

Vaccine Adverse Events: Separating Myth from Reality

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Vaccines are one of the most successful medical advances in modern times. Most vaccine-preventable illnesses are unfamiliar to modern parents. Because of this, parents are increasingly questioning the necessity of immunizing their children, especially because no vaccine is completely free of adverse effects or the risk of complications. Family physicians should be aware of the risks and benefits of recommended immunizations. Thimerosal is currently used only in multidose vials of influenza vaccine, and exposure through vaccines is not associated with adverse neurologic outcomes. The measles, mumps, and rubella vaccine is not associated with autism. Vaccines are associated with local reactions, such as pain and erythema. The rotavirus vaccine minimally increases the rate of intussusception, whereas other vaccines minimally increase the risk of syncope. Although immunization with the human papillomavirus vaccine is recommended for all boys and girls, vaccination rates remain low. Physicians should guide parents to credible resources if they are considering vaccine refusal. If a recommended vaccine is refused, proper documentation is essential. The Vaccine Adverse Event Reporting System and National Vaccine Injury Compensation Program track adverse events and allow compensation for documented harms from vaccinations. (*Am Fam Physician*. 2017;95(12):786-794. Copyright © 2017 American Academy of Family Physicians.)

► See related editorial at <http://www.aafp.org/afp/2016/0715/p94.html>.

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► **Patient information:** A handout on this topic, written by the authors of this article, is available at <http://www.aafp.org/afp/2017/0615/p786-s1.html>.

With the success of vaccinations, many parents no longer have contact with children who have vaccine-preventable illnesses. Because of this, parents have difficulty balancing the potential harms and benefits of vaccines. Some parents express concern that physicians are not well educated on the adverse effects of vaccines or that physicians purposefully withhold information on adverse effects.¹ Parents may seek out additional information from websites containing inaccurate information. Family physicians should gather accurate information about the harms and benefits of vaccines to advocate for vaccination and decrease the incidence of vaccine-preventable diseases.

Vaccine Adverse Events

Common local reactions to vaccines include pain, swelling, and erythema at the injection site. Systemic reactions, including fever, irritability, drowsiness, and rash, may also occur.² Use of a longer needle (25 mm vs. 16 mm) decreases injection site reactions.³ The fourth dose of the diphtheria and tetanus toxoids and acellular pertussis (DTaP) vaccine is associated with an increased incidence of

fever and injection site reactions compared with the first dose (one in four children).² One out of 30 children reports up to seven days of swelling of the entire thigh or upper arm after the fourth or fifth dose.² Syncope may occur—especially in adolescents—after administration of the human papillomavirus (HPV) vaccine; quadrivalent meningococcal conjugate vaccine (MCV4); or tetanus toxoid, reduced diphtheria toxoid, and acellular pertussis (Tdap) vaccine.⁴ Because of this, adolescents should be observed for 15 minutes after receiving these vaccines.^{2,5} Administration of acetaminophen at the time of vaccination or shortly afterward may alleviate some adverse effects, but there may be a decreased antibody response to some vaccine antigens in children who receive antipyretics.⁶ For this reason and because antipyretics do not prevent febrile seizures, the Centers for Disease Control and Prevention (CDC) no longer recommends routine prophylaxis before vaccination.⁷

Potential Allergens in Vaccines

Trace amounts of antibiotics, such as neomycin, are present in varicella; measles, mumps, and rubella (MMR); and inactivated

WHAT IS NEW ON THIS TOPIC: VACCINE ADVERSE EVENTS

In 2012, the United States had its largest pertussis outbreak since 1955, including 48,277 cases and 20 pertussis-related deaths. The most common adverse effects of the human papillomavirus vaccine are transient and similar to those of other vaccines, including mild pain and bruising at the injection site, headache, lightheadedness, and syncope. The American Academy of Family Physicians does not support immunization exemption policies except in cases of allergic or medical contraindication.

