virus among immunocompromised household contacts of vaccinated infants for future studies.

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Rubella


Complex regional pain syndrome type-I after rubella vaccine.

Genc H¹, Karagoz A, Saracoglu M, Sert E, Erdem HR.

Author information

Abstract

Complex regional pain syndrome type I (CRPS-I) is a complex disorder characterised by pain, autonomic dysfunction, and decreased range of motion. The syndrome was believed as a well-recognized disorder in adults but, less commonly recognized in children. CRPS-I after vaccination has been rarely reported. We reported an 11-year-old young girl with CRPS-I due to rubella vaccine.


A one year followup of chronic arthritis following rubella and hepatitis B vaccination based upon analysis of the Vaccine Adverse Events Reporting System (VAERS) database.

Geier DA, Geier MR.

Author information

Abstract

OBJECTIVES:
This analysis examined the incidence rate of chronic arthritis adverse reactions reported following adult rubella and hepatitis B vaccinations. In this analysis, etiologic mechanisms for chronic arthritis following adult rubella and hepatitis B vaccines were also explored.

METHODS:
The Vaccine Adverse Events Reporting System (VAERS) database was analyzed for the incidence rate of reported cases of chronic arthritis in comparison to Tetanus-diphtheria (Td) and tetanus toxoid adult vaccine control groups.

RESULTS:
Chronic arthritis adverse reactions following adult rubella vaccination were primarily reported in females (female/male ratio = 3.0), at about 45 years-old, and at a mean onset time of 10-11 days following vaccination. Chronic arthritis adverse reactions following adult hepatitis B vaccination were also primarily reported in females (female/male ratio = 3.5), at about 33 years-old, and with a mean onset time of 16 days following vaccination. The incidence rates of chronic arthritis following adult rubella and adult hepatitis B vaccinations were statistically significantly increased, by chi 2 analysis, in comparison to the adult vaccine control groups. The attributable risk of chronic arthritis following adult rubella vaccine ranged from 32 to 53 and from 5.1 to 9.0 following adult hepatitis B vaccine in comparison to the adult vaccine control groups.

CONCLUSION:
This study revealed that adult rubella and adult hepatitis B vaccines were statistically associated with chronic arthritis which persisted for at least one year. The etiology for these adverse reactions may involve autoimmune mechanisms. Furthermore, potential biases in the reporting rates of adverse reactions to VAERS were not observed.

Small Pox


Dermatofibrosarcoma protuberans occurring in a smallpox vaccination scar.

Green JJ1, Heymann WR.

Author information

Abstract

Dermatofibrosarcoma protuberans (DFSP) is a locally aggressive, rarely metastatic, spindle cell tumor. Trauma has been associated with its development. Since the 1940s, malignant tumors have been described to occur in sites of smallpox vaccination scars. Five cases in the literature document DFSP arising in sites of prior immunizations. We report a case of DFSP occurring in a smallpox vaccination scar and review the available literature.

Tetanus


[Preventive tetanus immunization and avoidance of side effects of booster immunization].

[Article in German]
Schröder JP, Kuhlmann WD.

Source
Fachbereich Immunologie, Ernst-Rodenwaldt-Institut, Koblenz.

Abstract
Prevalence of antibodies against tetanus toxoid (tetanus antitoxin titre) was measured in 5,235 males aged 17-60 years, 3,069 (59%) aged 20-22 years. Taking as criterion a threshold value of 0.1 IU/ml, 5,071 (97%) had adequate tetanus immunity. 1,301 of 4,355 aged 21-30 years (30%) actually had antibody concentrations above 6.3 IU/ml. Booster injections are especially contraindicated in this latter group because of the danger of side effects with further toxoid doses. Thoughtless routine booster immunization should therefore be avoided.

Typhoid


**Notes from the field: fatal yellow fever vaccine-associated viscerotropic disease--Oregon, September 2014.**

DeSilva M, Sharma A, Staples E, Arndt B, Shieh WJ, Shames J, Cieslak P; Centers for Disease Control and Prevention (CDC).

**Abstract**

In September 2014, a previously healthy Oregon woman in her 60s went to a hospital emergency department with malaise, dyspnea, vomiting, and diarrhea of 3-5 days' duration. She reported no recent travel, ill contacts, or dietary changes. Six days earlier, she had received a single dose of yellow fever vaccine and typhoid vaccine before planned travel to South America.

Varicella (Chicken pox)

In those previously infected with varicella, it appears that the immune system may be boosted by exposure to others with varicella, and that this may reduce the risk of developing shingles later in life. Based on this observation, mathematical modelling has suggested that rates of shingles in adults may temporarily increase over time following the introduction of universal varicella vaccination because of a reduced exposure to the virus in the community.

Outbreak of varicella in a highly vaccinated preschool population.

Fu J\textsuperscript{1}, Wang J\textsuperscript{2}, Jiang C\textsuperscript{2}, Shi R\textsuperscript{2}, Ma T\textsuperscript{2}.

Abstract

BACKGROUND:
Varicella vaccine is available for private purchase in Beijing, with single dose recommended for children aged ≥12 months before 2013. Despite the success achieved in reducing varicella incidence, varicella outbreaks continued to occur, including in schools and kindergartens among highly vaccinated children. We investigated a varicella outbreak in a preschool with high varicella vaccination coverage in Haidian district, Beijing.

METHODS:
Through questionnaires, data including children's medical and vaccination history were collected from their parents. A case of varicella was defined as an acute, generalized, maculopapulovesicular rash without other apparent cause in a child in the preschool from March 10 through March 29, 2010. Attack rates in vaccinated and unvaccinated children were calculated, and the analyses of vaccine effectiveness (VE) and of risk factors for breakthrough disease (varicella occurring >42 days after vaccination) were conducted.

