



Pediatric Vaccine Safety Monitoring

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With the recent release of a 9-valent human papilloma virus (HPV) vaccine and two new meningococcal serogroup B vaccines, the number of vaccines available for use in the pediatric population continues to grow. Establishing the safety profile of new vaccines does not end with premarketing clinical trials. Ongoing assessment is necessary to determine the incidence of adverse events associated with a vaccine, identify rare adverse events not seen during testing, and to rule out those adverse events that may be temporally but not causally related to vaccine administration. Vaccine safety data are available through multiple sources, including post-marketing epidemiologic surveillance studies, case reports in the medical literature, and manufacturer-based adverse effect registries, as well as databases such as the Vaccine Adverse Event Reporting System (VAERS), the National Vaccine Injury Compensation Program (VICP), and the Vaccine Safety Datalink (VSD).

Vaccine Safety Monitoring Programs

The VAERS program is a national surveillance program co-sponsored by the Centers for Disease Prevention and Control (CDC) and the Food and Drug Administration (FDA).¹ Both VAERS and the VICP were developed as the result of the National Childhood Vaccine Injury Act of 1986.² This act mandated the creation of systems to monitor vaccine safety and provide financial support for patients adversely affected by vaccines. Prior to the Act, damages awarded in vaccine-related civil cases had resulted in multiple manufacturers discontinuing vaccine production. The U.S. had reached a critical point in which the vaccine supply was at risk; regulations put forth in the Act provided compensation for families while reducing the risk of liability for manufacturers.

VAERS is a voluntary system for reporting an adverse event. Anyone may submit a report to VAERS, although most reports come from health care providers and vaccine manufacturers. It is considered to be the responsibility of a health care provider who suspects a serious

adverse event has occurred to file a report. Approximately 30,000 reports are submitted to VAERS each year, with 10% considered serious. The most frequently reported adverse effects are local reactions (swelling or redness at the site of injection), fever, or irritability. Suspected vaccine-related adverse events can be submitted to VAERS on-line at www.vaers.hhs.gov or by calling (800) 822-7967.

Submitting a report to VICP is necessary for serious adverse events in which the patient or family may require monetary compensation. As with VAERS, anyone may file a report. The program's Vaccine Injury Table, www.hrsa.gov/vaccinecompensation/vaccinetable.html, contains the adverse events and time frames for their occurrence that qualify for compensation. Funding for the program is provided through an excise tax on vaccines. The VICP website provides statistical data for the program. Since its initiation in 1988, a total of 16,038 claims have been filed, with 4,150 of these determined to be compensable. To add perspective to these numbers, it is estimated that over 2.5 billion vaccine doses were administered during that period of time. Total compensation paid over the life of the program is approximately \$3.2 billion. Of the compensated cases, 1,271 involved diphtheria, tetanus, whole cell pertussis (DTP) vaccine, 1,127 influenza vaccine, 371 measles, mumps, rubella (MMR) vaccine, 245 hepatitis B vaccine, and 185 diphtheria, tetanus, acellular pertussis (DTaP) vaccine.

VSD is the product of a collaboration between the CDC and nine health care organizations located throughout the U.S. It was created in 1990 to provide active surveillance of vaccine adverse events. The VSD system is estimated to include over 6 million patients and is updated weekly. This system compares the incidence of adverse events in vaccinated patients with the expected rate of the event in non-vaccinated individuals, allowing rapid cycle analysis so that health care providers and the public can be quickly made aware of new vaccine safety

information. Examples of the topics addressed by the VSD collaborative include the effects of vaccine preservatives in infants, the relationship between vaccines and febrile seizures, and the safety profile of rotavirus and HPV vaccines.

Each of these databases has been used to estimate the frequency of vaccine adverse events. The VAERS database is available to the public and may be searched on-line at <http://vaers.hhs.gov/data/index>. A video on the site describes how to use the VAERS search tool. Information on requesting permission to use VSD for research is available at www.cdc.gov/vaccinesafety/Activities/VSD.html.

Systematic Reviews

In addition to database analyses, several recent systematic reviews have added to our knowledge of vaccine adverse events. In 2014, Maglione and colleagues conducted an extensive review of the literature.⁵ Of the 20,478 resources identified, 67 met the authors' criteria for use. Strength of evidence was rated as high, moderate, low, or insufficient. There was a high level evidence only for the development of febrile seizures following administration of the MMR vaccine. There was moderate evidence to suggest an association between the rotavirus vaccines and intussusception. The authors found no evidence to support an association between MMR and autism.

Hypersensitivity Reactions to Vaccines

Injection site reactions and delayed urticaria or rash often occur after vaccine administration and may be mistaken for a hypersensitivity reaction.⁶ True allergic reactions appear to be rare. The incidence of anaphylaxis after vaccine administration is estimated to be between 0.65 and 1 reaction per million vaccine doses.

