Vaccine Adverse Events: Separating Myth from Reality

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Vaccines have turned many childhood diseases into distant memories in industrialized countries. However, questions have been raised about the safety of some vaccines because of rare but serious adverse effects that have been attributed to them. Pain, swelling, and redness at the injection site are common local reactions to vaccines. Fever and irritability may occur after some immunizations. Currently, no substantial evidence links measles-mumps-rubella vaccine to autism, or hepatitis B vaccine to multiple sclerosis. Thimerosal is being eliminated from routine childhood vaccines because of concerns that multiple immunizations with vaccines containing this preservative could exceed recommended mercury exposures. Family physicians should be knowledgeable about vaccines so that they can inform their patients of the benefits of immunization and any proven risks. If immunization rates fall, the incidence of vaccine-preventable illnesses may rise. (Am Fam Physician 2002;66:2113-20. Copyright© 2002 American Academy of Family Physicians.)

Vaccination was one of the 20th century's most successful methods of disease prevention and eradication. Smallpox was eradicated worldwide, and the Americas were declared free of wild poliovirus in 1994.[1] The reported incidence of measles in the United States declined to 100 cases per year in 1999; more than one half of these cases were due to the importation of measles from other countries.[2] In 1999, an outbreak of rubella occurred in Nebraska among Hispanic meatpackers who had not received rubella vaccine in childhood.[3] Because vaccine-preventable diseases continue to be imported from other countries and are a threat to unimmunized persons in the United States, family physicians and other health care workers should continue to maintain high immunization rates in their patients.

Unfortunately, maintaining high immunization rates is becoming more difficult, in part because vaccines have become victims of their own success. Diseases that are preventable by vaccination are no longer encountered by most people in this country; thus, the threat of these illnesses seems less real. In addition, vaccines are not 100 percent effective, and they can have mild or, occasionally, serious adverse effects.

Vaccine Adverse Event Reporting System

The U.S. Food and Drug Administration (FDA) established the Vaccine Adverse Event Reporting System (VAERS) as a passive surveillance system for clinical events that occur after immunization. VAERS reports are submitted by manufacturers, health care professionals, state health coordinators, and parents of vaccinated children.[4]

VAERS reports may be incomplete or inconsistent, and a reported adverse event may be only temporally related to a vaccine.[4] However, the effectiveness of VAERS as an early warning system was demonstrated by reports of an increased incidence of intussusception after immunization with rotavirus vaccine.[5] This vaccine was subsequently withdrawn from the market.

Public Perception and Tolerance of Vaccine Risks

A recent telephone survey[6] demonstrated that more than 80 percent of parents supported immunizing their children to keep them well. However, 25 percent incorrectly believed that too many immunizations could weaken their child's immune system. Respondents who were women, white, or college graduates, or who had an alternative medical orientation were more likely to opt out of

immunization for their children. More than 80 percent of respondents indicated that physicians were still their primary source of vaccine information.

What level of vaccine-related risk will most parents tolerate? A study[7] in western Ontario found that most mothers would accept a risk ranging from one adverse event per 100,000 to 1 million vaccinations. However, 14 percent would not accept any risk of a serious adverse event. This zero-risk tolerance group tended to have a lower income and to prefer a nonnumeric statement of risk. Another study[8] using a hypothetic vaccine found that 23 percent of persons would vaccinate only if the risk of a serious event was zero.

In the absence of a direct threat from disease, it is clear that some people will not undergo vaccination unless absolute safety can be assured. Although absolute vaccine safety is the optimal goal, it is difficult to achieve in the real world.

Common Adverse Events with Vaccines

Common local reactions to vaccines include pain, swelling, and redness at the injection site. Systemic reactions, including fever, irritability, drowsiness, and rash, may also occur. The administration of acetaminophen at the time of vaccination or shortly afterward may moderate these effects.