RESULTS:
A total of 12 cases occurred during the outbreak, and ten of them (83.3%) had breakthrough varicella. The index case with mild varicella occurred in a child who had been vaccinated four years previously. Questionnaires were returned for all of 150 children in the preschool. Of all the 150 children, 144 (96.0%) had no prior history of varicella disease. Among these children, 135(93.7%) had received single-dose varicella vaccine before the outbreak. VE was 84.5% [95% confidence interval (CI): 62.8%∼93.5%] in preventing varicella of any severity, and VE was 92.2% (95% CI: 81.4%∼96.8%) against moderate to severe varicella. Age at vaccination (<15 months vs. ≥15 months) and time since vaccination before the outbreak (<3 years vs. ≥3 years) were not associated with the increased risk of breakthrough varicella(P=0.124 and 1, respectively). All the varicella cases with vaccination history verified through immunization records had received varicella vaccine and measles-mumps-rubella vaccine >30 days apart.

CONCLUSIONS:
Breakthrough infection with fever in vaccinated person may be as infectious as varicella in unvaccinated persons. High single-dose varicella vaccination coverage is effective in reducing varicella incidence, but not sufficient to prevent outbreak. To control varicella outbreak a second dose may deserve additional consideration.

KEYWORDS:
Epidemiology; Vaccine effectiveness; Varicella attenuated live vaccine; Varicella outbreak
Varicella and Varicella Vaccination in South Korea

Sung Hee Oh, a Eun Hwa Choi, a Seon Hee Shin, b Yun-Kyung Kim, c Jin Keun Chang, a Kyong Min Choi, a Jae Kyun Hur, a Kyung-Hyo Kim, c Jae Youn Kim, c Eun Hye Chung, c Soo Young Lee, a Su Eun Park, a Sung Ho Cha, a Kwang-Nam Kim, a Sung Hyuk Ma, a Byung Wook Eun, a Nam Hee Kim, a Dae Sun Jo, a Bo Youl Choi, and Shin Ah Kim

S. A. Plotkin, Editor

ABSTRACT

With continuing occurrence of varicella despite increasing vaccine coverage for the past 20 years, a case-based study, a case-control study, and an immunogenicity and safety study were conducted to address the impact of varicella vaccination in South Korea. Varicella patients under the age of 16 years were enrolled for the case-based study. For the case-control study, varicella patients between 12 months and 15 years of age were enrolled with one control matched for each patient. For the immunogenicity and safety study, otherwise healthy children from 12 to 24 months old were immunized with Suduvax (Green Cross, South Korea). Fluorescent antibody to membrane antigen (FAMA) varicella-zoster virus (VZV) antibody was measured before and 6 weeks after immunization. In the case-based study, the median age of the patients was 4 years. Among 152 patients between 1 and 15 years of age, 139 children received varicella vaccine and all had breakthrough infections. Clinical courses were not ameliorated in vaccinated patients, but more vaccinated patients received outpatient rather than inpatient care. In the case-control study, the adjusted overall effectiveness of varicella vaccination was 54%. In the immunogenicity and safety study, the seroconversion rate and geometric mean titer for FAMA antibody were 76.67% and 5.31.

Even with increasing varicella vaccine uptake, we illustrate no upward age shift in the peak incidence, a high proportion of breakthrough disease, almost no amelioration in disease presentation by vaccination, and insufficient immunogenicity of domestic varicella vaccine. There is need to improve the varicella vaccine used in South Korea.

http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4018876/
Vaccination to prevent varicella: Goldman and King's response to Myers' interpretation of Varicella Active Surveillance Project data.

Goldman G1, King P.

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.

KEYWORDS:

Cell-mediated immunity, exogenous boosting, herpes zoster, herpes zoster incidence, immunity, vaccination, varicella, varicella costs, varicella vaccine efficacy, varicella zoster virus

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.

Goldman GS, King PG.

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.

Stevens-Johnson syndrome after varicella vaccination.

Christou EM, Wargon O.

To the Editor: A 12-year-old boy presented to a regional emergency department with a 3-day history of progressing bilateral conjunctival injection, fevers (39°C), a widespread erythematous bullous rash, and superficial erosions to his lips, oral mucosa and urethral meatus.


Comment [A47]: Death rate 1-5%
Varicella rates among unvaccinated and one-dose vaccinated healthy children in Izmir, Turkey.

Kurugol Z¹, Halicioglu O, Koc F, Koturoglu G, Aksit S.

Objective:
OBJECTIVES: We aimed to determine the rate of breakthrough varicella in Turkey, a country with low varicella vaccination coverage.

Methods:
METHODS: This study was conducted between April 2008 and March 2009 at the Well-Child Clinic at Ege University and pediatricians' offices. We collected information on vaccination status and varicella infection using a questionnaire. In order to elicit more details about the severity of illness, we interviewed all parents and reviewed the clinician records. Vaccination status was verified from the medical records or vaccination cards with dates.

Results:
RESULTS: A total of 2802 children were evaluated. Of these, 1683 had been vaccinated with a single dose of varicella vaccine and 1119 were unvaccinated. Among vaccinated children, 466 (27.7%) had breakthrough varicella. Vaccinated children tended to have mild varicella. However, about 25% of breakthrough cases had moderate or severe disease. Children who were vaccinated ≥ 5 years previously had a 3.7-fold higher risk of breakthrough disease than those who were vaccinated <5 years before. Vaccination at younger than 15 months of age was not significantly associated with an increased risk of breakthrough infection.

Conclusions:
CONCLUSIONS: Breakthrough varicella is not rare in Turkey where varicella infections are common. A longer interval since vaccination may be a risk factor for developing breakthrough varicella. Children who had been vaccinated ≥5 years previously were at risk for breakthrough disease. A two-dose varicella vaccine policy may be needed to provide improved protection.

One dose of varicella vaccine does not prevent school outbreaks: is it time for a second dose?

Lopez AS\(^1\), Guris D, Zimmerman L, Giadden L, Moore T, Haselow DT, Loparev VN, Schmid DS, Jumaan AO, Snow SL.

**Author information**

**Abstract**

**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 a second dose.
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.

Transmission of varicella-vaccine virus from a healthy 12-month-old child to his pregnant mother.

