

Current Issues in Vaccine Allergy

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Vaccines provide a safe and effective approach to prevent infectious and allergic diseases. Allergic reactions to vaccines and drug products have become an important feature of modern day clinical practice. Most of these reactions are mild, but healthcare providers should be aware of the potential serious adverse reactions. The diagnosis of vaccine allergy is usually based on a detailed history and physical examination. Prevention, avoidance, the use of

alternative agents, desensitization, and premedication remain the cornerstones of therapy even as more refined diagnostic and management tools are being developed. Additional studies that are aimed at identifying other causes of immediate hypersensitivity after immunization with live virus vaccines are warranted. (Korean J Asthma, Allergy Clin Immunol 2004;24:186-201)

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ADVERSE REACTIONS TO VACCINES

Vaccines are administered to healthy individuals to protect others in addition to themselves. Thus, it is quite important to understand the possible risks of serious adverse consequences of immunization. Overall, the serious side effects from currently licensed vaccines are so rare that it is hard to distinguish causation from coincidence.¹⁾ However, the increasing numbers of recommended available vaccines have led to concerns regarding possible adverse effects from multiple immunizations.²⁾

The active vaccine immunogens are remarkably safe as a group. Side effects are rare and mostly mild, predictable, and consistent with the benefits associated with immunity. A vaccine is generally expected to be completely safe when the likelihood of succumbing to the threatened illness is perceived to be remote. It is recommended that health care workers administering the vaccines record the vaccine producer's name and lot number, and report major reactions within the time frames indicated. In the United States, an approved vaccine information sheet on each of the covered vaccines has been prepared by the Department of Health and Human Services and must be given to the parent or

the patient at the time of immunization.

Variations in vaccine manufacturing techniques from time to time and from brand to brand make it difficult to compare various studies on vaccine allergy in order to determine the relative immunization risks. In addition, any of the preservatives, adjuvants, antibiotics, stabilizers and culture contaminants used in the vaccine manufacturing process also has the potential to cause untoward reactions. To further confound the picture, there are inter-regional variations in the immunization schedules and available agents and their compositions in different countries.

Adverse reactions to vaccines can be local or systemic, and they can be immediate or delayed in onset. Some reactions are mediated by hypersensitivity while the mechanisms for others are incompletely understood. Interestingly, these reactions are extensions of the intended beneficial responses to vaccines, which are also mediated by protective immunoglobulin G (IgG) antibodies and T-lymphocyte responses.³⁾

IMMUNE MECHANISMS UNDERLYING VACCINE ALLERGY

Gell and Coombs (1968)⁴⁾ proposed the original classification of immunologic reactions into four types. Of these, IgE-dependent type I reactions constitute the most important mechanism for vaccine hypersensitivity. The other

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three types of IgE-independent reactions are less frequently noted in this context. Further details can be found in a recent review by the authors of this article.⁵⁾

HYPERSENSITIVITY REACTIONS RELATED TO VACCINE CONSTITUENTS

The potential cause of adverse effects resulting from a vaccine may reside in the primary infectious disease agent or the accompanying vaccine constituents and excipients.⁶⁾ The latter components differ with brand, manufacturing process, and the time of manufacture. The different components of available vaccines that may be suspected during a vaccine related reaction are listed in the 2003 *Physicians' Desk Reference* (Table 1).⁷⁾

As a general rule, hypersensitivity reactions to vaccine constituents are rare. In some instances, although symptoms appear soon after administration of a vaccine, it is difficult to distinguish between an allergic reaction to the vaccine from a reaction to an environmental allergen. Although it is recommended that facilities and personnel should be available for treating immediate hypersensitivity reactions in all settings where vaccines are administered, this should not be used to preclude the administration of vaccines in school-based or other non-clinic settings. Whenever possible, patients should be observed for an allergic reaction for 15 ~ 20 minutes after receiving immunization (s).

Clinically, the following hypersensitivity reactions are usually considered to be related to vaccine constituents: (1) allergic reactions to egg-related antigens; (2) mercury sensitivity in some recipients of mercury-containing immune globulins and vaccines; (3) antibiotic-induced allergic reactions; and (4) hypersensitivity to other vaccine components, e.g., gelatin, infectious agents etc.

