

Update on Side Effects from Common Vaccines

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Vaccines have had a tremendous impact on public health by reducing morbidity and mortality from a variety of virulent pathogens. However, unintended side effects continue to pose a potential risk that may outweigh the vaccine's protective attributes. In this review, we discuss recent articles and controversies pertaining to vaccine-associated adverse events. Included in the discussion are influenza, hepatitis B, measles-mumps-rubella, diphtheria-tetanus-pertussis, polio, *Haemophilus influenzae* type b, and rotavirus vaccines. The importance and contribution of vaccine constituents (such as thimerosal) to side effects is also reviewed.

Introduction

Vaccines have played an integral role in protecting recipients from dangerous infectious diseases. However, because vaccines contain harmful components, including live viruses, killed viruses, purified viral proteins, inactivated bacterial toxins, and bacterial polysaccharides, unwanted adverse events remain a concern. Aside from components of infectious agents, vaccines frequently contain other constituents, notably thimerosal, gelatin, egg protein, aluminum salts, and residual antibiotics. Recent evidence suggests that these constituents might be playing a key role in vaccine-related adverse events. Many vaccines have been implicated for multiple side effects based solely on anecdotal or limited evidence. This article is focused briefly on describing the national system for monitoring adverse events, followed by a review of adverse events of individual vaccines. Agents to be discussed include influenza, hepatitis B, measles-mumps-rubella, diphtheria-tetanus-pertussis, polio, *Haemophilus influenzae* type b, and rotavirus. Vaccines related to bioterrorism are not reviewed, because they have already been recently described by this author [1•].

How Adverse Events Are Monitored in the United States

Adverse events that are possibly due to vaccinations are recorded by the Vaccine Adverse Event Reporting System (VAERS), which is a collaborative effort between the US Food and Drug Administration (FDA) and Centers for Disease Control and Prevention (CDC). Since its establishment in 1990, it has served as a national passive-event recording system to which anyone can submit reports. VAERS receives more than 14,000 reports annually. In the decade beginning 1991, VAERS received 128,717 adverse event reports from an estimated 1.9 billion vaccinations for an overall rate of 11.4 cases per 100,000 vaccinations [2]. The most commonly reported side effects were fever (25.8%), injection-site hypersensitivity (15.8%), rash (11%), injection-site edema (10.8%), and vasodilation (10.8%). Serious adverse events, defined as death, life-threatening illness, hospitalization, or permanent disability accounted for 14.2% of the reports; however, death could not be attributed to the vaccine in most (< 2% of cases) [3•]. Analysis of this database helps to determine the frequency of adverse events. However, important shortfalls exist with VAERS, including under-reporting due to its passive nature, incomplete or inaccurate reporting, biased reporting, temporality, and lack of proof of causality. Despite these shortcomings, the data from VAERS serves as an important resource to monitor unusual or new adverse effects, which otherwise may go unrecognized.

Adverse Events Listed by Vaccine Influenza

The yearly influenza vaccine, the most commonly administered vaccine, is composed of two type A and one type B antigens. According to VAERS, it has the lowest vaccine-specific adverse event reporting rate of three per 100,000 doses. Most commonly, reports involve local reactions, almost all of which are mild, followed by fever, myalgia, and malaise [2]. Exacerbation of respiratory symptoms is frequently cited by physicians as a reason to avoid vaccinating asthmatics or patients with chronic obstructive pulmonary disease (COPD). However, in a population cohort study of 12,000 older subjects with asthma or COPD, no increase in exacerbation rate was noted following immunization [4]. The most concerning reaction, anaphylaxis, is discussed later.