Salzman MB1, Sharrar RG, Steinberg S, LaRussa P.

Abstract
A 12-month-old healthy boy had approximately 30 vesicular skin lesions 24 days after receiving varicella vaccine. Sixteen days later his pregnant mother had 100 lesions. Varicella-vaccine virus was identified by polymerase chain reaction in the vesicular lesions of the mother. After an elective abortion, no virus was detected in the fetal tissue. This case documents transmission of varicella-vaccine virus from a healthy 12-month-old infant to his pregnant mother.


Miscellaneous points of concern

Administration errors


Notes from the field: rotavirus vaccine administration errors--United States, 2006-2013.
Hibbs BF, Miller ER, Shimabukuro T; Centers for Disease Control and Prevention (CDC).

Abstract
Two live rotavirus oral vaccines, RotaTeq (RV5) (Merck & Co., Inc.) and Rotarix (RV1) (GlaxoSmithKline Biologicals), are approved for prevention of rotavirus gastroenteritis and recommended at ages 2, 4 (RV5/RV1), and 6 (RV5) months by the Advisory Committee on Immunization Practices. Because most childhood vaccines are injectable, vaccination providers might have less experience administering oral vaccines. To assess that hypothesis, CDC searched for reports to the Vaccine Adverse Event Reporting System (VAERS) of rotavirus vaccine administration errors involving injection and eye splashes in the United States during the period January 1, 2006-August 1, 2013. A total of 66 reports were found.

Contamination of Vaccines


Simian virus 40 (SV40)-like DNA sequences not detectable in finnish mesothelioma patients not exposed to SV40-contaminated polio vaccines.


Source
Department of Industrial Hygiene and Toxicology, Finnish Institute of Occupational Health, Helsinki, Finland.

Abstract
Occupational asbestos exposure can be demonstrated in 80% of mesothelioma cases. A possible role of simian virus 40 (SV40) in the etiology of mesothelioma was raised because several studies reported the presence and expression of SV40-like DNA sequences in human mesotheliomas. It is also known that expression of SV40 large T antigen inhibits cellular Rb and p53. This suggests that SV40 might render infected cells more susceptible to asbestos carcinogenicity. The SV40-like sequences are suggested to have arisen from contaminated polio vaccines. Millions of people in the United States and most European countries were inoculated with SV40-contaminated polio vaccine in 1955-1963. However, in Finland, where polio vaccination started in 1957, no SV40-contaminated vaccine was used. We used a polymerase chain reaction-based method to test for the presence of SV40-like sequences in DNA extracted from the frozen tumor tissues of 49 Finnish mesothelioma patients, most of whom had been occupationally exposed to asbestos. All of the Finnish tumor tissues tested negative for SV40-like sequences. The results suggest that the SV40-like sequences detected in mesothelioma tissue in some previous studies may indeed originate from SV40-contaminated polio vaccines. It is a matter of speculation whether the absence of SV40 infection has contributed to the relatively low incidence of mesothelioma in Finland (1/10(5) in 1990-1995).

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Efficacy of Vaccinations


Haemophilus influenzae type B in an immunocompetent, fully vaccinated ALL survivor.

Nevin J, Kanter Washko J, Arnold J.

Source

Departments of Pediatrics, Naval Medical Center, San Diego, San Diego, California, USA.
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Abstract

A 7-year-old boy with a history of recurrent acute lymphoblastic leukemia (ALL), in remission, presented to primary care clinic after 2 days of progressive right hip pain with weight-bearing activities. He was otherwise asymptomatic at the time of presentation. Blood cultures revealed Gram-negative diplococci, which prompted an MRI that was significant for a hip joint effusion and femoral head bone marrow edema. The patient had no sick contacts and no significant past medical history other than ALL. The patient had been given all recommended childhood vaccinations. Arthrocentesis and needle biopsy of the femoral neck were not diagnostic for malignancy and revealed only mild hip joint inflammation, leading to a diagnosis of osteomyelitis. The organism in the original blood culture was identified as Haemophilus influenzae type b, β-lactamase negative. Review of the patient's medical records showed a history of complete immunization to Haemophilus influenzae type b. An immunologic evaluation was made to determine if the patient retained immunity from his other vaccinations. Pathogen-specific antibody testing revealed detectable antibodies to polio but not measles, mumps, rubella, varicella-zoster virus, tetanus, diphtheria, pertussis, or hepatitis B. This loss of immunologic memory appears to be a rarely described side effect of ALL chemotherapy. There is currently no protocol to evaluate the immunologic memory of patients who underwent chemotherapy for ALL or to revaccinate them after their treatment. It is unclear whether the loss of immunologic memory is genuinely rare or is underdiagnosed because affected patients are protected by herd immunity.

KEYWORDS:

Haemophilus influenzae type b, cancer, chemotherapy, infectious disease, leukemia, vaccine

How do medical professionals vaccinate their own children/themselves?


Overcoming healthcare workers vaccine refusal--competition between egoism and altruism.

Betsch C.

Author information
Abstract

Vaccination reduces the risk of becoming infected with and transmitting pathogens. The role of healthcare workers (HCWs) in controlling and limiting nosocomial infections has been stressed repeatedly. This has also been recognised at a political level, leading the European Council of Ministers in 2009 to encourage coverage of 75% seasonal influenza vaccine in HCWs. Although there are policies, recommendations and well-tolerated vaccines, still many HCWs refuse to get vaccinated. This article uses literature from psychology and behavioural economics to understand vaccination decisions and the specific situation of HCWs. HCWs are expected to be highly motivated to protect others. However, their individual vaccination decisions follow the same principles (of weighting individual risks) as everyone else's vaccination decisions. This will lead to decisional conflict in a typical social dilemma situation, in which individual interests are at odds with collective interests. Failure to get vaccinated may be the result. If we understand the motivations and mechanisms of HCWs' vaccine refusal, interventions and campaigns may be designed more effectively. Strategies to increase HCWs' vaccine uptake should be directed towards correcting skewed risk perceptions and activating pro-social motivation in HCWs.
How do physicians immunize their own children? Differences among pediatricians and nonpediatricians.