Caubet and Ponvert classify systemic reactions to vaccines into three categories: 1) delayed urticaria with or without angioedema and rash, likely resulting from a nonspecific activation of the immune system and degranulation of mastocytes, 2) immediate reactions presenting with urticaria, angioedema, rhinitis, wheezing, and hypotension, or 3) undefined reactions, such as Guillain-Barre syndrome with certain strains of the influenza vaccine.⁶ Patients with an immediate or delayed hypersensitivity reaction should be evaluated by an allergist. Skin testing is recommended in patients with an immediate allergic reaction after vaccine administration, or in those allergic to gelatin, latex, yeast, or eggs. Measurement of serum IgE levels may also be beneficial in some cases. If skin testing is negative, immunization can proceed. If positive,

antibody titers should be checked to determine if additional doses are needed. If additional doses are required, graded doses may be administered according to recommendations published by the American Academy of Pediatrics.⁷

For patients with egg allergy, skin tests for influenza vaccine have been shown to provide false positive results and are not considered useful in predicting response. According to current guidelines from the Advisory Committee for Immunization Practices (ACIP), individuals who developed hives without cardiovascular, respiratory, or gastrointestinal symptoms with an earlier exposure to the vaccine may receive the inactivated influenza vaccine if observed for at least 30 minutes after vaccination.⁸

Dermatologic Adverse Events

Vaccines have been associated with a wide spectrum of cutaneous reactions, ranging from local site reactions to generalized reactions.^{6,9} While most patients will experience self-limited local site reactions following intramuscular vaccine administration, a small number of patients may develop Nicolau syndrome (embolia cutis medicamentosa) with painful swelling, erythema, and hemorrhagic patches, followed by localized necrosis and scarring. The vaccines most often associated with this reaction include influenza, inactivated polio, *Haemophilus influenzae* type b, hepatitis B, and diphtheria, tetanus, pertussis. The mechanism for this reaction is not well understood, but may involve vasospasm due to pressure changes in the tissue during the injection, embolization of the vaccine, or pressure on the tissues from the volume of the injected material. Treatment consists of methods to improve blood flow, with hyperbaric oxygen or administration of pentoxifylline or heparin. Intralesional corticosteroid administration has also been used in this setting.

Immune-mediated erythema multiforme has been reported following administration of HPV and MMR vaccines.⁹ In most cases, this reaction presents as target-like lesions over the entire body, including the palms and soles. In some cases, patients have also developed urticaria and angioedema. There is a single case report of Stevens-Johnson syndrome following MMR vaccination, but the patient continued to have similar episodes up to 7 years later, following other infections.

Vaccine-Associated Seizures

In the March issue of the *Journal of Pediatrics*, Lateef and colleagues evaluated reports of seizures and encephalopathy in the VICP

database.¹⁰ The authors evaluated all cases occurring in children 2 years of age and younger filed between 1995 and 2005. A total of 165 claims were identified with enough clinical information to include in the evaluation. Sixty-one percent of the cases were associated with DTP vaccine and 19.3% with DTaP. The remaining vaccines implicated included MMR (17.8%), *Haemophilus influenzae* type b (9.1%), inactivated polio (6%), hepatitis B (4.8%), oral polio (3%), pneumococcal conjugate (2.4%), and tetanus diphtheria (Td) (0.6%). Sixteen percent of children had received more than one vaccine at the visit associated with a neurologic adverse event. Fifty-nine percent of the cases involved seizures, while another 36% included both seizures and encephalopathy. Less than half of the reported seizures occurred within 72 hours of vaccine administration. Forty percent were associated with a fever. Fourteen of the patients had a previous history of seizures and 10% had been diagnosed with a neurologic or developmental impairment prior to vaccination.

Information on the subsequent evaluation of the patients involved in these claims was limited. Of those claims including a final diagnosis by a pediatric neurologist, 69% received a diagnosis of epilepsy. Of those children, 17% had myoclonic epilepsy, most considered to be severe myoclonic epilepsy of infancy (SMEI or Dravet syndrome), 12% had infantile spasms, 8% had primary generalized epilepsy, and 8% had febrile seizures. Twenty-six children had other neurologic conditions not believed to be related to the vaccine, including tuberous sclerosis and cerebral dysgenesis. The authors concluded that a significant number of the cases of seizures and encephalopathy reported to VCIP occurred in children with pre-existing neurologic conditions or neurodevelopmental impairment. The findings of their study are similar to those reported in a study using VSD data which found no relationship between vaccination and encephalopathy, as well as a recent study from the Netherlands showing that 65% of children described as having vaccine-related seizures had underlying seizures or neurologic conditions.^{11,12}