Influenza has also been linked to possible neurologic events, including seizures, Guillain-Barré syndrome (GBS), Bell's palsy, and multiple sclerosis (MS). In 1976 and 1977, Schonberger *et al.* [5] were the first to note an increased rate of GBS after influenza swine flu vaccination, with a relative risk of 7.6, or 10 cases per million doses. Despite a postulated "trigger element," no conclusive explanation has been uncovered. In subsequent studies, a similar association was found, but to a much smaller degree. During an 8-year period, 382 cases of GBS were reported to VAERS, yielding an overall incidence of 0.95 cases per million doses. There was a slight male predominance, and symptoms started approximately 12 days after vaccination. Compared with tetanus, the relative risk of GBS after influenza vaccination was 4.3 [6•]. This same study noted endotoxin levels to be 125- to 1250-fold greater in influenza than tetanus vaccines, implicating a possible association, because endotoxin is known to boost nonspecific antibody response and potentially disrupt the blood-brain barrier. However, endotoxin content is not routinely measured in vaccines, and others have not studied the role of endotoxin in GBS. The relative risk for contracting GBS from a vaccination is estimated to be 1.7, which has been deemed by expert panels as tolerable and acceptable [2], because vaccination would yield only one additional case of GBS above background rates. Although flares or development of MS have been attributed to influenza, a retrospective study involving 180 relapsing MS subjects found that wild-type infection was more likely than vaccination to exacerbate underlying disease [7]. Bell's palsy occurs at an elevated rate following intranasal administration of inactivated killed virosome influenza vaccine compared with parenteral vaccination. This particular intranasal vaccine, which consists of hemagglutinin and neuraminidase surface antigens, was only available in Switzerland. Within 3 months of releasing this vaccine, 46 cases of Bell's palsy were reported and resulted in a relative risk of 19 compared with traditional parenteral administration [8]. This would have led to an estimated 1300 excess cases per million vaccinations and, thus, resulted in its withdrawal from the Swiss market. Today, in the United States, a live, attenuated, intranasal version is on the market and is being closely monitored. No reports of Bell's palsy have been recorded, and none is postulated to occur, because natural influenza vaccination has not been associated with Bell's palsy. Influenza vaccination has been anecdotally linked to depression, but no proof has emerged.

Another recently described entity associated with influenza vaccination is oculorespiratory syndrome (ORS). First described in 2000, ORS is defined as bilateral conjunctivitis, photophobia, blurry vision, and ocular pain (but normal ophthalmologic examination), with concomitant respiratory symptoms or facial edema beginning within 24 hours after vaccination and resolving within 48 hours. ORS has been reported to occur in as many as 5% of vaccinees [9]. Younger patients tend to have a quick onset, whereas older subjects

typically have a more prolonged course [10]. Symptoms are self-limited and without permanent sequelae. In patients with a previous history of ORS, the odds ratio (OR) of recurrence is 9.5 [9], although symptoms resolve without long-lasting effects.

Hepatitis B

Hepatitis B vaccine is the second most commonly administered vaccine, and although it is only given half as frequently as influenza, its adverse event reporting rate is almost 4 times higher at 11.8 reports per 100,000 [2]. The most common side effects are injection-site pain (13%–29% of adults and 3%–9% of children [11]) and fever; however, these do not occur more frequently than with placebo. Recently, the hepatitis B vaccine fell under intense public scrutiny because of its thimerosal content, but this issue is reviewed under vaccine constituents later. Complex regional pain syndrome (CRPS), characterized by pain, edema, autonomic dysfunction, and decreased range of motion typically follows injury, surgery, or a vascular event but it has also been reported to occur within 1 hour after hepatitis B vaccination, at an estimated rate of four cases per million doses [11]. CRPS tends to affect adolescent females and has not been reported in infants or older individuals; the pathogenesis remains unclear. Treatment is generally conservative, because it gradually resolves. Anaphylaxis has been reported after hepatitis B vaccination at a rate of 1 per 600,000, but no deaths have occurred. A residual yeast protein has been cited as the hypersensitivity-inducing antigen as opposed to the hepatitis B proteins themselves.

Diabetes, multiple sclerosis, rheumatoid arthritis, chronic fatigue syndrome, and lymphoblastic leukemia have been reported following hepatitis B vaccination. However, none of these has been confirmed by international independent review committees, and, in fact, these committees have rejected a causal relationship, specifically with multiple sclerosis [12]. Henoch-Schönlein purpura has been described in eight cases, and acute transverse myelitis has been reported in a boy with concomitant viral upper respiratory infection. None of these side effects has been demonstrated in blinded clinical trials, and they have not occurred with greater prevalence than background disease; rather, the cases are a result of passive reporting and, therefore, questionable causality.