Source

Centre for Vaccinology and Neonatal Immunology, Department of Pathology-Immunology, University of Geneva, Switzerland.

Abstract

CONTEXT:

Immunization has an essential impact on public health worldwide. Numerous studies have shown the efficacy of different vaccines to protect individuals from various diseases. However, some parents choose not to vaccinate their children for reasons such as, among others, doubts regarding their usefulness, concerns over safety or efficacy, etc. Physicians are known to exert a direct influence on immunization rates by answering questions and clarifying misconceptions. Yet, it is unknown how they immunize their own children.

OBJECTIVE:

We sought to assess how physicians interested in vaccination issues immunized, or would immunize, their own children.

DESIGN, SETTING, AND PARTICIPANTS:

An 11-question, Web-based survey with a total of 102 discrete answers was sent to 2070 Swiss physicians in October 2004. All physicians were subscribers to a nonprofit, Web-based expert network (InfoVac, www.infovac.ch) that distributes monthly newsletters and answers question within 2 days on immunization issues. The InfoVac network reaches > 95% of pediatricians in Switzerland but < 20% of general practitioners. All responses were anonymous, and no identifier could be used to trace the participants of the survey. Questions were divided into 2 parts: (1) physicians who were parents were asked which vaccines they gave to their own children and at what age, and (2) all physicians were asked which vaccines they would give to their own child and at what age if they had a newborn child in 2004. Vaccines available in Switzerland at the time of the survey were offered as possible replies, and recommended vaccines were considered as those noted in the Swiss federal immunization schedule issued yearly. One question compared their immunization practice between their own children and their patients. Sociodemographics, qualifying year, membership in different professional groups, and their type of practice were also requested. Statistics. Standard descriptive statistics were used for sociodemographic characteristics. Univariate statistical analyses were performed for each variable to determine its relationship to the dependent variable, being a pediatrician or nonpediatrician. Logistic-regression analysis was used to calculate the adjusted odds ratios (ORs) and 95% confidence intervals (CIs), controlling for any statistically significant demographic variables that might function as confounders (gender, parenthood, workplace, year of diploma, and type of practice). For all statistical tests, differences were considered significant at P < .05.
MAIN OUTCOME MEASURE:

We performed a comparison of past and projected immunization rates in the children of pediatricians and nonpediatricians.

RESULTS:

One thousand seventeen valid questionnaires were received (response rate: 49.1%; pediatricians: 53.3%). Nine hundred fifteen physicians (90%) had > or = 1 child. All physicians reported immunizing children in their practice. Pediatricians were more likely to be women and to work in private practice than nonpediatricians but less likely to belong to a self-reported alternative medicine association. Among the nonpediatricians, 317 were general practitioners, 144 were internists, and 95 were other specialists. Ninety-two percent of pediatricians followed the official immunization recommendations for their own children. In contrast, after controlling for gender, workplace, type of practice, and year of diploma, nonpediatricians were more likely not to have immunized their children against measles, mumps, hepatitis B, or Haemophilus influenzae type b. They more frequently postponed diphtheria-tetanus-pertussis (DTP) (OR: 4.5; 95% CI: 2.0-10.19) and measles-mumps-rubella (MMR) vaccination. Although projected immunization rates were higher than effective rates, 10% of nonpediatricians would still not follow the official immunization recommendations in 2004. They would more frequently refrain from using combination vaccines and postpone DTP and MMR immunization to later in life. Several comparisons confirmed the weaker use of the more recently licensed vaccines by nonpediatricians. In addition to vaccines currently recommended in Switzerland, both groups of physicians added hepatitis A, influenza, and varicella vaccines to the vaccination schedule of their own children. Pediatricians were more likely to give pneumococcal (OR: 2.26; 95% CI: 1.004-4.68) and meningococcal C (OR: 2.26; 95% CI: 1.62-3.17) vaccines to their own children. In contrast, they were less likely to give tick-borne encephalitis virus vaccine (OR: 0.65; 95% CI: 0.44-0.95).

CONCLUSIONS:

Ninety-three percent of the surveyed physicians agree with the current official vaccination recommendations and would apply them to their own children. However, the observation that 5% of nonpediatricians would not use Haemophilus influenzae type b vaccine if they had a child born in 2004 is unexpected and concerning. In contrast, both groups gave additional vaccines than those recommended to their own children. Among physicians in Switzerland interested in immunization, a significant proportion of nonpediatricians decline or delay the immunization of their own children with the recommended MMR- or DTP-based combination vaccines, which indicates that clarification of misconceptions such as fear of "immune overload" has not yet reached important targets among health care providers who thus are unlikely to answer parental concerns adequately.


Acceptance of hepatitis B vaccine by hospital personnel.
Crossley KB, Gerding DN, Petzel RA.

Abstract

Personnel at high risk of acquiring hepatitis B in two university-affiliated teaching hospitals were offered immunization against this disease. Of the 1,193 employees, 454 (38%) requested immunization. Individuals who declined or deferred immunization were sent questionnaires requesting the reasons for their decisions. Responses to the questionnaire were received from 487 of 674 personnel (72%). Most respondents (greater than 90%) indicated that they: 1) were aware of being at risk of acquiring hepatitis B, and 2) recognized the potential danger of the disease. A majority of respondents (56%) indicated that they had decided not to be immunized because they wanted to wait until more was known about the vaccine. Concern about specific side effects (eg, Guillain-Barré syndrome or acquired immunodeficiency syndrome) was cited much less often as a reason for declining immunization. Nearly one-fifth of questionnaire respondents either did not know the date of their last tetanus-diphtheria immunization or had not received a booster within the past decade.

Individual differences


Cortisol and cardiovascular reactions to mental stress and antibody status following hepatitis B vaccination: a preliminary study.
Burns VE¹, Ring C, Drayson M, Carroll D.