Compared with the first dose, the fourth dose of currently licensed diphtheria and tetanus toxoids and acellular pertussis vaccine (DTaP) has been associated with increased incidences of fever and erythema, swelling, and pain at the injection site. In a small percentage of children, swelling of the entire thigh or upper arm for about four days has been reported after the fourth or fifth dose of DTaP. This self-limited reaction has been documented for multiple products from different manufacturers.[9]

One comparative study[10] found no significant differences in immunogenicity or reactions for a fifth-dose booster of six DTaP vaccines and one U.S.-licensed diphtheria and tetanus toxoids and whole-cell pertussis vaccine (DTwP). Redness, swelling, and pain at the injection site were increased for the fifth-dose booster compared with the fourth DTaP dose, but all common reactions occurred less frequently after DTaP than after DTwP.

Traces of antibiotics such as neomycin, which is present in varicella (chickenpox), trivalent inactivated poliovirus (IPV), and measles-mumps-rubella (MMR) vaccines, have been considered possible causes of adverse reactions. A history of anaphylactic reaction to neomycin is a contraindication to future immunization, whereas a local reaction is not.[11(pp30-9)]

Gelatin, which is used as a stabilizer in some live-virus vaccines (e.g., varicella and MMR vaccines), might cause a reaction. Children with a history of egg allergy may be given MMR vaccine, even though it is derived from chick embryo fibroblast tissue culture. However, influenza vaccine should not be given to a person with a history of egg allergy.[11(p35)]

MMR Vaccine and Autism

On November 12, 2000, the CBS television show *60 Minutes* featured a story on the MMR vaccine and its alleged link to autism. In 1998, investigators published a report[12(pp637-41)] on 12 children referred to a London pediatric gastroenterology unit for the evaluation of gastrointestinal diseases associated with developmental regression. The parents of eight of these children associated the onset of behav-

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ioral symptoms with the administration of MMR vaccine. The investigators identified lymphoid nodular hyperplasia in 10 children and postulated that "the consequences of an inflamed or dysfunctional intestine may play a part in behavioural changes in some children."[12(p639)] However, behavioural symptoms preceded bowel symptoms in four of the six children for whom the onset of bowel symptoms was known. The investigators stated, "We did not prove an association between measles, mumps, and rubella vaccine and the syndrome described."[12(p641)]

In 1999, other investigators published the findings of a much larger population-based study conducted in North London.[13(pp2026-9)] The study identified 498 children with autism but found no temporal association between onset of the disorder and receipt of MMR vaccine in the previous one to two years. Cases of developmental regression were not clustered in the months after vaccination. The investigators concluded, "Our analyses do not support a causal association between MMR vaccine and autism. If such an association occurs, it is so rare that it could not be identified in this large regional sample."[13(p2026)]

Another set of investigators found no vaccine-associated cases of inflammatory bowel disease or autism in 1.8 million Finnish children who received almost 3 million doses of MMR vaccine over 14 years.[14] In California, retrospective analyses[15] of MMR immunization coverage and children with autism also did not suggest an association between MMR vaccine and an increased incidence of autism.

The Institute of Medicine (IOM) recently concluded that "the evidence favors rejection of a causal relationship at the population level between MMR vaccine and ASD (autistic spectrum disorders)."[16(p9)] However, the IOM could "not exclude the possibility that MMR vaccine could contribute to ASD in a small number of children."[16(p9)]

Data on measles, mumps, and rubella disease and MMR vaccine[11,14,17-23] are summarized in *Table 1*.[24]

Investigators in several studies concluded that there is no causal relationship between MMR vaccine and autism.

Thimerosal in Vaccines

Thimerosal, a preservative containing ethyl mercury, has been used to prevent bacterial and fungal contamination of vaccines since the 1930s. In 1999, the FDA determined that infants who received multiple thimerosal-containing vaccines might be exposed to more mercury than is recommended. As a result, initial hepatitis B immunization was deferred until two to six months of age in infants of hepatitis B surface antigen (HBsAg)–negative mothers.[25] However, birth immunization continued to be recommended for the infants of HBsAg–positive mothers and the infants of mothers whose hepatitis B status was unknown.[25] Unfortunately, some unimmunized infants contracted hepatitis B, and at least one unimmunized infant born to an HBsAg–positive mother died of fulminant hepatitis B.[26] Routine hospital immunization of newborns with currently available thimerosal-free hepatitis B vaccines is now recommended.