Measles, Mumps, and Rubella

The measles, mumps, and rubella (MMR) combination vaccine, consisting of live, attenuated viruses, was originally licensed for use in 1971, and during the ensuing decades, it has slowly replaced the individual measles, mumps, and rubella vaccines. The frequency of adverse events with the MMR vaccine is as high as 16.3 reports per 100,000 with the most common reports describing local pain, edema, and induration. Anaphylaxis due to gelatin hypersensitivity occurs occasionally and is described

further later. Confirmed associations include thrombocytopenia, febrile seizures, anaphylaxis, and acute arthritis, whereas vasculitis, otitis media, conjunctivitis, optic neuritis, and GBS remain unconfirmed [2].

The onset of idiopathic thrombocytopenic purpura (ITP) usually occurs within the first 4 to 6 weeks after vaccination and presents with bruising and a low platelet count. The relative risk of ITP after MMR is 6.3; however, the attributable risk is only one in 25,000 vaccinees [13]. In a Canadian prospective study from 1992 to 2001, an average of six cases per year was reported. The average age of affected children was 13 months, and symptoms began 1 month after vaccination. Within a month of onset, platelet counts normalized in 80.7% of subjects, but 8.2% developed persistent thrombocytopenia lasting longer than 3 months [14]. Overall, ITP after MMR is rare and benign.

Aseptic meningitis has also been confirmed to increase after MMR vaccination. Onset of neurologic symptoms peaks 3 weeks after vaccination and is more likely in children younger than 18 months of age. In a case-crossover study comparing rates of aseptic meningitis, an association was found, but was strain-dependent. The relative risk was 5.5 for Urabe or Hoshino strains, and the risk was not elevated following Jeryl Lynn or Rubini strain vaccinations [15•]. Because the risk after Urabe or Hoshino strain vaccination varied from one in 900 to one in 120,000, these strains were eliminated from the American market. The only available MMR vaccine in the United States is derived from the Jeryl Lynn strain. Another neurologic complication, febrile seizures, has also been linked to MMR vaccination. In an active surveillance of Canadian children from 1995 to 2001, 98% of reported post-MMR febrile seizures occurred in 1- to 2-year-old children, and 50% of these occurred from 5 to 10 days after vaccination. However, seizures as far out as 1 month after vaccination account for the remainder of the episodes [16•]. Developing MMR-associated febrile seizures is not a significant risk factor for subsequent epilepsy.

Perhaps the most controversial side effect attributed to MMR is its purported association with autism. Wakefield *et al.* [17] first reported this link in 1998 when they described a case series of 12 children with autism and gastrointestinal symptoms of which eight were reported by the parents to have started after MMR vaccination. As a result of the fear generated by the publicity, vaccination rates fell from 92% in 1998 to 84% in subsequent years. Since 1998, numerous studies have repeatedly demonstrated no association of autism or autistic spectrum disorder with MMR vaccination. Kaye [18] performed a crude time-trend analysis of British children younger than 12 years of age. Newly diagnosed autism increased seven-fold from 0.3 per 10,000 person years in 1988 to 2.1 per 10,000 person years in 1999. However, despite the significant rise in autism diagnoses, MMR vaccination rate remained stable at 97% and, thus, demonstrated no correlation between the two [18]. When an illness incidence

climbs rapidly while the exposure remains stable and almost universal, the exposure cannot account for the rise in illness. In the United States, a retrospective analysis of Californian children with autism was examined from 1980 to 1994. From 1980 to 1987, MMR vaccination rates remained stable and increased slightly in 1988, followed by a rapid plateau. However, autism rates have increased exponentially even before the minimal increase in MMR rates in 1988. Autism jumped 373%, from 44 cases per 100,000 in 1980 to 208 cases per 100,000 in 1994 [19]. A retrospective cohort of 537,303 Danish children [20], case series of 498 autistic British children [21], population study of London children [22], and systematic literature review [23••] all showed increased autism rates without a correlating increase in MMR vaccinations, which further supports evidence against MMR playing a causative role in autism. In the face of all these negative studies, proponents of the association postulated that the studies were negative because MMR vaccination causes a "variant" of autism and not the typical autism that these studies were statistically powered to examine. However, even this theory has been disproved [24]. Andrews *et al.* [25•] found that recall bias on the part of the parents of autistic children following the publicity of the Wakefield announcement could account for the apparent inconsistency with earlier investigations. The sheer burden of evidence from much more detailed, comprehensive, and large-scale studies have all concurred and cleared MMR vaccination of any autistic propensities. Recently, the Institute of Medicine released an immunization safety committee report stating "the hypothesis regarding how MMR could trigger autism lacks supporting evidence and is theoretical only" [26].