Author information

Abstract

This study examined possible neuroendocrine mechanisms underlying the association between stress and antibody response to vaccination. Hepatitis B antibody titers were obtained, and salivary cortisol and cardiovascular activity measured during baseline, mental arithmetic, and recovery in 30 undergraduates. It was hypothesised that higher reactivity would be associated with poorer antibody status. Compared to individuals with high antibody titers, those with low titers had significantly lower cortisol levels throughout, exhibited a significantly attenuated end-of-task reduction in cortisol relative to resting baseline, and had larger cardiac output and inotropic reactions, but smaller increases in total peripheral resistance, to mental arithmetic. In sum, variations in indices of both hypothalamic pituitary adrenocortical axis and sympathetic nervous system activity were associated with individual differences in immune response to vaccination.

http://www.ncbi.nlm.nih.gov/pubmed/?term=Cortisol+and+cardiovascular+reactions+to+mental+stress+and+antibody+status+following+hepatitis+B+vaccination%3A+A+preliminary+study
“Placebo” vaccines aren’t really “Placebo’s”


Evaluation of immunogenicity and safety of the new tetanus-reduced diphtheria (Td) vaccines (GC1107) in healthy Korean adolescents: a phase II, double-blind, randomized, multicenter clinical trial.


Source

Department of Pediatrics, The Catholic University of Korea, Seoul, Korea.

Abstract

This phase II clinical trial was conducted to compare the immunogenicity and safety of a newly developed tetanus-reduced diphtheria (Td) vaccine (GC1107-T5.0 and GC1107-T7.5) and control vaccine. This study was also performed to select the proper dose of tetanus toxoid in the new Td vaccines. Healthy adolescents aged between 11 and 12 yr participated in this study. A total of 130 subjects (44 GC1107-T5.0, 42 GC1107-T7.5 and 44 control vaccine) completed a single dose of vaccination. Blood samples were collected from the subjects before and 4 weeks after the vaccination. In this study, all subjects (100%) in both GC1107-T5.0 and GC1107-T7.5 groups showed seroprotective antibody levels (≥ 0.1 U/mL) against diphtheria or tetanus toxoids. After the vaccination, the geometric mean titer (GMT) against diphtheria was significantly higher in Group GC1107-T5.0 (6.53) and GC1107-T7.5 (6.11) than in the control group (3.96). The GMT against tetanus was 18.6 in Group GC1107-T5.0, 19.94 in GC1107-T7.5 and 19.01 in the control group after the vaccination. In this study, the rates of local adverse reactions were 67.3% and 59.1% in GC1107-T5.0 and GC1107-T7.5, respectively. No significant differences in the number of adverse reactions, prevalence and degree of severity of the solicited and unsolicited adverse reactions were observed among the three groups. Thus, both newly developed Td vaccines appear to be safe and show good immunogenicity. GC1107-T5.0, which contains relatively small amounts of tetanus toxoid, has been selected for a phase III clinical trial.

KEYWORDS:

Immunogenicity, Safety, Tetanus-Reduced Diphtheria (Td) Vaccine

“Rare” Events

Very common events: ≥10%; (1/10)

Common events: ≥1% and <10%; (1/10 – 1/100)

Uncommon events: ≥0.1% and <1%; (1/100 – 1/1000)

Rare events: ≥0.01% and <0.1%; (1/1000 – 1/10,000)

Very rare events: <0.01%. (less than 1/10,000)
According to the Australian Immunisation Schedule we should cumulatively receive:

- 30 vaccines by 12 months
- 38 vaccines by 4 years
- 46 vaccines by 15 years
- 73 vaccines by 80 years (life expectancy is 82 in Australia)

Including the annual influenza vaccination:

- 60 vaccines by 15 years
- 153 vaccines by 80 years

These figures don't include travel vaccines (Hep A etc), additional doses of DTaP now recommended with every pregnancy or repeat doses of MMRV due to waning immunity or Men B.

**Lifetime Risk of Vaccine Reaction**

Assuming a life expectancy of 80 years.

**Guillain-Barre Syndrome after Annual Influenza Vaccination (1.7 per million doses)**

Lifetime risk = 1.36 in 1 million

- 1.36 in 10,000

**GBS after HPV 80.23 per 10 million people receiving the full schedule (2.7 per million doses)**

Lifetime risk = 8 in 1 million

- 0.08 in 10,000

Anaphalaxis after vaccination (1.6 per million doses of any vaccine) 0.36 cases per 100,000 doses for DTaP, 1.25 per 100,000 doses MMR, 2.6 per 100,000 HPV doses)

Assuming current schedule, of 5 childhood/adolescent DTaP doses and 10 yearly adult boosters

Lifetime risk = 43.2 in 1 million

- 0.432 in 10,000

Assuming current schedule, of 2 childhood/adolescent MMR doses (adult boosters may be required)

Lifetime risk = 25 in 1 million
0.25 in 10,000
Assuming current schedule (including annual flu vaccination) of 153 vaccines
Lifetime risk = 244.8 in 1 million
2.448 in 10,000
Assuming current schedule of 3 HPV vaccines
Lifetime risk = 78 in 1 million
0.78 in 10,000
Intussusception after oral Rotavirus vaccination (1.36 per 100,000 doses)
Lifetime risk = 40.8 in 1 million
0.408 in 10,000
Risk of febrile seizure after MMRV vaccination (MMRV is 3.52 seizures per 10,000 doses relative to MMR+V. Minimum 2 doses recommended over lifetime)
Lifetime risk = 704 per 1 million
7.04 per 10,000
Risk of idiopathic thrombocytopenic purpura (1 in 25,000 doses of MMR also given as 1 in 23,500 doses assuming a schedule of 3 doses)
Lifetime risk = 80 in 1 million OR 127.65 in 1 million
0.8 in 10,000 OR 1.28 in 10,000
Vasculitis following influenza vaccination
GBS following Hepatitis B
SLE following Hep B
MS following Hep B
Encephalitis from MMR (1 in 1 million doses, 2 doses)
Lifetime risk = 2 in 1 million
0.02 in 10,000
Risk of Kawasaki disease after Men B vaccination (1 in 1000 to 1 in 10,000 risk, 3 doses recommended)

Lifetime risk = 3000 in 1 million to 300 in 1 million

16.5 in 10,000

Total = 1224.1 in 1 million

12.241 in 10,000

Administration errors

Pancreatitis following Hep A, Hep B vaccination
Tonsillectomies as cause for increase in paralytic poliomyelitis


Effect of Tonsillectomy and Adenoidectomy on Nasopharyngeal Antibody Response to Poliovirus

Pearay L. Ogra, M.D.