poliovirus vaccines. Therefore, these vaccines are contraindicated in patients with a history of anaphylactic reaction to these antibiotics.^{8,9} Gelatin is used in some live virus vaccines, such as varicella and MMR; these vaccines should not be given to patients with a history of anaphylaxis to gelatin.⁸ Egg allergy is not a contraindication to the MMR vaccine, even though it is derived from chick embryo fibroblast tissue culture.⁹ Patients with anaphylaxis to egg proteins should not receive the inactivated influenza vaccine and should receive the egg-free trivalent inactivated influenza vaccine instead.¹⁰ The CDC publishes tables detailing the inactive ingredients or excipients and other potential allergens found in vaccines.^{8,11} Anaphylactic reactions to vaccines occur in approximately one per 1 million doses.¹² A patient who has an anaphylactic reaction to a vaccine should undergo immediate type allergy skin testing to confirm that the reaction was immunoglobulin E mediated and to determine which vaccine component was responsible. If the

skin test is negative, the vaccine can be readministered under close observation with resuscitation, including epinephrine, readily available.^{10,12} Every effort should be made to avoid unnecessarily withholding a disease-preventing vaccine. *Table 1* lists serious adverse reactions to vaccines.^{8,11-26}

Thimerosal in Vaccines

Thimerosal, a preservative containing ethyl mercury, was used to prevent bacterial and fungal contamination of vaccines beginning in the 1930s. In 1999, the U.S. Food and Drug Administration (FDA) determined that the child immunization schedule may expose infants to more mercury than recommended by the Environmental Protection Agency.²⁷⁻²⁹ There is no link between thimerosal exposure and adverse outcomes such as autism or abnormal neuropsychological functioning.³⁰⁻³² Thimerosal has been removed from all routine childhood vaccines except multidose vials of influenza vaccines.³³ Inactivated influenza vaccines are formulated in both multidose vials and preservative-free single-dose vials. Annual exposure to a thimerosal-containing influenza vaccine is considered safe.³⁴

MMR Vaccine

An article linking autism to the MMR vaccine was retracted for fraud, but this misinformation persists and has caused long-lasting public health consequences.^{35,36} Multiple studies have found no causal link between vaccination and autism, but the falsified report continues to cause parental concern.³⁵ Physicians must acknowledge these fears and inform concerned parents about

Table 1. Serious Adverse Reactions to Vaccines

Vaccine	Documented reaction	Approximate rate	Potential allergen
Diphtheria and tetanus toxoids and acellular pertussis (DTaP)	Serious allergic reaction ¹²⁻¹⁴	1 per 1,000,000 doses ¹³	Infanrix syringe contains latex ¹¹
Measles, mumps, and rubella	Immune thrombocytopenic purpura ¹⁴⁻¹⁸	1 per 20,000 doses ^{19,20}	Contains neomycin and gelatin ⁸
	Serious allergic reaction ^{14-19,21}	< 1 per 1,000,000 doses ^{19,22,23}	
Measles, mumps, rubella, and varicella	Febrile seizure ^{14,15,17-21,24}	8.5 per 10,000 doses ²⁰	Contains neomycin and gelatin ⁸
Meningococcal	Serious allergic reaction ^{14,25}	Rare ²⁵	Menomune and Bexsero contain latex ¹¹
Rotavirus	Intussusception ^{12,26}	1 per 20,000 to 100,000 doses ²⁶	Rotarix contains latex in oral applicator of diluents ¹¹

Information from references 8, and 11 through 26.