1. Chicken egg protein and related antigens

Measles, mumps, influenza, yellow fever, and a brand of rabies vaccine are all egg-derived vaccines (Table 1). MMR (measles, mumps and rubella) vaccine has been suspected in the majority of reported cases of vaccine allergy to date.⁸⁾ Vaccine package inserts have traditionally indicated egg allergy to be a contraindication to vaccination with egg-derived vaccines. Most of the attention has focused on

the attenuated measles vaccine virus propagated in cultures of chick embryo fibroblasts. It is interesting to note here that its egg protein content is four log scales lower than Influenza vaccine virus harvested from the allantoic fluids of infected chick embryos.⁹⁾ The next few paragraphs highlight this and other clinical issues relevant to individual egg-derived vaccines.

2. Measles, Mumps and Rubella Vaccine

It is clinically difficult to calculate the true incidence of systemic allergic reactions to MMR vaccine¹⁾ since the diagnosis of these adverse reactions relies heavily on self-reporting of retrospective cases, with few cases in most prospective trials. This is further confounded by variations in protocols and vaccine-manufacturing techniques, and the imprecise and variable definitions of allergy, anaphylaxis, and skin tests in different situations.

Although the currently manufactured measles and mumps vaccines are derived from chick embryo fibroblast tissue cultures, they do not contain significant amounts of chicken egg cross-reacting proteins. Immediate hypersensitivity reactions to measles vaccines have been reported in medical literature since the early 1980s¹⁰⁻¹⁴⁾ after the vaccine had already been in use for 2 decades. Most of these reactions were reported in individuals who were *not* allergic to chicken egg or feathers.

Herman, et al (1983)¹¹⁾ published a retrospective analysis of two individuals who had experienced anaphylaxis after MMR vaccine and reported history of severe anaphylaxis to eggs and serum IgE antibodies to MMR vaccine and ovalbumin. Subsequently, they prospectively studied 24 children who had no clinical allergy to chicken egg despite positive skin tests to egg protein, and 6 subjects with a history of severe anaphylaxis to chicken eggs. All 24 non-anaphylactic subjects had negative skin tests to MMR vaccine and received it uneventfully. The six subjects with a history of egg anaphylaxis had positive skin tests to MMR vaccine and received gradual, incremental doses of the vaccine until the full dose was given without any adverse effects. However, they did not attempt to identify allergy to other components of the vaccine (e.g., gelatin, neomycin etc.), and did not include a control group of chicken egg-anaphylactic subjects to assess the efficacy of their desensitization protocol. Even

Table 1. Vaccine constituents listed in the 2003 Physicians' Desk Reference

Vaccine	Source (s) of Vaccine	Adjuvants/Excipients/Preservatives
<i>Toxoid Vaccines</i>		
Infanrix (Diphtheria and tetanus toxoids and acellular pertussis vaccine adsorbed) <i>GlaxoSmithKline</i>	1. Toxoid from <i>C. diphtheriae</i> grown in Linggoud and Fenton medium containing bovine extract 2. Toxoid from <i>C. tetani</i> grown in Latham medium 3. Three acellular antigens (inactivated pertussis toxin PT, filamentous hemagglutinin FHA, and pertactin OMP) isolated from <i>B. pertussis</i> grown in modified Stainer-Scholte medium	Aluminum hydroxide (0.625 mg aluminum/dose) 2-phenoxyethanol (2.5 mg/dose) Formaldehyde ($\leq 0.02\%$ w/v) Polysorbate 80 (Tween 80)
Tripedia (Diphtheria and tetanus toxoids and acellular pertussis vaccine adsorbed) <i>Aventis Pasteur</i> Note: Also marketed combined with ActHIB as Trihibit	1. Toxoid from <i>C. diphtheriae</i> grown in modified Mueller and Miller medium 2. Toxoid from <i>C. tetani</i> grown in peptone-based medium containing a bovine extract 3. Two acellular pertussis antigens (pertussis toxin and filamentous hemagglutinin) isolated from <i>B. pertussis</i> grown in modified Stainer-Scholte medium	Aluminum potassium sulfate (0.170 mg aluminum/dose) Formaldehyde ($\leq 0.02\%$) Gelatin (trace amounts) Polysorbate 80 (trace amounts) <0.3 μg of mercury left after post-production Thimerosal removal*
Tetanus and diphtheria toxoids adsorbed for adult use <i>Aventis Pasteur</i>	Toxoid from <i>C. diphtheriae</i> grown in modified Mueller and Miller medium Toxoid from <i>C. tetani</i> grown in peptone-based medium	Thimerosal (.01%) Aluminum potassium sulfate (0.28 mg aluminum/dose) Formaldehyde ($\leq 0.02\%$)
Diphtheria and tetanus toxoids adsorbed for adult and pediatric use <i>Lederle</i> Note: adult formulation (Td) contains less diphtheria toxoid than pediatric vaccine (DT)	Toxoid from <i>C. diphtheriae</i> grown in medium containing an enzymatic digest of casein Toxoid from <i>C. tetani</i> grown in medium containing beef heart infusion	Thimerosal (.01%) Aluminum phosphate (0.23–0.3 mg aluminum/dose) Formaldehyde ($\leq 0.02\%$)
Tetanus toxoid adsorbed <i>Lederle</i>	Toxoid from <i>C. tetani</i> grown in medium containing beef heart infusion	Thimerosal (.01%) Aluminum phosphate (0.80 mg aluminum/dose) Formaldehyde ($\leq 0.02\%$)
<i>Live, Attenuated Vaccines</i>		
M-M-R II (Measles, mumps and rubella virus vaccine live) <i>Merck</i> Note: each component of this vaccine is also marketed separately as Attenuvax (measles), Mumpsavax (mumps), MeruvaxII (rubella), M-R- VaxII (measles and rubella), and BiavaxII (mumps and rubella). The rubella component is not propagated in eggs and contains no residual egg protein.	Live, attenuated measles virus grown in chick embryo fibroblast culture Live, attenuated mumps virus grown in chick embryo fibroblast culture Live, attenuated rubella virus grown in human diploid lung fibroblasts	Neomycin (25 μg /dose) Gelatin (14.5 mg/dose) Human albumin (0.3 mg/dose) Sorbitol (14.5 mg/dose) Sucrose (1.9 mg/dose) Egg protein (trace) Fetal bovine serum (<1 ppm)

