Allergenic Components of Vaccines and Avoidance of Vaccination-Related Adverse Events

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Vaccines have had a dramatic effect on the prevalence of communicable diseases, but, in selected individuals, the injection presents a risk of anaphylaxis. Fortunately, most people have no allergic reactions to vaccines. In egg-allergic individuals, care must be taken before administering specific vaccines; the algorithm provided in this article gives specific recommendations for skin testing and desensitization. This algorithm is not needed for individuals receiving the measles-mumps-rubella vaccine because the risk of anaphylaxis is extremely low, even in those with known egg-protein sensitivity. Some individuals have gelatin sensitivity, which may cause anaphylaxis. Selected vaccines contain antibiotic drugs, so it is important to note if an individual has any known drug sensitivity, especially to neomycin, polymyxin B, or amphotericin B. Lastly, vaccine preservatives may cause reactions, but this occurs very infrequently.

Introduction

The ultimate goal of immunization is eradication of disease, whereas the immediate goal is prevention of disease in individuals and populations. This is achieved via timely vaccination with both active and passive immunoprophylaxis. Vaccination is a high priority for infants, children, and adolescents and is also important for adults.

Prime examples of successful vaccination programs are the global eradication of small pox in 1977 and the elimination of poliomyelitis in the United States in 1991. In the United States alone, vaccinations have dramatically reduced or almost eliminated diphtheria, measles, mumps, poliomyelitis, rubella, tetanus, and *Haemophilus influenzae* type B (HIB) disease [1••].

Vaccines are developed to be immunogens. Active vaccination provides an immunogen that yields the greatest protection, whereas passive vaccination provides protection via infusion of a protective antibody but is effective only as long as the antibody is circulating [1••,2,3••]. The true intent of vaccination is replacement of the natural primary contact with a safer "artificial" contact such that a heightened immune response occurs before natural exposure. An effective vaccine does not produce disease yet provides an immunogen that induces long-lasting or permanent protection. The ideal vaccine also should be free of contaminants, stable, easy to store, and simple and inexpensive to produce and administer.

If the childhood vaccination schedule is followed, an infant receives hepatitis B vaccination at birth, repeated twice within the first 18 months. The infant also is vaccinated for diphtheria, tetanus, and acellular pertussis (DTaP) at 2, 4, and 6 months with a booster between 15 and 18 months and again at 4 to 6 years of age. A HIB vaccination usually is administered at 2, 4, and 6 months with a booster between 12 and 15 months. Poliomyelitis vaccination, which previously was administered orally, is now administered intramuscularly at 2 and 4 months with a third dose usually between 6 and 18 months and a repeat dose at 4 to 6 years. The measles-mumps-rubella (MMR) vaccine is administered at 12 to 15 months with a repeat around 5 years of age (before school). Varicella vaccine also is administered between 12 to 18 months. In selected areas, hepatitis A vaccine is administered at 24 months to 12 years. In children aged 11 to 12 years up to adolescents, the hepatitis B, tetanus, MMR, and varicella vaccines are often repeated.

For world travelers, other vaccinations for diseases such as yellow fever and typhoid are available. Table 1 lists vaccines that are licensed in the United States. Vaccines are not pure; they contain a mixture of active-agent antibiotic drugs, preservatives, culture-media proteins, and other additives. Therefore, vaccination can cause allergic reactions to any of these components. New vaccines are being developed. The rotavirus vaccine was associated with adverse events and currently is under investigation.