Except for local hypersensitivity reactions, a recent review[27] found no evidence of harm from thimerosal in vaccines. Thimerosal-free vaccines are now available for all routine childhood immunizations. The American Academy of Family Physicians (AAFP), American Academy of Pediatrics (AAP), and Public Health Service (PHS) continue to recommend the reduction or removal of thimerosal from vaccines and note substantial progress in this effort.[28]

Vaccines and Multiple Sclerosis

Allegations have been raised that hepatitis B (HepB) vaccine can cause chronic fatigue syndrome, multiple sclerosis, and other autoimmune disorders.[29] However, the National

TABLE 1

Measles, Mumps, and Rubella Disease and Vaccine Fact Sheet*

Disease factor/ risk of sequelae	*Measles*	*Mumps*	*Rubella*	*MMR vaccine*
Disease factor				
Highest number of U.S. cases	894,134 cases in 1941[17]	152,209 cases in 1968[18]	12 million cases in 1964-1965; 57,686 cases in 1969[19] Congenital rubella: 20,000 cases in 1964-1965[19]	Highly efficacious in preventing disease†
Recent number of U.S. cases	86 cases in 2000[20]	338 cases in 2000[20]	176 cases in 2000[20] Congenital rubella: 9 cases in 2000[20]	No cases of congenital rubella reported after immunization of pregnant women, but theoretic risk is 2%[21]
Transmission route	Droplets	Direct contact, airborne droplets, fomites by saliva	Oral droplets Congenital rubella: transplacental passage	—
Transmission risk in susceptible household contacts	90% in susceptible household contacts[17]	Rate not available, because 30% to 40% of infections are subclinical[18]	50% to 60% in susceptible family members and almost 100% in closed populations[19] Incidence of defects in congenital rubella: ≥50% with infection during first month of pregnancy; 20% to 30% with infection during second month; 5% with infection during third or fourth month[11(pp495-500)]	—
Risk of sequelae				
Mortality	1 to 2 deaths per 1,000 measles cases[11(pp385-96),17]	2.5 to 50 deaths per 1 million mumps cases, because of 1.4% to 2% fatality rate from encephalitis[18,22]	1 death per 30,000 rubella cases, because of 20% fatality rate from encephalitis[19] Congenital rubella: no data available	1 death, but not attributed to vaccine[14] Fatal measles pneumonitis in a 21-year-old man with advanced HIV infection[23]
Encephalitis	1 to 2 cases per 1,000 measles cases[17]	1 case per 400 to 6,000 mumps cases[22]	1 case per 5,000 to 6,000 rubella cases[19]	1 case per 1 million doses[14]
Subacute sclerosing panencephalitis	8.5 cases per 1 million measles cases[17]	—	20 reported cases of progressive rubella panencephalitis[19]	0 to 0.7 cases per 1 million doses[14,17]
Pneumonia	3% of young adults with measles[23]	—	—	2 cases per 1 million doses[14]
Thrombocytopenia		Rare[22]	1 case per 3,000 rubella cases[19]	0.5 to 33 cases per 1 million doses[11(pp385-96),14]
Orchitis	—	14% to 35% of adolescent and adult men with mumps[14,18]	—	0.3 cases per 1 million doses[14]
Anaphylaxis	—	—	—	5 cases per 1 million doses (none fatal)[14]

MMR = measles, mumps, rubella; HIV = human immunodeficiency virus.