Table 2. Statistics on Measles, Mumps, Rubella, and the MMR Vaccine

<i>Disease factor</i>	<i>Measles</i>	<i>Mumps</i>	<i>Rubella</i>	<i>MMR vaccine</i>
Highest number of U.S. cases	894,134 cases (1941) ³⁹	152,209 cases (1968) ⁴⁰	12 million cases (1964 to 1965); 57,686 cases (1969) ⁴¹ Congenital rubella: 20,000 cases (1964 to 1965) ⁴¹	—
Number of recent U.S. cases	189 cases (2015) ⁴²	1,057 cases (2015) ⁴³	6 cases (2015) ⁴⁴ Congenital rubella: 4 cases (2005 to 2011) ⁴⁵	None in vaccinated persons ⁴⁶
Transmission route	Oral and airborne droplets	Direct contact, airborne droplets, and saliva	Oral droplets Congenital rubella: transplacental	—
Transmission risk in susceptible household contacts	90% ⁴⁷	Not available because 30% to 40% of infections are subclinical ⁴⁰	50% of infections are subclinical During first trimester, the risk of fetal infection may be as high as 90% Congenital rubella syndrome is rare when infection occurs after 20 weeks' gestation ⁴⁸	—
Mortality risk	2 deaths per 1,000 measles cases ¹⁹	None reported ²²	0% to 50% ¹⁶ Congenital rubella: 0% ⁴¹	397 cases (according to the Vaccine Adverse Event Reporting System; unknown number of vaccinations) ²¹
Encephalitis risk	1 case per 1,000 measles cases ¹⁹	1 case per 300 to 6,000 mumps cases ²²	1 case per 6,000 rubella cases ¹⁶	1 case per 3 million vaccinations ¹⁸
Subacute sclerosing panencephalitis risk	8.5 cases per 1 million measles cases ³⁹	—	Rare ¹⁶	0 to 0.7 cases per 1 million vaccinations ^{39,49}
Pneumonia risk	1 case per 20 measles cases (the most common cause of death from measles in young children) ⁵⁰	—	—	2 cases per 1 million vaccinations ⁴⁹
Thrombocytopenia risk	—	—	1 case per 3,000 rubella cases ¹⁶	1 case of immune thrombocytopenic purpura per 40,000 vaccinated children (risk increased in the 6 weeks following vaccination) ²⁴
Orchitis risk	—	3 to 10 cases per 100 adolescent and adult men with mumps ⁵¹	—	0.3 cases per 1 million vaccinations ²²
Anaphylaxis risk	—	—	—	0.65 cases per 1 million vaccinations ²³

MMR = measles, mumps, and rubella.
Information from references 16, 18, 19, 21 through 24, and 39 through 51.

the benefits of immunization and the potential harm of vaccine refusal. Febrile seizures that occur seven to 10 days after the first dose of the MMR vaccine are uncommon, but the risk is increased when the first dose is given

after the recommended age of 12 to 15 months.^{37,38} The risk of immune thrombocytopenic purpura is increased after both natural measles infection and for up to six weeks after MMR vaccination (Table 2).^{16,18,19,21-24,39-51}

Infection with measles, mumps, or rubella causes more severe adverse effects than the MMR vaccine, and vaccine refusal has been linked to recent outbreaks of these infections.⁴⁵

HPV Vaccine

HPV is a sexually transmitted infection that can cause genital warts and anogenital and oropharyngeal cancers.^{52,53} The HPV vaccine has been recommended for all adolescents since 2011.⁵³ However, as of 2013 only 57.3% of girls and 34.6% of boys had received at least one dose.⁵³ HPV immunization rates are suboptimal partly because of unfounded concerns that it encourages sexual activity at a younger age and reduces other protective behaviors.^{52,54,55} Although hepatitis B can also be sexually transmitted, this vaccine has had near universal uptake. Despite concerns about the safety of the vaccine, the most common adverse effects are transient and similar to those of other vaccines, such as mild pain and bruising at the injection site, headache, lightheadedness, and syncope.^{53,56,57}

Rotavirus Vaccine

The first rotavirus vaccine licensed in the United States was withdrawn because of an increased incidence of intussusception. Children who have received the newer vaccines have only a slightly increased risk of intussusception compared with unvaccinated infants and a lower risk compared to those with rotavirus infection. Intussusception occurs during the time of maximum viral replication after vaccination: three to five days after immunization with the pentavalent vaccine (Rotateq) and four to six days after immunization with the monovalent vaccine (Rotarix).⁵⁸ The risk of intussusception is about one event per 100,000 vaccine doses.⁵⁸ Immunizing a birth cohort of 4 million children would avert 255,000 physician visits, 137,000 visits to the emergency department, and 44,000 hospitalizations, and would prevent 13 deaths.⁵⁹