Share:

Abstract

Poliovirus antibody levels in nasopharynx and serum were studied before and after tonsillectomy and adenoidectomy in 40 children previously immunized with live poliovaccine. Before operation, γA poliovirus antibody was present in the nasopharynx of all children, but no γG or γM antibody was detectable. Shortly after operation low levels of γG antibody appeared in the nasopharynx of 50 per cent of subjects. The response was short lived, and disappeared in two months. Pre-existing γA antibody in the nasopharynx declined sharply after operation in all children studied. Mean antibody titers decreased three to four times, and individual titers in several children four to eight times. Four children who had had antibody levels in the nasopharynx failed to demonstrate any such antibody activity after operation. Reduced or absent antibody activity persisted for as long as seven months. In nine children with intact tonsils the antibody response in the nasopharynx after immunization with live poliovaccine was two to four times higher than in eight children whose tonsils had previously been removed.

Safety of Vaccines in Preterm Infants


Safety of DTaP-IPV-Hib-HBV hexavalent vaccine in very premature infants.

Faldella G¹, Galletti S, Corvaglia L,Ancora G,Alessandroni R.

**Author information**

**Abstract**

**OBJECTIVES:**
To assess the clinical safety of DTaP-IPV-Hib-HBV hexavalent immunization in very premature infants and to verify if the first administration of vaccine is by itself a reason for close monitoring hospitalized VLBW infants born at less than 31 weeks’ gestation.

**PATIENTS AND METHODS:**
Eighty-one preterm newborns less than 31 weeks' gestational age, admitted in the NICU, were eligible to be immunized with hexavalent vaccine under close monitoring, including pre-and post-immunization continuous monitoring of heart rate, oxygen saturation, respiratory rate, resistance index at the anterior cerebral artery and ECG cQT interval.

**RESULTS:**
Of the 81 eligible premature newborns, 36 were graduated from the NICU before the least date for immunization, at 7 weeks of age. The other 45 were vaccinated in the NICU and entered the study. Twenty-three of them were under medical treatment for chronic disease at the time of the immunization while 22 were healthy and stable. Five infants (11%) had apnoea/bradycardia/desaturation, related to vaccine administration and required medical support. All five infants were in the group of newborns with chronic disease (21.7% prevalence of adverse reactions in this group). No significant variation of cQT or RI before and after the immunization was observed either in the whole groups of patients or in the five infants who showed cardio-respiratory events related to vaccination.

**CONCLUSIONS:**
Hexavalent DTaP-IPV-Hib-HBV immunization is not associated with cardiac electric activity and cerebral blood flow variations in both stable and unstable very premature infants. However, it can cause apnoea/bradycardia/desaturation in premature babies with chronic disease. Therefore, if the baby is in the NICU for chronic diseases at 2 months post-birth, it should be monitored for apnoea, bradycardia and desaturation in association with vaccination. Hospitalized healthy preterm infants without chronic disease and therapy seem to be less vulnerable to cardio-respiratory adverse reactions. Nevertheless, it is advisable to immunize and monitor them at 8 weeks before discharge instead of possibly delaying immunization for several weeks and not monitor them.

Safety of Multiple Vaccines in one visit

"The chance of developing at least one AEFI with the administration of multiple vaccines is greater than with just one vaccine."

Safety of measles-containing vaccines in 1-year-old children.

Abstract

BACKGROUND AND OBJECTIVES:
All measles-containing vaccines are associated with several types of adverse events, including seizure, fever, and immune thrombocytopenia purpura (ITP). Because the measles-mumps-rubella-varicella (MMRV) vaccine compared with the separate measles-mumps-rubella (MMR) and varicella (MMR + V) vaccine increases a toddler's risk for febrile seizures, we investigated whether MMRV is riskier than MMR + V and whether either vaccine elevates the risk for additional safety outcomes.

METHODS:
Study children were aged 12 to 23 months in the Vaccine Safety Datalink from 2000 to 2012. Nine study outcomes were investigated: 7 main outcomes (anaphylaxis, ITP, ataxia, arthritis, meningitis/encephalitis, acute disseminated encephalomyelitis, and Kawasaki disease), seizure, and fever. Comparing MMRV with MMR + V, relative risk was estimated by using stratified exact binomial tests. Secondary analyses examined post-MMRV or MMR + V risk versus comparison intervals; risk and comparison intervals were then contrasted for MMRV versus MMR+V.

RESULTS:
We evaluated 123,200 MMRV and 584,987 MMR + V doses. Comparing MMRV with MMR + V, risks for the 7 main outcomes were not significantly different. Several outcomes had few or zero postvaccination events. Comparing risk versus comparison intervals, ITP risk was higher after MMRV (odds ratio [OR]: 11.3 [95% confidence interval (CI): 1.9 to 68.2]) and MMR + V (OR: 10 [95% CI: 4.5 to 22.5]) and ataxia risk was lower after both vaccines (MMRV OR: 0.8 [95% CI: 0.5 to 1]; MMR + V OR: 0.8 [95% CI: 0.7 to 0.9]). Compared with MMR + V, MMRV increased risk of seizure and fever 7 to 10 days after vaccination.
CONCLUSIONS:
This study did not identify any new safety concerns comparing MMRV with MMR + V or after either the MMRV or the MMR + V vaccine. This study provides reassurance that these outcomes are unlikely after either vaccine.