**—Data on measles, mumps, and rubella disease represent reported or estimated disease and sequelae; data on vaccine represent estimated risks.*
†—A single dose of vaccine given at 12 to 15 months of age has an efficacy of 95%; efficacy is further improved by a second dose given at 4 to 6 years of age.[11(pp385-96)]

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Multiple Sclerosis Society[30] cited a French report that found a lower frequency of neurologic disease among recipients of 60 million doses of HepB vaccine. The fact that genetic sequencing has not demonstrated a similarity between HepB vaccine and myelin basic protein casts doubt on a theory proposing that immunization provokes the formation of antimyelin antibodies (molecular mimicry).[31]

A recent report[32] from the Nurses' Health Study, which included more than 200,000 women, found no association between HepB vaccine and the development of multiple sclerosis. A study from the European Database for Multiple Sclerosis[33] found that vaccination against tetanus, hepatitis B, and influenza did not increase the risk of short-term relapse in patients with multiple sclerosis.

Vaccines and Type 1 Diabetes

Concerns have been expressed that vaccines could be linked to type 1 diabetes. A Swedish study[34] found that children with type 1 diabetes were less likely to have received measles vaccine than children without diabetes. No connection was reported between type 1 diabetes and tetanus toxoid or pertussis, rubella, mumps, and bacille Calmette-Guérin vaccines.[34] A Vaccine Safety Datalink project of the Centers for Disease Control and Prevention (CDC) did not find an increased risk of type 1 diabetes with whole-cell or acellular pertussis–containing vaccines, MMR vaccine, HepB vaccine, and varicella vaccine.[35] Similarly, there has been no association between type 1 diabetes and *Haemophilus influenzae* type b conjugate vaccine.[36]

Influenza Vaccine and Guillain-Barré Syndrome

The 1976 swine influenza vaccine was associated with an increased risk of Guillain-Barré syndrome (slightly less than 10 cases per 1 million persons vaccinated) compared with the background risk.[37] Later studies found either no statistically significant increase in risk or an increase of about one additional case of Guillain-Barré syndrome per 1 million persons vaccinated.[37] This risk is significantly less than that for severe influenza and its complications. However, influenza vaccine may be avoided or antiviral chemoprophylaxis may be used in patients who are not at high risk and who developed this syndrome within six weeks after receiving influenza vaccine. Inactivated influenza vaccine contains noninfectious killed viruses and cannot cause influenza.[37]

Varicella Vaccine and VAERS

The use of varicella vaccine is increasing in the United States because of state mandates and reports of secondary infection with invasive group A streptococcal disease in children with varicella-zoster virus infection.[38] Deaths from varicella pneumonia, encephalitis, and disseminated disease have also occurred in adults exposed to children with varicella.[39]

Significant risks of varicella disease and adverse events attributed to varicella vaccine[11,38,40-43] (many of them reported from VAERS) are listed in *Table 2*.[24] Although events reported to VAERS may be temporally related to vaccination, this relationship does not establish causation. Adverse events such as anaphylaxis may be related to a sensitivity to vaccine components (e.g., gelatin) rather than to the attenuated vaccine virus itself.

Consequences of Failure to Vaccinate

A recent study[44] in Colorado demonstrated that children who were exempted from immunization were 22 times more likely to develop measles and almost six times more likely to acquire pertussis than vaccinated children. School was the site of infection in more than 20 percent of the children who developed measles or pertussis. In this study, each 1 percent increase in children exempted from immunization increased the risk of a pertussis outbreak by 12 percent.[44] Because immunizations against measles and pertussis are not 100 percent effective, there was a 60 percent and a 90 percent annual increased risk of measles and pertussis among vaccinated