Diphtheria, Tetanus, and Pertussis

Prior to the introduction of the current acellular pertussis formulation (DTaP) in 1996, the diphtheria, tetanus, and pertussis (DTP) vaccine consisted of a pertussis whole-cell homogenate (DTwP), which was used widely until 2000. The high rate of adverse events drove the development of the newer formulation. Most commonly, reported side effects are local reactions, such as pain and tenderness (50%), edema (40%), and erythema (33%) [2]. Systemic reactions, such as fever, drowsiness, irritability, and anorexia, are less frequent and milder with the acellular preparation than the DTwP. Neurologic symptoms have been a significant issue and are described later. Intractable crying has also been noted commonly by pediatricians, but the frequency has declined with the DTaP. Although it is disturbing to the parents, the prolonged crying and irritability do not predict more ominous events.

After the conversion to DTaP, reports of adverse events dropped significantly from 26.2 reports per 100,000 doses to 12.5 reports per 100,000 doses [2]. Injection-site erythema greater than 5 cm was not found to differ between the two formulations; however, swelling, tenderness, and decreased range of motion were more common following DTwP [27]. Furthermore, children rated more frequent and severe pain

following DTwP, and parent satisfaction was lower with DTwP. Pronounced local reactions have been noted with pertussis-containing vaccines, leading to the description of extensive limb swelling (ELS). ELS is defined as any report of edema extending at least to the elbow or knee of the vaccinated extremity. Only 497 cases have been reported from approximately 2 billion doses. Onset of ELS is within 1 day of vaccination and most likely to occur after higher numbers of doses of pertussis-containing vaccines [28]. Reactions after the 4th and 5th doses of DTP account for 64% of the scenarios. No association has been found with age or gender. Generally, symptoms resolve with supportive care and without any permanent sequelae. A history of ELS has not been verified as a risk factor for future reactions and, thus, does not serve as a contraindication.

Although review of data has not substantiated an association of DTwP with permanent neurologic damage, it has been causally linked to febrile seizures (0.06%), hypotonic-hyporesponsive episodes (0.06%), persistent crying and irritability, and acute encephalopathy. In a Canadian surveillance study by LeSaux *et al.* [16•], which bracketed the year the whole-cell formulation was completely changed to the acellular version, the febrile seizure rate dropped 79%. Overall seizure rate (including febrile and afebrile) decreased 71%, from 1.7 reports per 100,000 doses to 0.5 reports per 100,000 doses [16•]. LeSaux *et al.* also investigated hypotonic-hyporesponsive episodes (HHEs), which were first described by Hopper as a sudden onset of hypotonia, hyporesponsiveness, and cyanosis occurring within 48 hours of vaccination. Classically, HHEs have been associated with children younger than 2 years of age who received DTP. LeSaux *et al.* found that 95.6% of children with HHE were previously healthy, and all recovered from the episode without permanent deficit. The rate of HHEs dropped 67% after pertussis vaccine became acellular. In a similar US study, 84% of HHEs occurred within 3 to 4 hours in children under 1 year of age following pertussis-containing vaccines [24]. Within an average of 6 hours, 98.6% returned to normal, and only one had a repeat episode, but this was after a hepatitis B vaccination. The rate of occurrence following DTwP was 1 per 1750 injections [29], but yearly counts decreased from 99 in 1996 to 38 in 1998 when the transition from DTwP to DTaP occurred [30]. Because HHEs are considered benign and nonrecurrent, the American Academy of Pediatrics relabeled HHEs from a contraindication to a precaution.