According to the *Red Book 2000: Report of the Committee on Infectious Diseases* from the American Academy of Pediatrics [1••], all vaccines licensed in the United States are safe and effective, but no vaccine is absolutely safe or

Table 1. Vaccines licensed in the United States

Vaccine	Type	Route	Culture media	Preservatives	Antibiotic drugs	Stabilizers	Potential for reactions
Diphtheria*	Toxoid	IM	Mueller-Miller media	Thimerosal, aluminum, formaldehyde	—	—	Components
Hepatitis A*	Inactivated virus	IM	Human diploid cells	Aluminum, formalin, phenoxyethanol	—	—	Components, aluminum
Hepatitis B*	Recombinant Subunit	IM	Yeast cells†	Thimerosal, formaldehyde, aluminum	—	—	Components, thimerosal, aluminum, yeast cells
HIB*	Polysaccharide	IM	Complex fermenation media	Thimerosal	—	—	Components, thimerosal
Influenza*	Live virus	IM	Chick embryo	Thimerosal, formaldehyde	Neomycin, polymyxin B, gentamicin, streptomycin	Gelatin, polysorbent 80	Natural dry latex rubber stoppers, gelatin, antibiotic drugs, thimerosal
Lyme*	Recombinant	IM	Inorganic salts, vitamins, silicon	Aluminum, phenoxyethanol	Kanamycin	Gelatin, sorbitol	Gelatin, antibiotic drugs, aluminum
Measles*	Live virus	IM	Chick embryo	—	Neomycin	Gelatin, sorbitol	Gelatin, antibiotic drugs
Meningococcal*	Polysaccharide	IM	Mueller-Hinton agar, Watson-Sharp media	Thimerosal	—	Lactose	Thimerosal
Mumps*	Live virus	IM	Chick embryo	—	Neomycin	Gelatin, sorbitol	Gelatin, antibiotic drugs
Pertussis*	Acellular toxoid	IM	Modified Stainer-Scholte media	Thimerosal	—	Gelatin, sorbitol	Gelatin, thimerosal
Pneumococcal*	Polysaccharide-7 with tetanus toxoid	IM	Capsular antigens, yeast cells	Aluminum	—	—	Aluminum
Pneumococcal*	Polysaccharide 23	IM	Capsular antigens	Phenol	—	—	—
Poliomyelitis*	Virus	IM	Monkey kidney cells	Formaldehyde, phenoxyethanol	Neomycin, streptomycin, polymyxin B	Gelatin, calf serum protein	Gelatin, antibiotic drugs
Rubella*	Live virus	IM	Human diploid cells	—	Neomycin	Gelatin, sorbitol	Gelatin, antibiotic drugs
Tetanus*	Toxoid	IM	Peptone based	Aluminum, thimerosal	—	—	Thimerosal
Varicella*	Live virus	SC	Yeast cells†	—	Trace neomycin	Gelatin	Gelatin, antibiotic drugs
Cholera‡	Killed bacteria	SC or IM	Trypticase soy agar	Phenol	—	Gelatin	Components, gelatin
Japanese encephalitis‡	Inactivated virus	SC	Mouse brain	Thimerosal, formaldehyde	—	Gelatin, sorbitol	Gelatin, thimerosal

*Common vaccines for infants, children, and adults.
†Yeast cells are *Saccharomyces cerevisiae.*
‡Vaccines for specific situations.
HIB—*Haemophilus influenzae* type B; IM—intramuscular; SC—subcutaneous.

Table 1. Vaccines licensed in the United States *(Continued)*

Vaccine	Type	Route	Culture media	Preservatives	Antibiotic drugs	Stabilizers	Potential for reactions
Rabies‡	Live virus	IM	Monkey or human diploid cells or chicken fibroblasts	Aluminum, thimerosal	Neomycin, chlorotetracycline, amphotericin B	Gelatin	Gelatin, antibiotic drugs, aluminum, thimerosal
Rotavirus‡	Live virus	Oral	Rhesus diploid cells	*Information not yet available*	Neomycin, amphotericin B	—	Antibiotic drugs
Typhoid‡	Polysaccharide	IM	Trypticase soy agar or veal infusion agar	Phenol	—	Gelatin	Gelatin
Yellow fever‡	Live virus	SC	Chick embryo	—	Trace neomycin	Gelatin, sorbitol	Gelatin, antibiotics

*Common vaccines for infants, children, and adults.
†Yeast cells are *Saccharomyces cerevisiae.*
‡Vaccines for specific situations.
HIB—*Haemophilus influenzae* type B; IM—intramuscular; SC—subcutaneous.

completely effective. Some recipients will have untoward reactions and some will not be protected fully. The goal of vaccination is to achieve the highest degree of protection with the lowest incidence of untoward effects. Unfortunately, the risks of vaccinations can range from trivial and inconvenient to severe and life threatening. Difficulty arises in distinguishing allergic reactions from other adverse events [3••].