Table 1. Continued

Vaccine	Source (s) of Vaccine	Adjuvants/Excipients/Preservatives
Vivotif Berna (Live oral typhoid vaccine) <i>Berna</i>	Live, attenuated <i>Salmonella typhi</i> Ty21a grown in yeast cultures with casein, dextrose, and galactose	Sucrose (26–130 mg/dose) Ascorbic acid (1–5 mg/dose) Amino acid mixture (1.4–7 mg/dose) Lactose (100–180 mg/dose) Magnesium stearate (3.6–4.4 mg/dose) Gelatin capsule
Varivax (Varicella virus vaccine) <i>Merck</i>	Live, attenuated varicella virus, propagated in human diploid cell cultures	Sucrose (25 mg/dose) Gelatin (12.5 mg/dose) Monosodium L-glutamate (0.5 mg/ dose) Residual DNA and protein from diploid cells (trace) Neomycin (trace) Fetal bovine serum (trace) EDTA (trace)
Yf-Vax (Yellow fever vaccine) <i>Aventis Pasteur</i>	Live, attenuated yellow fever virus grown in chicken embryos	Gelatin Sorbitol Egg protein
<i>Inactivated Vaccines</i>		
Cholera vaccine <i>Wyeth-Ayerst</i>	Killed <i>Vibrio cholerae</i> grown on trypticase soy agar medium	Phenol (0.5%)
Havrix (Hepatitis A vaccine, inactivated) <i>GlaxoSmithKline</i> Note: adult dose is 1 ml, pediatric dose is 0.5 ml	Inactivated Hepatitis A virus grown in MRC-5 human diploid fibroblasts	2-phenoxyethanol (0.5%) Aluminum hydroxide (0.5 mg aluminum/ml) Polysorbate 20 (0.05 mg/ml) Residual MRC-5 proteins ($\leq 5 \mu\text{g/ml}$) Formalin ($< 0.1 \text{ mg/ml}$) Amino acid supplement (0.3%)
Vaqta (Hepatitis A vaccine) <i>Merck</i> Note: adult dose is 1 ml, pediatric dose is 0.5 ml	Inactivated Hepatitis A virus grown in MRC-5 human diploid fibroblasts	Aluminum hydroxide (0.45 mg aluminum/ml) Nonviral proteins ($< 0.1 \mu\text{g}$) Bovine albumin ($< 0.0001 \mu\text{g}$) Formaldehyde ($< 0.8 \mu\text{g}$) Chemical residuals ($< 10 \text{ ppb}$)
Fluogen (Influenza virus vaccine, trivalent, types A and B) <i>Parkdale</i>	Subvirion influenza antigens, ether extracted from influenza virus propagated in embryonated chicken eggs	Thimerosal ($50 \mu\text{g/dose}$) Polysorbate 80 Egg protein
Flushield (Influenza virus vaccine, trivalent, types A and B) <i>Wyeth-Ayerst</i>	Subvirion vaccine from influenza virus propagated in embryonated chicken eggs	Thimerosal ($50 \mu\text{g/dose}$) Polysorbate 80 Egg protein
Fluzone (Influenza virus vaccine, trivalent, types A and B) <i>Aventis Pasteur</i>	Subvirion vaccine from influenza virus propagated in embryonated chicken eggs	Thimerosal ($50 \mu\text{g/dose}$) Gelatin (0.05%) Egg protein
JE-Vax (Japanese encephalitis virus vaccine) <i>Aventis Pasteur</i>	Inactivated Japanese encephalitis virus harvested from infected mouse brain	Thimerosal ($70 \mu\text{g/dose}$) Gelatin ($500 \mu\text{g/dose}$) Formaldehyde ($< 100 \mu\text{g/dose}$) Polysorbate 80 ($< 0.0007\%$) Mouse serum protein ($< 50 \text{ ng/dose}$) Myelin basic protein undetectable ($< 2 \text{ ng/ml}$)