TABLE 2
Varicella Disease and Vaccine Fact Sheet*

Disease factor/risk of sequelae	*Varicella*	*Varicella vaccine*
Disease		
Average annual number of U.S. cases	3.7 million cases per year in 1980-1990[40]	Efficacious in preventing disease†
Transmission route	Direct contact or airborne spread of respiratory tract secretions; transplacental passage	
Transmission rate to susceptible contacts	90% in susceptible household contacts[40] ≤30% in classroom contacts[41]	3 confirmed cases secondary to transmission in immunocompetent persons[42]
Risk of sequelae		
Mortality	94 deaths per year in 1987-1992[40]	14 deaths in 1995-1998‡; vaccine not implicated or confirmed as cause[42]
Localized rash		3% to 5% of vaccine recipients[11(pp624-38)]
Generalized varicella-like rash	100% of persons with varicella	3% to 5% of vaccine recipients[11(pp624-38)]
Invasive group A streptococcal disease	5.2 cases per 100,000 varicella cases[38]§	1 case[42]
Anaphylaxis	—	30 nonfatal cases[42]‡
Herpes zoster (children under 20 years of age)	68 cases per 100,000 person-years[11(pp624-38)]	2.6 cases per 100,000 doses[11(pp624-38),42]‡
Thrombocytopenia	1% to 2% of persons with varicella[41]	0.3 cases per 100,000 doses[42]‡
Arthropathy	—	0.5 cases per 100,000 doses[42]‡
Cerebellar ataxia	1 case per 4,000 varicella cases[43]	0.4 cases per 100,000 doses[41]‡
Encephalitis	0.1% to 0.2% of persons with varicella[43]	0.3 cases per 100,000 doses[42]‡
Pneumonia	1 case per 400 varicella cases in adults[43]	0.2 cases per 100,000 doses[42]‡
Congenital varicella syndrome	0.4% of infants zero to 12 weeks of gestational age who have varicella[11(pp624-38),40] 2% of infants 13 to 20 weeks of gestational age who have varicella[11(pp624-38),40]	No cases in 87 women who received vaccine before or during pregnancy[42]‡

*—*Data on varicella disease represent reported or estimated disease and sequelae; data on varicella vaccine represent estimated risks.*
†—*The vaccine has an efficacy of 70% to 90%[40]; it is 95% to 100% effective in preventing moderate to severe disease.*[11(pp624-38),42]
‡—*Based on reports to the Vaccine Adverse Event Reporting System (VAERS) from March 17, 1995, through July 25, 1998. Data from VAERS do not prove association of an adverse event with a vaccine, but may prompt further investigation. The VAERS reporting rate is the number of adverse events per estimated vaccine doses sold.*[42]
§—*In children without varicella, the incidence of invasive group A streptococcal disease is 0.09 cases per 100,000.*

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children three to 18 years of age for each 1 percent increase in the proportion of unimmunized children (exemptors) by county.[44,45]

Consequently, the choice of some parents not to immunize their children increases the risk for children who are immunized. These parents may not realize that the individual choice not to vaccinate a child has public health consequences.

National Vaccine Injury Compensation Program

The National Childhood Vaccine Injury Act of 1986 established the National Vaccine Injury Compensation Program (VICP) as a federal no-fault system to compensate persons (or families of persons) who are injured by covered childhood vaccines. This act also requires physicians and other health care providers who administer VICP-covered vaccines or vaccines purchased under CDC contract to record the date of administration, the vaccine manufacturer, the lot number, and their name, business address, and title in the patient's permanent medical record.[46]

Health care providers must also give the vaccine recipient or the recipient's legal guardian the corresponding and most up-to-date Vaccine Information Statement (VIS) each time a VICP-covered vaccine is administered. The VIS for a non–VICP-covered vaccine must also be given if the vaccine is pur-

chased through a CDC contract. The CDC requires that the VIS version date and the date the VIS is provided be documented in the patient's medical record.[46]

The VIS for each vaccine may be obtained from the CDC (www.cdc.gov/nip/publications/vis/default.htm), the state health department, or the Immunization Action Coalition (www.immunize.org/vis). VIS translations in different languages are available on the Immunization Action Coalition Web site.

Manufacturers, state health coordinators, health care professionals, and parents may submit reports of adverse events following immunization. The table of reportable events is available at www.vaers.org/pdf/reportable.pdf. VAERS reporting forms can be obtained from the VAERS Web site (www.vaers.org) or by telephone (800-822-7967). A written form is available at the end of the *Physicians' Desk Reference*. Definitions of possibly compensable injuries and further information regarding eligibility and documentation of claims may be obtained from the VICP (www.hrsa.gov/bhpr/vicp) or by telephone (800-338-2382).

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