Common adverse effects of vaccines usually are very mild to moderate in severity and do not have permanent sequelae. Examples of this include local inflammation after diphtheria, tetanus toxoids, and pertussis (DTP) vaccination and fever or rash 1 to 2 weeks after measles vaccination. Sterile abscesses can occur at the injection site with several of the inactivated vaccines. More serious adverse reactions can result in permanent sequelae or be life threatening. An example of this is vaccine-associated paralytic poliomyelitis after administration of the oral poliomyelitis vaccine in an apparently healthy child. Because of this adverse effect, intramuscular poliomyelitis vaccination using the inactivated virus is now recommended.

The National Childhood Vaccination Injury Act of 1986 requires physicians and other healthcare professionals to maintain permanent vaccination records and to report occurrences of certain adverse events [1••]. This currently applies to vaccination for measles, mumps, rubella, varicella, poliomyelitis, hepatitis B, pertussis, diphtheria, tetanus, and HIB. Adverse reactions can be reported to the Vaccine Adverse Events Reporting System. There is also a vaccine adverse event reporting form, which can be obtained online at www.fda.gov/cber/vaers/new.htm/.

The National Vaccine Injury Compensation Program is a no-fault system in which compensation may be sought for persons thought to have suffered injury or death as a result of administration of a covered vaccine. Claims are adjudicated first through the program before civil litigation can be pursued. This has resulted in fewer lawsuits against healthcare professionals and manufacturers and has helped ensure a stable vaccine supply and marketplace. Further, precautions and contraindications are meant to help prevent adverse events associated with administration of vaccines.

Possible Allergic Reactions to Vaccines

Components of vaccines include the active agent or antigen, antibiotic drugs, preservatives, culture medium, proteins, and additives. Studies have demonstrated the formation of specific IgE antibodies to tetanus and diphtheria toxoid after vaccination. Allergic reactions occur within minutes to 1 to 2 hours after vaccination; therefore, they should be easily identifiable. Despite the possibly common development of IgE antibodies to tetanus and diphtheria toxoid, classic allergic reactions to this vaccination seem to be relatively rare.

More importantly, reactions can occur in egg-allergic individuals upon administration of vaccines containing egg protein. Vaccines with the highest egg-protein content are those grown in extraembryonic tissue (*eg*, yellow fever vaccine); next are those grown in whole embryos (*eg*, mumps, rabies, and influenza), and those using fibroblasts have the lowest egg-protein content (*eg*, rubella and measles). In some reactions, however, the sensitizing antigen is not obvious. For example, six cases of anaphylactic reactions to the measles vaccine could not be attributed to egg sensitivity. Traces of fetal calf serum were found in the vaccine but could not be identified as the antigen. In another report, three cases of reactions occurred within 30 minutes of measles vaccination; the reactions were not obvious, and the antigen was not identified.

A review of the international reports of adverse reactions to vaccinations shows that the incidence of true allergic reactions to DTP, MMR, and other vaccines is rare. In New Zealand, vaccine safety reports show that the incidence of rash or urticaria was less than two cases per 100,000 vaccinations. The incidence of urticaria after administration of DTP-HIB vaccine was 2.5 cases per 100,000 vaccinations [4]. The incidence of rash after administration of influenza, hepatitis B, and HIB vaccines was zero, two, and 4.5 cases per 100,000 vaccinations, respectively; there was one case of anaphylaxis with influenza vaccination. For the MMR vaccine, the incidence of rash was 17, the incidence of urticaria was 2.5, and the incidence of anaphylaxis was 0.29 cases per 100,000 vaccinations. The incidence of anaphylaxis associated with the MMR vaccine was similar to that reported in Finland (0.15 cases per 100,000 vaccinations) but lower than that reported in England (1.0 cases per 100,000 vaccinations).