Table 1. Continued

Vaccine	Source (s) of Vaccine	Adjuvants/Excipients/Preservatives
Ipol (Poliovirus vaccine inactivated) <i>Aventis Pasteur</i> Note: oral, live, attenuated poliovirus vaccine no longer available in the United States	Types 1, 2, and 3 inactivated poliovirus grown in cultures of monkey kidney cells supplemented with calf serum	2-phenoxyethanol (0.5%) Formaldehyde (<0.02%) Neomycin (<5 ng) Streptomycin (<200 ng) Polymyxin B (<25 ng) Calf serum (<1 ppm)
IMOVax (Rabies virus vaccine) <i>Aventis Pasteur</i>	β -Propiolactone-inactivated rabies virus grown in MRC-5 human diploid fibroblasts	Human albumin (<100 mg/dose) Neomycin (<150 μ g/dose) Phenol red (20 μ g/dose)
Rabavert (Rabies virus vaccine) <i>Chiron</i>	β -Propiolactone-inactivated rabies virus grown in chicken fibroblast cultures supplemented with bovine gelatin and human albumin	Egg protein (<3 ng/dose) Neomycin (<1 μ g) Chlortetracycline (<20 ng) Amphotericin B (<2 ng) Phenol (0.5%)
Typhoid vaccine (Typhoid vaccine) <i>Wyeth-Ayerst</i>	Inactivated <i>Salmonella typhi</i> harvested from veal infusion agar	
Polysaccharide Vaccines		
ActHIB (Haemophilus B conjugate vaccine-tetanus toxoid conjugate) <i>Aventis Pasteur</i> Note: also marketed in combination with Tripedia as Trihibit	Haemophilus b capsular polysaccharide from <i>Haemophilus influenzae</i> grown in a semi-synthetic medium, covalently bound to tetanus toxoid from <i>C. tetani</i> grown in modified Mueller and Miller medium	Sucrose (8.5%)
HIBtiter (Haemophilus b conjugate vaccine-diphtheria CRM ₁₉₇ protein conjugate) <i>Lederle</i>	Haemophilus b capsular polysaccharide from <i>H. influenzae</i> grown in a medium of mineral salts and amino acids, conjugated to a modified toxin of <i>C. diphtheriae</i> grown in a medium containing yeast extract and casamino acids	Thimerosal (50 μ g/dose)
Liquid PedvaxHib (Haemophilus b conjugate vaccine-meningococcal protein conjugate) <i>Merck</i>	Haemophilus b capsular polysaccharide from <i>H. influenzae</i> grown in complex fermentation media, covalently bound to an outer membrane protein complex of <i>N. meningitides</i> grown in complex fermentation media	Aluminum hydroxide (0.225 mg aluminum/dose)
Comvax (Haemophilus b conjugate-meningococcal protein conjugate, and recombinant hepatitis B vaccine) <i>Merck</i>	Haemophilus b capsular polysaccharide from <i>H. influenzae</i> grown in complex fermentation media, covalently bound to an outer membrane protein complex of <i>N. meningitides</i> grown in complex fermentation media Hepatitis B surface antigen produced by recombinant yeast cells	Aluminum hydroxide (0.225 mg aluminum/dose) Yeast proteins ($\leq$ 1%) Sodium borate (35 μ g/dose)
Menomune—A/C/Y/W-135 (Meningococcal polysaccharide vaccine) <i>Aventis Pasteur</i>	Mixture of group-specific polysaccharide antigens from Group A, Group C, Group Y and Group W-135 strains of <i>Neisseria meningitides</i> cultivated with Mueller Hinton agar and Watson Scherp media	Thimerosal (50 μ g/dose in multidose vials) Lactose (2.5–5 mg/dose)