MacDonald SE, Dover DC, Simmonds KA, Svenson LW.

Author information

Abstract

BACKGROUND:
The combination measles-mumps-rubella-varicella (MMRV) vaccine currently used in Canada (Priorix-Tetra) may increase the risk of febrile seizures relative to the separate vaccines (MMR and varicella) previously administered. We determined the risk of febrile seizure after the first dose of MMRV, as well as any additional risk for children at high risk for seizures because of pre-existing medical conditions.

METHODS:
In this retrospective, population-based cohort study, we compared the risk of seizures after the first dose of MMRV with the risk after same-day administration of separate MMR and varicella vaccines (MMR+V) in children 12 to 23 months of age in the province of Alberta. We deterministically linked vaccination data to health service utilization data for seizures. We used Poisson regression, with adjustment for age and calendar year, to determine the risk for the full cohort and for high-risk children.

RESULTS:
The risk of seizures 7 to 10 days after vaccination was twice as high with MMRV as with MMR+V (relative risk [RR] 1.99, 95% confidence interval [CI] 1.30-3.05). The excess absolute risk of seizures was 3.52 seizures per 10 000 doses of MMRV relative to MMR+V. In high-risk children, the risk was not differentially higher for MMRV (RR 1.30, 95% CI 0.60-2.79).

INTERPRETATION:
Despite an increased risk of febrile seizures following MMRV (compared with MMR+V), the absolute level of risk was small. Policy-makers need to balance these findings with the potential benefits of administering the combination vaccine or determine whether the choice of vaccine rests with clinicians and/or parents.

Combined DTP-HBV-HIB vaccine versus separately administered DTP-HBV and HIB vaccines for primary prevention of diphtheria, tetanus, pertussis, hepatitis B and Haemophilus influenzae B (HIB).

Bar-On ES, Goldberg E, Hellmann S, Leibovici L.

Author information

Abstract

BACKGROUND:
Advantages to combining childhood vaccines include reducing the number of visits, injections and patient discomfort, increasing compliance and optimising prevention. The World Health Organization (WHO) recommends that routine infant immunisation programmes include a vaccination against Haemophilus influenzae (H. influenzae) type B (HIB) in the combined diphtheria-tetanus-pertussis (DTP)-hepatitis B virus (HBV) vaccination. The effectiveness and safety of the combined vaccine should be carefully and systematically assessed to ensure its acceptability by the community.

OBJECTIVES:
To compare the effectiveness of combined DTP-HBV-HIB vaccines versus combined DTP-HBV and separate HIB vaccinations.

SEARCH METHODS:
We searched the Cochrane Central Register of Controlled Trials (CENTRAL) (The Cochrane Library 2011, Issue 4), which contains the Cochrane Acute Respiratory Infections Group's Specialised Register, MEDLINE (January 1966 to week 1, November 2011), EMBASE (January 1990 to November 2011) and www.clinicaltrials.gov (up to April 2011).

SELECTION CRITERIA:
Randomised controlled trials (RCTs) or quasi-RCTs comparing vaccination with any combined DTP-HBV-HIB vaccine, with or without three types of inactivated polio virus (IPV) or concomitant oral polio vaccine (OPV) in any dose, preparation or time schedule, compared with separate vaccines or placebo, administered to infants up to two years old.
**DATA COLLECTION AND ANALYSIS:**
Two review authors independently inspected references identified by the searches and evaluated them against the inclusion criteria, extracted data and assessed the methodological quality of included trials.

**MAIN RESULTS:**
Data for the primary outcome (prevention of disease) were lacking. We performed a meta-analysis to pool the results of 20 studies with 5874 participants in an immunogenicity analysis and 5232 participants in the reactogenicity analysis. There were no data on clinical outcomes for the primary outcome (prevention of disease) and all studies used immunogenicity and reactogenicity (adverse events). The number of vaccine doses differed significantly between the studies. Heterogeneous interventions, study location, healthcare environment and combining research across disparate geographical locations, may have lead to bias. The risk of bias was unclear across most of the included studies. Comparisons found little heterogeneity. In two immunological responses the combined vaccine achieved lower responses than the separate vaccines for HIB and tetanus. No significant differences in immunogenicity were found for pertussis, diphtheria, polio and hepatitis B. Serious adverse events were comparable with mainly hospitalisation and acute bronchiolitis cases. Minor adverse events such as pain and redness were more common in children given the combined vaccine. Overall, the direction shown by the results is in favour of the DTPw (diptheria-tetanus-whole cell pertussis)-HBV-HIB vaccine rather than the DTPa (diptheria-tetanus-acellular pertussis)-HBV-HIB vaccine when compared to the separate vaccines (size of effect: risk ratio (RR) 1.43; 95% confidence interval (CI) 0.98 to 2.10, for 5269 participants).

**AUTHORS’ CONCLUSIONS:**
We could not conclude that the immune responses elicited by the combined vaccine were different from or equivalent to the separate vaccines. There was significantly less immunological response for HIB and tetanus and more local reactions in the combined injections. However, these differences rely mostly on one study each. Studies did not use an intention-to-treat (ITT) analysis and we were uncertain about the risk of bias in many of the studies. These results are therefore inconclusive. Studies
addressing clinical end points whenever possible, using correct methodology and a large enough sample size should be conducted.

Update of


Risk of febrile seizures and epilepsy after vaccination with diphtheria, tetanus, acellular pertussis, inactivated poliovirus, and Haemophilus influenzae type B.


Abstract

CONTEXT: Vaccination with whole-cell pertussis vaccine carries an increased risk of febrile seizures, but whether this risk applies to the acellular pertussis vaccine is not known. In Denmark, acellular pertussis vaccine has been included in the combined diphtheria-tetanus toxoids-acellular pertussis-inactivated poliovirus-Haemophilus influenzae type b (DTaP-IPV-Hib) vaccine since September 2002.