In the United States, Chen *et al.* [5] reported odds ratios with vaccinations in four health maintenance organizations. Interestingly, even though they looked at allergic reactions including anaphylaxis, asthma, and bronchitis, there is no report on these types of reactions. It may be surmised that the incidence of anaphylaxis in the US population is low and that other adverse events are more important with childhood vaccination.

Allergic reactions to egg-related antigens

Recent studies have indicated that egg-allergic children—even those with severe manifestations—are at risk for anaphylactic reactions to vaccines either singularly or in combination; however, skin testing with a diluted vaccine does not predict the allergic reaction that may occur with the vaccination. Most immediate allergic reactions following MMR vaccination appear to be caused by components such as the gelatin or neomycin in the vaccine [6,7]. Therefore, the *Red Book* currently recommends that children with egg allergy can be given MMR, measles, or mumps vaccination without prior skin testing.

Yellow fever and influenza vaccines do contain egg proteins and rarely can cause immediate allergic reactions

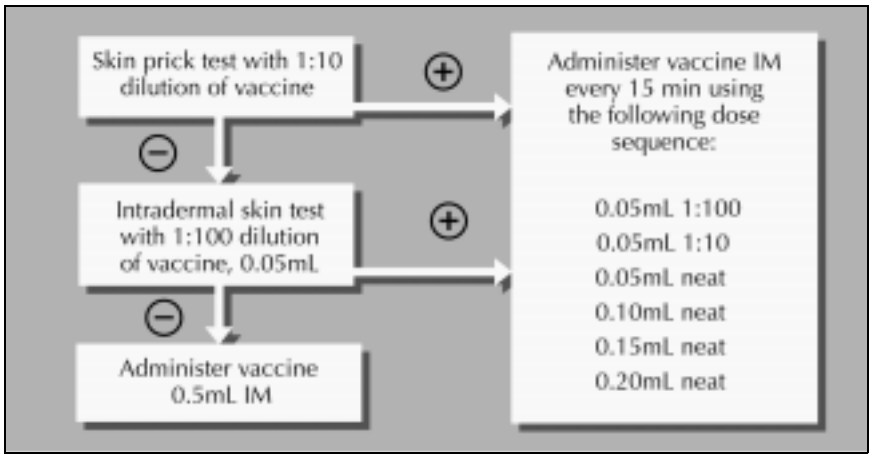

Figure 1. Vaccine skin testing and desensitization algorithm. IM—intramuscularly.

including anaphylaxis. Therefore, skin testing with these vaccines is recommended before administration in patients with a history of systemic anaphylaxis after egg exposure [1••,8].

Skin testing is done using a standard algorithm for egg-allergic individuals with a history of anaphylaxis (Fig. 1) [9]. Initially, a scratch, prick, or puncture test with a 1:10 dilution of the vaccine, histamine, and physiologic saline is performed on the skin with histamine and saline being the positive and negative controls. If there is a positive wheal (3 mm or larger than the saline control) then the desensitization protocol is followed. If the prick or puncture skin test is negative, then intradermal testing is performed. If the intradermal skin test is negative, then the vaccine may be administered to the patient under observation for 15 to 20 minutes. If the skin prick or intradermal tests are positive (wheal greater than 5 mm larger than the negative control), then the desensitization protocol is followed in a setting with personnel who are trained and experienced in the management of anaphylaxis.

Allergic reactions to preservatives

Thimerosal is a mercury-containing preservative often used as a vaccine additive and also present in eye drops and contact lens cleaning and storage solutions. It is meant to prevent bacterial and fungal contamination, particularly in multidose containers. Currently, thimerosal is found in DTP, DTaP, HIB, and diptheria and tetanus (DT) vaccines, one hepatitis B vaccine, influenza vaccines, meningococcal vaccines, one pneumococcal vaccine, and one rabies vaccine. None of the live-virus vaccines contain thimerosal.