Most of the adverse events of DTP have been attributed to the pertussis component; however, tetanus has been reported to cause anaphylaxis and GBS. IgE-mediated anaphylaxis may occur with an incidence of 0.001%. In four children with immediate hypersensitivity to tetanus, no skin-test reactivity was found to thimerosal or aluminum phosphate. In addition, IgE and IgG antibodies were detected against tetanus, but not thimerosal or aluminum phosphate. After 5 years, IgG titers remained high, whereas IgE titers fell an average of 50% [31]. A VAERS evaluation

from 1991 to 1999 revealed a GBS incidence of 2.2 per 10 million doses of tetanus [6•].

Polio

The original, effective Salk oral polio virus (OPV) vaccine was switched to killed inactivated polio virus (IPV) vaccine, primarily because of vaccine-associated paralysis occurring at a rate of 1 per 2.4 million doses. Although the OPV has greater protective herd immunity characteristics, the excessively low frequency of natural infection in the United States does not justify its increased risk for paralysis. After the change, overall adverse events only declined slightly from 15.1 reports per 100,000 to 13.1 reports per 100,000; however, no reports of paralysis have been described since 1997 [2]. Some lots of OPV made in 1955 to 1963 were contaminated with simian virus 40 (SV40), which has been associated with numerous malignancies in mouse models. A Danish birth cohort was followed from 1943 to 1977 (encompassing the era with the SV40-contaminated vaccine followed by an era with SV40-free vaccine). During this study period of 69.5 million person-years of follow-up, SV40 exposure via OPV was not shown to increase cancer incidence [32].

The IPV is grown in a monkey kidney cell line and is inactivated with formaldehyde. IPV also contains trace amounts of neomycin, streptomycin, and polymyxin-B, discussed later.

Haemophilus influenzae type b

Adverse events after *Haemophilus influenzae* type b (Hib) vaccination is reported approximately 18 times per 100,000 doses [2]. However, this rate is likely exaggerated because of the typical temporal association in routine pediatric immunization schedules of Hib with DTaP, which is known to have a much higher rate of adverse events. Commonly reported events are injection-site erythema, edema, warmth, and fever. Local and systemic reactions are infrequent, but tend to happen more commonly with increasing number of doses, but again, this is a known problem with DTP; Hib is only a likely culprit by association. In a recent Swedish prospective cohort study, Hib vaccination appeared to be a risk factor for the development of two autoantibodies frequently associated with type 1 diabetes [33]. Hib vaccination may drive a nonspecific polyclonal stimulatory response, promoting the increased production of these autoantibodies, although the clinical significance is unclear.

Rotavirus

Rotavirus, a live, oral, rhesus-reassortant based vaccine, was licensed in 1998 but remained on the market for only 9 months. More than 700 total adverse event reports were generated from fewer than 0.5 million doses, yielding a case rate of 156 reports per 100,000 doses, which is the highest among all vaccines [2]. Fifteen cases of intussusception were found in a compilation of three studies (cohort, case control, and case series studies) sponsored by

the CDC. The increase in attributable risk (1 in 10,000) of intussusception would have resulted in an excess rate of 34 cases per 100,000, and, therefore, the vaccine was removed from the market [34•]. Since then, other rotavirus vaccines have been developed, and more than 40,000 children have entered phase III trials.

Varicella

The live, attenuated varicella vaccine was licensed for use in the United States in 1995. Since then, more than 40 million doses have been distributed, resulting in a tremendous reduction of the classic presentation and severity of chicken pox. The adverse event rate is 50 reports per 100,000 doses, which is elevated; however, only 5% of the reports are classified as serious [2]. Most events are local reactions, including pain and redness; however, 3% to 4% develop varicella-like rash at the injection site, and another 3% to 4% develop a generalized varicella-like rash, but average only five lesions [2]. Herpes zoster has been reported after varicella vaccination; however, it is extremely rare in healthy children (fewer than 40 cases reported) [35]. Only five severe incidents have been reported, and an immunodeficient state was present in each of those [35]. Even in vaccinated leukemic patients, zoster occurs in eight per 1000 person-years, which is three times less frequent than in leukemic patients with natural infection [35]. No one has died from varicella vaccination, which is a significant accomplishment when compared with wild-type infection.