Table 1. Continued

Vaccine	Source (s) of Vaccine	Adjuvants/Excipients/Preservatives
Pneumovax 23 (Pneumococcal vaccine polyvalent) <i>Merck</i>	Mixture of polysaccharides from the 23 most prevalent or invasive types of <i>Streptococcus pneumoniae</i>	Phenol (0.25%)
Pnu-Imune 23 (Pneumococcal vaccine polyvalent) <i>Lederle</i>	Mixture of polysaccharides from the 23 most prevalent or invasive types of <i>S. pneumoniae</i>	Thimerosal (50 µg/dose)
Prevnar (Pneumococcal 7-valent conjugate vaccine-diphtheria CRM ₁₉₇ protein conjugate) <i>Lederle</i>	Mixture of polysaccharides from seven serotypes of <i>S. pneumoniae</i> grown in soy peptone broths, directly conjugated to a modified toxin of <i>C. diphtheriae</i> grown in a medium containing yeast extract and casamino acids	Aluminum phosphate (0.125 mg aluminum/dose)
Typhim Vi (Typhoid Vi Polysaccharide vaccine) <i>Aventis Pasteur</i>	Typhoid cell surface Vi polysaccharide extracted from <i>Salmonella typhi</i> grown in semisynthetic medium without animal proteins	Phenol (0.25%) Polydimethylsiloxane (trace)
<i>Recombinant Vaccines</i>		
Engerix-B (Recombinant hepatitis B vaccine) <i>GlaxoSmithKline</i> Note: adult dose is 1 ml, pediatric dose is 0.5 ml; less than 0.5 µg thimerosal in pediatric vaccine is residual from the manufacturing process and is not considered significant	Hepatitis B surface antigen produced by recombinant yeast cells	Thimerosal (25 µg/adult dose, <0.5 µg/pediatric dose) Aluminum hydroxide (0.5 mg aluminum/ml) Yeast proteins (≤5%)
Recombivax HB (Recombinant hepatitis B vaccine) <i>Merck</i> Note: adult dose is 1 ml, pediatric dose is 0.5 ml; pediatric formulation available without thimerosal as of mid-2000. Also available combined with Haemophilus b conjugate vaccine, marketed as Thimerosal-free Comvax	Hepatitis B surface antigen produced by recombinant yeast cells	Thimerosal (50 µg/ml for adult formulations; pediatric vaccine available without thimerosal) Aluminum hydroxide (0.5 mg aluminum/ml) Yeast proteins (≤1%)
Lymerix (Lyme disease vaccine) <i>GlaxoSmithKline</i>	Lipoprotein OspA (an outer surface protein of <i>Borrelia burgdorferi</i>) produced by recombinant <i>E. coli</i> grown in fermentation medium of inorganic salts, vitamins, kanamycin sulfate, antifoam and yeast extract	2-phenoxyethanol (2.5 mg/dose) Aluminum hydroxide (0.5 mg aluminum/dose)

Summarized from Physicians' Desk Reference, ed 57. Montvale, NJ, Medical Economics, 2003.

*JAMA 1999;282(18) and JAMA 2000;283(16).

so, following this study, the American Academy of Pediatrics (AAP) recommended the inclusion of skin testing to MMR vaccine in egg-allergic subjects in the *Red Book*, with the recommendation to use the desensitization protocol in those

with positive skin tests to the vaccine.