Allergic reactions to thimerosal are well documented and include worsening of atopic dermatitis, conjunctivitis, and large local reactions at the injection site. Testing for thimerosal sensitivity is done using the patch method. Interestingly, in one study, five infants were reported to have worsening of their atopic dermatitis after injections with thimerosal-containing vaccine, yet the infants were able to complete the recommended vaccination schedule without any serious reactions [10].

Several vaccines contain aluminum salts as an adjuvant. Aluminum currently is found in six single-antigen and eight combination vaccines in the United States. Aluminum allergy is rare, usually presenting as contact dermatitis; respiratory symptoms due to inhalation also have been reported [11]. Patch testing is recommended for identification of aluminum allergy. Because of other adverse events, the addition of aluminum to vaccines is now being questioned [12].

Phenoxyethanol is another preservative that is found in vaccines. The positive patch-test rate for phenoxyethanol was found to be 2%, compared with a 10.7% rate for thimerosal. Systemic allergic reactions during vaccination with preparations containing phenoxyethanol may occur but are probably rare [13].

Allergic reactions to antibiotic drugs

Antibiotic drugs are well-known causes of mild to life-threatening allergic reactions. Vaccines contain trace amounts of antibiotic drugs; therefore, antibiotic-sensitive individuals are at risk. However, it is often difficult to prove the relationship between antibiotic sensitivity and allergic reactions and sometimes impossible to confirm it [1••].

The inactivated poliomyelitis vaccine (IPV) contains trace amounts of streptomycin, neomycin, and polymyxin B. The live-virus MMR and varicella vaccines contain trace quantities of neomycin. Some patients who are allergic to neomycin may experience a delayed type of local reaction 48 to 96 hours after an IPV, MMR, or varicella vaccination. This reaction usually consists of a papule and is often of little importance; it should not be considered a contraindication for administration of the vaccine. In patients with anaphylactic reactions to neomycin, avoiding a neomycin-containing vaccine is imperative. Penicillin allergy is more common, but none of the current vaccines contain penicillin or its derivatives.

Allergic reactions to other vaccine components including infectious agents

Gelatin is often used as a stabilizer in live-virus vaccines such as MMR, varicella, and yellow fever vaccines. Individuals

with a history of food allergy to gelatin rarely develop anaphylaxis after receiving a gelatin-containing vaccine. Skin testing of these patients before administration of the gelatin-containing vaccine should be considered, but there is no protocol or reportable experience available. Vaccine gelatin is usually porcine in origin, whereas food gelatins may be derived from bovine sources; thus a negative food history does not exclude the possibility of a vaccination reaction due to gelatin. Recent studies have demonstrated gelatin-specific IgE in patients who developed anaphylaxis after receiving gelatin-containing vaccines [14•,15,16].

Other vaccines, such as plague or typhoid whole-cell parenteral vaccine, may be associated with local or, occasionally, systemic reactions. These are usually toxic rather than allergenic in nature. Similar types of reactions may occur with DTP vaccinations but less frequently with the acellular pertussis–containing vaccines (DTaP). On occasion, urticaria and anaphylactic reactions have occurred with the combination tetanus vaccines. However, a transient urticarial rash is not a contraindication for further vaccination.

Reactions related to the diphtheria, tetanus toxoids, and pertussis vaccine

Serious adverse effects have been associated with this vaccination, often attributed specifically to pertussis. The classic example is encephalopathy associated with pertussis vaccination. The incidence is estimated to be one case in 110,000 to 140,000 vaccinations. It is manifested by a convulsion occurring within 72 hours of the vaccination with general complete recovery. However, there is a risk of permanent neurologic damage, which is estimated at one case in 310,000 vaccinations. One study looked at 784 DT vaccinations and 15,752 DTP vaccinations in children up to 6 years of age. Nine children were identified with convulsions within 48 hours of vaccination. Seven of the nine had elevated temperatures, and the seizures were brief with no sequelae detected.

Shock-like syndromes after DTP, such as hypotonic-hyporesponsive episodes, also have been reported with DTP and DT vaccinations. Young infants were found to be limp, pale, and unresponsive within 12 hours of vaccination. Fortunately, these episodes were self limited, lasting for several minutes to several hours with the majority being without residual damage. However, there are reports of death after a shock-like syndrome.