Importance of Vaccine Constituents

Aside from the infectious component, vaccines may contain numerous other constituents that might induce adverse events. Preservatives, such as thimerosal, prevent bacterial and fungal contamination. Adjuvants, such as aluminum, help boost immune response. Additives, such as human serum albumin and gelatin, help stabilize viruses. Sometimes, residuals are left over from the manufacturing process, and these can range from formaldehyde to egg proteins to trace antibiotics.

Of these constituents, thimerosal has received the most publicity recently because of its mercury content. Methylmercury is a known neurotoxin. Thimerosal, which has been used as a preservative since the 1930s, is metabolized to ethylmercury. Concern first arose in 1999 when routine pediatric immunization schedules could lead to a cumulative dose of ethylmercury, which exceeded the safety guidelines set for methylmercury [36••]. As a precaution, thimerosal was removed from all vaccines except influenza, which contains 12.5 µg/dose, a dose that is far below the 200 to 230 µg safety level set for infants. Because of thimerosal's potential for neurotoxicity, it has been implicated as a cause of autism. Only one study demonstrated this link with an increased relative risk of 6 [37]. However, in a Danish population cohort of

children older than 6 years, autism risk did not increase in those immunized with thimerosal-containing vaccines [38]. Another large study of children from three countries showed that, despite increasing diagnoses of autism, vaccine-associated thimerosal levels were declining [39•], which argues against an association. In fact, the American Academy of Pediatrics concurs with the CDC that no credible evidence exists to associate thimerosal with autism. The only proven association is thimerosal's ability to induce a delayed hypersensitivity skin reaction in 1% to 18% of subjects [40].

Aluminum, an adjuvant, is present in DTaP, Hib, pneumococcal conjugate, and hepatitis B vaccines as aluminum hydroxide, aluminum phosphate, or alum. Comparing aluminum-containing to aluminum-free vaccines, young children had significantly more erythema and induration (OR = 1.87). Older children experienced significantly more frequent, prolonged, local pain lasting up to 2 weeks (OR = 2.05) [41]. No evidence supports long-term or serious side effects from aluminum.

Gelatin hypersensitivity was deduced from careful examination of egg allergic patients with anaphylaxis to MMR. These patients demonstrated IgE to gelatin (and not to egg) in 25% of US patients, but as high as 93% in Japan. In Japanese vaccines, a minimally hydrolyzed, high-molecular weight gelatin historically was used; however, after converting to an extensively hydrolyzed gelatin, Japanese anaphylaxis rates dropped to mirror US rates [36••].

Of the manufacturing residuals, formaldehyde is concerning because of its carcinogenic potential at high concentrations. However, the miniscule amount found as residuals is even less than the normal biological concentration that is essential to human metabolic pathways [36••]. Residual antibiotics include neomycin, streptomycin, polymyxin-B, chlortetracycline, and amphotericin B [36••]. Only neomycin is found to any appreciable degree and has been implicated as a cause for anaphylaxis associated with MMR. Significant residual egg proteins are only found in influenza and yellow fever vaccines. In the influenza vaccine, egg protein concentrations vary significantly between companies and years of production by as much as three logs and can be as high as 42 µg/dose [42•]. This concentration is more than sufficient to sensitize and potentially induce severe anaphylaxis [36••]. However, if the egg protein is less than 1.2 µg/dose, a graded vaccination regimen can be used to safely administer influenza vaccine to egg-allergic patients [36••]. Alternately, MMR vaccine has no appreciable egg protein and can be given safely, even in severely egg-allergic patients.

Conclusions

Adverse events from vaccinations vary from mild, benign local injection-site irritation to severe, life-threatening reactions. Through the years, lists of undesirable outcomes have been attributed to various vaccines. Many of these

claims fail to be proven, but the VAERS has been established to help determine the legitimacy of these associations and to monitor for new or unusual side effects. Despite some concerning adverse events, the relatively small likelihood of severe adverse events pales in comparison to the tremendous benefits vaccines offer.

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