In the last 20 years since the above study, there have been multiple instances of uneventful administration of this vaccine to hundreds of children with known hypersensitivity

to chicken egg, as well as reports of anaphylaxis to MMR in people without the history of allergy to chicken eggs. Current body of evidence raises doubts that egg proteins in the vaccine play a major role in reactions to MMR.^{8,9,12)} Any of the other MMR components and excipients-viral antigens, neomycin, sorbitol, gelatin, and latex from vaccine vial rubber stoppers-could potentially be responsible for an IgE-mediated reaction. Children with severe hypersensitivity to egg protein have been demonstrated to be at low risk for anaphylactic reactions to these vaccines, singly or in combination (i.e., MMR). Skin testing with dilute vaccine is not predictive of an allergic reaction to immunization. In the light of above evidence, the AAP no longer recommends skin testing egg-allergic individuals to MMR, measles, or mumps vaccine before immunization.

3. Yellow Fever Vaccine

Currently available yellow fever and influenza vaccines are prepared in embryonated chicken eggs and contain up to 4-log higher egg protein content than measles and mumps vaccines which are propagated in cell cultures of chick fibroblasts. These vaccines contain chicken egg proteins and may rarely induce immediate allergic reactions including anaphylaxis.

The AAP currently recommends skin testing with yellow fever vaccine before its administration to persons with a history of systemic anaphylactic symptoms after egg ingestion. A graded-dose subcutaneous desensitization procedure (described later in this article) may be considered in an individual with positive skin tests to chicken egg if immunization is warranted because of the subject's risk of acquiring yellow fever.

4. Influenza Vaccine

The AAP recommends that children with severe anaphylactic reactions to eggs should not routinely receive influenza vaccine because of the risk of reaction. This recommendation is based on the likely recurrent (annual) need for this immunization, and the availability of chemoprophylaxis against influenza infection. Skin testing has been tried in these situations but is not routinely recommended. The drawback of this approach is that it prevents influenza vaccination of a large number of atopic

individuals who are more likely to have asthma and would therefore benefit from yearly influenza vaccination.

Practical guidelines are now emerging to address the question of influenza vaccination in subjects with egg allergy. James, et al (1998)⁹⁾ prospectively examined 83 subjects with egg allergy and 124 nonallergic controls. Twenty-seven of these subjects had convincing histories of life-threatening anaphylaxis after egg ingestion, and the remainder was screened by a combination of history, skin testing, and double-blind placebo-controlled food challenge (DBPCFC). All subjects underwent skin-prick testing to egg and undiluted influenza vaccine. Regardless of skin test results to the vaccine, egg-allergic subjects were vaccinated in two graded doses: one-tenth of the recommended intramuscular dose followed 30 minutes later by the remaining nine-tenths. All controls were given the entire vaccine in a single dose. Four (4.8%) study subjects and one (0.8%) control subject had positive skin tests to the vaccine. Eight (9.6%) allergic and four (3.2%) control subjects experienced mild symptoms such as pruritus, nausea, vomiting, and mild hives. Interestingly, all subjects tolerated the vaccine without any serious systemic reaction. A large variation in egg protein content in different batches and brands of influenza vaccine was observed in this study. We did not find any published prospective studies in which influenza vaccine has been administered to egg-allergic subjects in the usual single dose.

More recently, Zeiger (2002)¹⁵⁾ has highlighted some important clinical considerations that may be helpful in making a decision regarding influenza vaccination in the presence of egg allergy:

- (1) Although AAP does not generally recommend influenza vaccination in children with egg allergy and a history of anaphylaxis, it indirectly acknowledges that vaccination may be pursued in some cases. The ACIP recommends that individuals with a history of anaphylactic hypersensitivity to vaccine components who are also at high risk for influenza complications might benefit from vaccine after appropriate allergy evaluation and desensitization;¹⁶⁾
- (2) Influenza vaccination in individuals with egg allergy appears to be generally safe when vaccines with no more than 1.2 µg/ml egg protein are used in a two-dose protocol;⁹⁾
- (3) Egg protein concentrations in influenza