Meningococcal Vaccine

Universal immunization with MCV4 has been recommended for adolescents since 2005. The initial dose is recommended at 11 to 12 years of age, with a booster at 16 years of age. This vaccine protects against serogroups A, C, W135, and Y. Previous concerns about an increased risk of Guillain-Barré syndrome associated with the vaccine were unfounded.⁶⁰ The most common adverse effects are fever, headache, injection site erythema, and dizziness. Immunity wanes over time, even after the booster dose.⁶⁰ There are now two well-tolerated serogroup B

meningococcal vaccines that the FDA approved in 2015. Previous vaccines against serogroup B meningitis caused adverse effects from cross allergenicity with antigens in the human central nervous system.⁶¹ The CDC's Advisory Committee on Immunization Practices recommends routine use of these vaccines only in high-risk persons and during outbreaks because of the low prevalence of the disease.⁶² These two meningococcal serogroup B vaccines are not interchangeable.⁶²

Influenza Vaccine and Guillain-Barré Syndrome

The 1976 swine influenza vaccine was associated with a four- to eightfold increased risk of Guillain-Barré syndrome, or an attributable risk of one case per 100,000 persons vaccinated.^{57,63} A study of the 2009 influenza vaccine did not show a similar association.⁶⁴ Although the literature is conflicting, the influenza vaccine may at worst slightly increase the risk of Guillain-Barré syndrome: one hospital admission per 1 million vaccinations, or one additional case per 1.25 million vaccinations.^{57,63,65} Studies suggest that influenza infection has a stronger association with Guillain-Barré syndrome than does the vaccine, so vaccination may actually decrease the overall incidence.^{57,63}

Varicella and Zoster Vaccines

Before routine vaccination, wild-type varicella caused approximately 10,000 hospitalizations and 100 deaths annually.⁶⁶ All 50 states mandate vaccination of school-aged children with the varicella vaccine.⁶⁷ Adverse effects are generally mild and include erythema and pain at the injection site (*Table 3^{14,66,68-76}*). Local reactions occur in 19% of vaccinated children and 24% of vaccinated adolescents and adults (slightly more after the second dose).⁶⁶ Both the varicella and the zoster vaccines contain the same attenuated Oka varicella strain. A recent Institute of Medicine report supports a causal relationship between varicella vaccination and disseminated Oka strain varicella-zoster infections such as pneumonia, meningitis, or hepatitis, especially in persons with demonstrated immunodeficiencies.²⁷ Adverse events such as anaphylaxis may be related to sensitivity to vaccine components (e.g., gelatin) rather than to the attenuated vaccine virus itself. Nearly one in three unvaccinated persons in the United States will develop herpes zoster, and this risk increases with age.⁷⁷ In general, zoster vaccine is well tolerated. The most common adverse effects are erythema (36%), pain or tenderness (35%), swelling (26%), and itchiness (7%) at the injection site.⁷⁶ The benefits of vaccination and rates of adverse events are greater in persons 60 to 69 years of age compared with older adults.⁷⁷