The classic local reactions—redness, pain, and swelling—occur in 30% to 50% of those receiving DTP vaccinations but are less common in those receiving only the DT vaccine. Persistent crying, often identified by parents, occurs in approximately 3.1% of DTP recipients. A review of adverse events after DTP vaccination failed to show a relationship with autism, infantile spasms, hypsarrhythmia, Reye's syndrome, or sudden infant death syndrome. There was a plausible relationship between DTP and protracted inconsolable crying, acute encephalopathy, shock and shock-like states and, more recently, seizures when a MMR vaccination was administered within 3 weeks. An phylaxis was not noted by the authors [5]. Other conditions with insufficient data were aseptic meningitis, chronic neurologic damage, erythema multiforme, other rashes, Guillain-Barré syndrome, hemolytic anemia, juvenile diabetes, learning disorders, attention deficit disorder, peripheral mononeuropathy, and thrombocytopenia. Because most of the problems seem to be associated with the cellular pertussis components, an acellular vaccine is now available

According to the *Red Book* [1••], the following are not contraindications for administration of the vaccine.

- Mild acute illness with low-grade fever or mild diarrhea
- Convalescent phase of an illness
- Current antimicrobial therapy
- Reaction to a previous DTP that involves only soreness, redness, or local reaction with a temperature less than 40.5°C
- Prematurity
- Pregnancy of the mother and other household contacts
- Recent exposure to an infectious disease
- Breastfeeding
- History of nonspecific allergies or relatives with allergies
- Allergies to penicillin except anaphylactic reactions to neomycin or streptomycin
- Allergies to duck meat or duck feathers
- History or family history of seizures
- Family history of sudden infant death
- Family history of an adverse event after vaccination
- Malnutrition

New Vaccines and Possible Reactions

Rotavirus and herpes zoster vaccines are being developed. The rotavirus vaccine was developed in animals but produced disappointing results in clinical trials. The increased appearance of gastrointestinal obstruction associated with use of the vaccine resulted in its removal from the market and further clinical investigations. The herpes zoster vaccine also has been problematic. Reactions to a Japanese vaccine have included low-grade transient fever and rash. Future vaccine development will include recombination vaccines with recombinant viral vectors. There are several adjuvant materials undergoing tests, including detoxified lipid A_1 liposomes, biodegradable microspheres, murayl peptides, and saponins.

Conclusions

Under the current recommendations for children and adults, there is a small risk of allergic reactions to vaccines [1••,17]. MMR vaccinations can be administered to egg-allergic children and adults without prior skin-test

evaluation. However, in individuals with significant egg hypersensitivity who need influenza or yellow fever vaccinations, skin testing is recommended before its administration. With other vaccines, administration followed by close observation is important, as is consideration of other vaccine components—such as thimerosal, protein components, or gelatin—that may cause reactions.

References and Recommended Reading

Papers of particular interest, published recently, have been highlighted as:

- • Of importance
- •• Of major importance

1.•• American Academy of Pediatrics: **Report of the Committee on Infectious Diseases.** In *Red Book,* edn 25. Edited by Pickering LK. Elk Grove Village: American Academy of Pediatrics; 2000:1–82.

These are the current recommendations for vaccines and infectious diseases as of 2000. The section on allergic reactions to vaccines contains the schedule and recommendations for patients needing vaccines. This should be used as the resource for any vaccine-related questions.

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This article shows that IgE to components of vaccines can be measured and that one should consider this as the possible cause of an allergic reaction. More importantly, gelatin may be assumed to be an inert component, but these authors demonstrate IgE directed to gelatin.

15. Nakayama T, Aizawa C, Kuno-Sakai H: **A clinical analysis of gelatin allergy and determination of its causal relationship to the previous administration of gelatin-containing acellular pertussis vaccine combined with diphtheria and tetanus toxoids.** *J Allergy Clin Immunol* 1999, **103:**321–325.

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