While an association between epilepsy and vaccines in healthy children appears unlikely, several studies suggest the potential for a causal relationship between the MMR or MMR-varicella (MMRV) vaccines and febrile seizures.⁵ Two studies published in 2014 evaluated the incidence of febrile seizures in children receiving the MMRV vaccine. Using a claims database of more than 17 million German people, Schink and colleagues compared the incidence of febrile seizures among children who

were vaccinated with MMRV and one of three other methods: a group who received MMR without varicella vaccine, a group that received MMR and varicella vaccine administered separately, and a group that received a dose of each MMR and MMRV.¹³ The risk for febrile seizures in the 5-12 days after immunization was similar among all groups, with adjusted odds ratios for MMRV compared to the other groups of 4.1 (95% CI 1.3-12.7) with MMR, 3.5 (0.7-19.0) with MMR and varicella vaccine, and 4.1 (1.5-11.1) with the combined group. Excluding children with underlying neurologic conditions provided comparable results.

In a second retrospective cohort study, MacDonald and colleagues compared the risk of febrile seizures after MMRV and the two vaccines given separately to children 12-23 months of age using Alberta health care registry data.¹⁴ The risk of seizures 7 to 10 days after vaccine administration was significantly higher with MMRV compared to the separate vaccines, with a relative risk of 1.99 (95% CI 1.3-3.05). Despite the greater relative risk, the absolute level of risk was small, approximately 3.5 seizures per 10,000 doses. In children with a history of febrile seizures or other neurologic conditions, the risk was not significantly higher for MMRV. The authors suggest that this small increase in relative risk be weighed against the potential benefits in the administration of fewer vaccines on improving adherence and reducing costs.

Lack of Association between Vaccines and Multiple Sclerosis

Two recent studies examined the potential relationship between vaccines given during adolescence and the development of multiple sclerosis (MS) or other central nervous system (CNS) demyelinating diseases. In 2014, Langer-Gould and colleagues performed a nested case-control study using data from records of Kaiser Permanente Southern California members between 2008 and 2011.¹⁵ There were no associations between the hepatitis B vaccine, the HPV vaccine, or administration of any vaccine and the risk of MS or other CNS demyelinating diseases for up to 3 years after immunization (odds ratio 1.12, 95% CI 0.72-1.73 for hepatitis B, 1.05, 95% CI 0.62-1.78 for HPV, and 1.03, 95% CI 0.86-1.22 for any vaccine). Analysis of short-term effects (onset of symptoms within 30 days) was significant in the analysis of patients receiving any vaccine, suggesting that some patients with subclinical autoimmune disease may develop overt autoimmunity after receiving a vaccine.

Earlier this year, Scheller and colleagues used the nationwide registers of Denmark and Sweden to evaluate the relationship between HPV vaccine and MS or other CNS demyelinating diseases.¹⁶ The study included nearly 4 million women, of whom nearly 2 million had received the HPV vaccine. In the cohort analysis, there was no difference in risk of MS, with crude incidence rates of 6.12 events/100,000 person-years in the vaccinated group and 21.53 events/100,000 person-years in the unvaccinated group, and an adjusted odds ratio 0.90 (95% CI 0.70-1.15). There was also no difference in other CNS demyelinating diseases, with crude incidence rates of 7.54 events/100,000 person-years and 16.14 events/100,000 person-years in the vaccinated and unvaccinated groups, respectively. The adjusted odds ratio for this analysis was 1.00 (95% CI 0.80-1.26).

Intussusception after Rotavirus Vaccination

Two studies published in 2014 evaluated the risks of rotavirus vaccine administration. A U.S. study of more than 1.2 million rotavirus vaccine doses found the vaccine to be associated with 1.5 additional cases of intussusception per 100,000 recipients of the first dose (95% CI 0.2-3.2).¹⁷ There was no increased risk with doses 2 or 3. The authors concluded that this small risk should be considered in light of the relative benefits of vaccination. In England, use of a monovalent rotavirus vaccine was estimated to cause one additional case of intussusception for every 18,551 infants vaccinated.¹⁸ The analysis estimated that vaccination would prevent 3 deaths, 13,000 hospital admissions, 27,000 visits to an emergency department, and 74,000 clinic visits. As in the previous paper, the authors concluded that the benefits of the vaccine greatly exceeded the potential risk.

Summary

Establishing an accurate adverse event profile for the vaccines given to infants and children is essential in assuring families of their safety and promoting adherence to the immunization schedule. Twenty-five years of surveillance data from VAERS, VCIP, and VSD, as well as database analyses from other countries have added significantly to the information that health care providers have on vaccine adverse events. Continued surveillance will be necessary to provide the same information for new vaccines.

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