OBJECTIVE: To estimate the risk of febrile seizures and epilepsy after DTaP-IPV-Hib vaccination given at 3, 5, and 12 months.

DESIGN, SETTING, AND PARTICIPANTS: A population-based cohort study of 378,834 children who were born in Denmark between January 1, 2003, and December 31, 2008, and followed up through December 31, 2009; and a self-controlled case series (SCCS) study based on children with febrile seizures during follow-up of the cohort.

MAIN OUTCOME MEASURES: Hazard ratio (HR) of febrile seizures within 0 to 7 days (0, 1-3, and 4-7 days) after each vaccination and HR of epilepsy after first vaccination in the cohort study. Relative incidence of febrile seizures within 0 to 7 days (0, 1-3, and 4-7 days) after each vaccination in the SCCS study.

RESULTS: A total of 7811 children were diagnosed with febrile seizures before 18 months, of whom 17 were diagnosed within 0 to 7 days after the first (incidence rate, 0.8 per 100,000 person-days), 32 children after the second (1.3 per 100,000 person-days), and 201 children after the third (8.5 per 100,000 person-days) vaccinations. Overall, children did not have higher risks of febrile seizures during the 0 to 7 days after the 3 vaccinations vs a reference cohort of children who were not within 0 to 7 days of vaccination. However, a higher risk of febrile seizures was found...
on the day of the first (HR, 6.02; 95% CI, 2.86-12.65) and on the day of the second (HR, 3.94; 95% CI, 2.18-7.10), but not on the day of the third vaccination (HR, 1.07; 95% CI, 0.73-1.57) vs the reference cohort. On the day of vaccination, 9 children were diagnosed with febrile seizures after the first (5.5 per 100,000 person-days), 12 children after the second (5.7 per 100,000 person-days), and 27 children after the third (13.1 per 100,000 person-days) vaccinations. The relative incidences from the SCCS study design were similar to the cohort study design. Within 7 years of follow-up, 131 unvaccinated children and 2117 vaccinated children were diagnosed with epilepsy, 813 diagnosed between 3 and 15 months (2.4 per 1000 person-years) and 1304 diagnosed later in life (1.3 per 1000 person-years). After vaccination, children had a lower risk of epilepsy between 3 and 15 months (HR, 0.63; 95% CI, 0.50-0.79) and a similar risk for epilepsy later in life (HR, 1.01; 95% CI, 0.66-1.56) vs unvaccinated children.

**CONCLUSIONS:**

DTaP-IPV-Hib vaccination was associated with an increased risk of febrile seizures on the day of the first 2 vaccinations given at 3 and 5 months, although the absolute risk was small. Vaccination with DTaP-IPV-Hib was not associated with an increased risk of epilepsy.

Safety of Vaccination During Pregnancy


Obstetrician-gynecologists' practices and perceived knowledge regarding immunization.

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Author information

Abstract

BACKGROUND:
Obstetrician-gynecologists can play a key role in providing appropriate vaccinations to women of childbearing age.

PURPOSE:
This study investigated immunization knowledge and practices, and opinions concerning potential barriers to immunization, among obstetrician-gynecologists.

METHODS:
In 2007, surveys were sent to Collaborative Ambulatory Research Network members, a representative sample of practicing Fellows of the American College of Obstetricians and Gynecologists; 394 responded (51.2%). Data analysis was completed in 2008.

RESULTS:
Most responding obstetrician-gynecologists disagreed that "routine screening for vaccine-preventable diseases falls outside of the routine practice of an ob/gyn." A majority (78.7%) stock and administer at least some vaccines. Among those who stock vaccines, 91.0% stock the human papillomavirus vaccine, and 66.8% stock the influenza vaccine. All other vaccines were stocked by <30% of practices that stock vaccines. A majority of physicians agreed that financial factors (e.g., inadequate reimbursement) were barriers to vaccine administration. Most were aware that the influenza (89.8%); hepatitis B (64.0%); and tetanus, diptheria, pertussis (58.6%) vaccines are safe to administer during pregnancy, and that the measles, mumps, rubella (97.5%); and varicella (92.9%) vaccines are not. Most (84.5%) were in concordance with recommendations that all pregnant women should receive the influenza vaccine. A majority believed their immunization training was less than...
adequate and believed their practice would benefit from continuing medical education courses.

CONCLUSIONS:
Immunization is an important part of women's health care and has been, at least partially, incorporated into obstetrician-gynecologist practice. Financial burdens and knowledge regarding vaccine recommendations remain barriers to vaccine administration. Additional training and professional information may benefit obstetric-gynecologic practice.

Immunization of pregnant women: reproductive, medical and societal risks.
Brent RL.

Source
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Abstract
Establishing successful vaccine programs for pregnant women would be the quintessence of preventive medicine when you realize the preventive potential for reproductive problems of many of the new and old vaccines. The development of vaccines to prevent maternal, fetal and newborn disease is actually in its infancy. The risks and benefits are discussed in detail as well as the most appropriate and inappropriate time to immunize women of reproductive age and pregnant women. The great majority of risks are theoretical, but the problem is that birth defects and other developmental and reproductive problems are in the group of "diseases of affliction" which means that there are tremendous emotional upheavals in families affected with serious reproductive problems. The failures in reproduction are so common that immunization of a pregnant woman has potential deleterious consequences. A consortium of government, academia and industry must work together and an appeal to the more responsible members of the law profession to solve the problem of non-meritorious litigation has be in place before manufacturers of vaccines will be willing to initiate the development of new vaccines. The potential for reducing the incidence of birth defects, prematurity and neonatal infectious disease exists, but it will be difficult to initiate these programs because vaccine makers may be unwilling to assume an additional burden of negligence litigation. Certainly, it is clear that we could provide a safe vaccine for Group B streptococcus and infant botulism that would be of immediate benefit and the potential for reducing other diseases is realistic. This is not going to be an easy task.

Toxicity and Heavy metals


Porphyrinuria in childhood autistic disorder: implications for environmental toxicity.


Source

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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.