Table 3. Statistics on Varicella and the Varicella Vaccine

<i>Disease factor</i>	<i>Varicella</i>	<i>Varicella vaccine</i>
Average annual U.S. cases	4 million cases per year from 1980 to 1990 ^{14,66}	Prevents an estimated 3.5 million cases per year ⁶⁸
Transmission route	Direct contact or airborne spread of respiratory secretions; transplacental	—
Transmission rate to susceptible contacts	90% in susceptible household contacts ^{14,69} 10% to 35% of persons with limited exposure ¹⁴	Varicella zoster virus was transmitted from vaccine recipients with postvaccination rash to 3 household contacts from 1995 to 2005 ⁷⁰
Mortality	Prevaccine era: 105 deaths per year from 1970 to 1994 ⁶⁹ Postvaccine era: 17 deaths per year from 2008 to 2011 ⁷¹	2 deaths ever reported from Oka strain of varicella zoster virus in immunocompromised or likely immunocompromised individuals ⁷²
Localized rash incidence	—	3% of children have a varicella-like rash at injection site ⁶⁶
Generalized varicella-like rash incidence	100% of persons with varicella ¹⁴	37 reports of rash from 1995 to 2005, some in immunocompromised patients ⁷⁰
Fever incidence	Most children	11.4 per 100,000 vaccinations ⁷³
Adverse event risk	—	20.8 per 100,000 vaccinations (2005) ⁷³
Anaphylaxis risk	—	76 cases ever reported ¹⁴
Herpes zoster risk (in children younger than 18 years)	230 cases per 100,000 varicella cases in 2008 ⁷⁴	48 cases per 100,000 vaccinations (2008) ⁷⁴
Cerebellar ataxia risk	1 case per 4,000 varicella cases in children younger than 15 years ¹⁴	Weak evidence ¹⁴
Encephalitis risk	1.8 cases per 10,000 varicella cases ⁶⁶	12 cases from 1995 to 2005 ⁷⁰
Pneumonia risk	1 case per 400 varicella cases in adults ⁷⁵	5 cases ever reported (4 in immunocompromised children) ¹⁴
Congenital varicella syndrome risk	< 2% risk from primary maternal varicella infection ⁶⁶ 2% of infants 13 to 20 weeks of gestational age who have varicella ¹⁴	0 cases in 87 women vaccinated before or during pregnancy ⁷⁶

Information from references 14, 66, and 68 through 76.

Vaccine Refusal

The rate of parental refusal of all or selective immunizations is increasing.⁷⁸ The American Academy of Family Physicians (AAFP) does not support immunization exemption policies except in cases of allergic or medical contraindication.⁷⁹ Physicians should provide vaccine information statements to parents who are considering vaccine refusal or delay and direct them to credible sources of information (*Table 4*).^{80,81} If parents decide against a recommended vaccine, they should sign a refusal to vaccinate form, and this declination should be documented with provision of the vaccine information statement.⁸² The American Academy

Table 4. Credible Immunization Resources for Parents

American Academy of Pediatrics

<https://www.healthychildren.org/english/safety-prevention/immunizations/pages/default.aspx>

Centers for Disease Control and Prevention

<http://www.cdc.gov/vaccines/vac-gen/default.htm>

Children's Hospital of Philadelphia

<http://www.chop.edu/centers-programs/parents-pack#.VsIAQLQrJmo>

Every Child by Two Initiative, Vaccinate Your Family Program

<http://www.vaccinateyourfamily.org>

Immunization Action Coalition

<http://www.vaccineinformation.org>

Information from references 80 and 81.

Vaccine Adverse Events

VAERS. The program monitors vaccine safety when a new vaccine is approved or when there are new vaccine recommendations.⁹²

National Vaccine Injury Compensation Program

The National Childhood Vaccine Injury Act of 1986 established the no-fault National Vaccine Injury Compensation Program to compensate patients and families injured by recommended vaccines. This law requires physicians who administer vaccines to document the provision of current vaccine information statements along with the vaccine manufacturer and lot number. The program's website includes a table of covered vaccine injuries.⁹³ Injuries outside those listed and suspected to be vaccine related can also be compensated but require additional evidence. The program is funded by an excise tax on vaccines.

This article updates a previous article on this topic by Kimmel.⁹⁴

Data Sources: Essential Evidence Plus was searched using the key word vaccine. PubMed was also searched using the key words vaccine adverse effects and thimerosal. Searches were also performed for individual vaccines, and the websites of the Centers for Disease Control and Prevention, the American Academy of Pediatrics, the American Academy of Family Physicians, the Vaccine Adverse Event Reporting System, and the Health Resources and Services Administration were also searched. Search dates: October 28, 2015, to January 17, 2017.

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