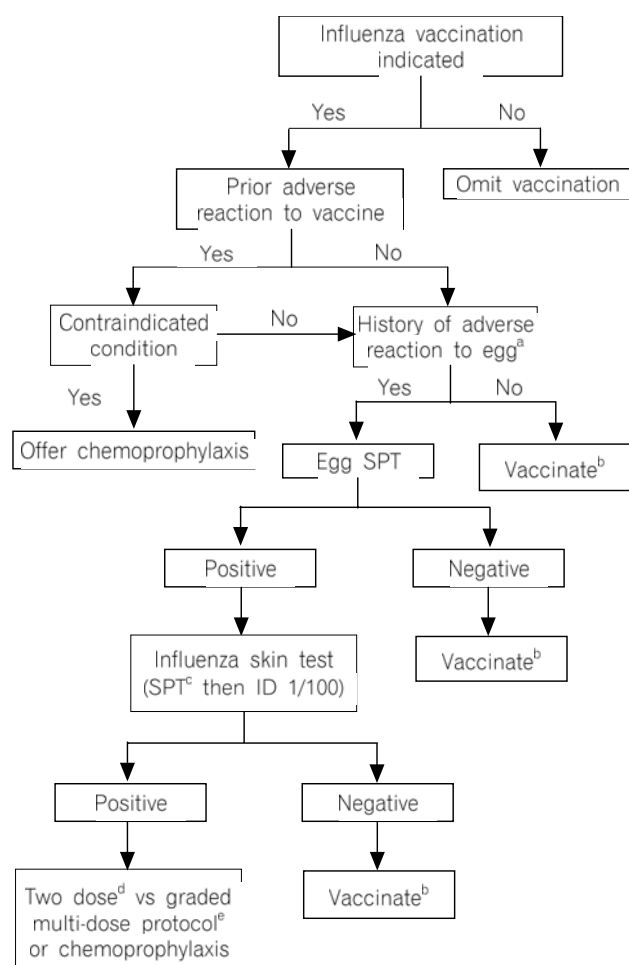


Fig. 1. Algorithm for administering influenza vaccination in patients with egg allergy. ID, intradermal; IM, intramuscular; SPT, skin prick test. (a) If egg allergy has not already been definitively diagnosed, do so at a later evaluation; (b) single IM dose appropriate for age; (c) start with 1/10 dilution if egg content unknown or >1.2 mg/ml, otherwise full strength; (d) egg content (1.2 mg/ml); (e) egg content unknown or >1.2 mg/ml. Modified from: Zeiger RS. Current issues with influenza vaccination in egg allergy. *J Allergy Clin Immunol*, 2002;110:834–40.

vaccines vary by several logs from manufacturer to manufacturer and from year to year; and (4) No manufacturer analyzes or reports the egg content of its influenza vaccine (s).

With these in mind, a clinical algorithm has been suggested to facilitate influenza vaccination in patients with a history of or confirmed egg allergy (Fig. 1). Less severe or local manifestations of allergy to egg or chicken feathers are not contraindications to yellow fever or influenza vaccine administration and do not warrant vaccine skin testing.

5. Skin Testing for Egg Allergy

The remarkable variation in the definition of egg allergy used by different authors makes it difficult to identify subjects suitable for skin testing to egg protein. Some investigators consider vomiting or urticaria following egg ingestion to be significant, while others reserve skin testing only for subjects who exhibit respiratory or anaphylactic symptoms following antigen exposure. Further, the exact role of confirmatory oral, double-blind placebo-controlled food challenges (DBPCFC) in subjects with a history of egg intolerance is not clearly outlined in the current literature. In one literature review, none of the 233 subjects with DBPCFC-confirmed egg allergy, reacted adversely to MMR vaccine.¹⁷⁾ Kelso reported a woman with a negative history of egg allergy who experienced an anaphylactic reaction after yellow fever vaccination. Subsequent testing demonstrated allergy to raw, but not cooked, eggs.¹⁸⁾ In the pediatric population, the physician must also keep in mind the symptoms resulting from the trauma of skin testing that may mimic a hypersensitivity reaction.¹⁹⁾ Distress over multiple injections can make a child irritable or cause vomiting and even vasovagal collapse. Persistent crying can result in wheezing, and may cause an irritable atopic child to scratch, leading to erythema and urticaria.

Both intradermal and skin prick techniques have been used to test for egg allergy by various authors. Some have demonstrated a high correlation between positive intradermal vaccine skin tests and a history of egg anaphylaxis,^{11,13)} while others have found skin-prick testing to be a more specific predictor of vaccine tolerance.⁷⁾ Clearly, the method of testing and the size criteria used to define a positive skin test will eventually determine the incidence of positive skin tests.⁸⁾

Regardless, the current body of evidence suggests that skin testing to egg protein does not predict tolerability to MMR vaccine.^{8,17,20)} In a recent meta-analysis¹⁾ of prospective studies of egg-allergic subjects administered single doses of measles, mumps, or MMR vaccine, 11 of the 1486 subjects experienced vaccination-related reactions, but only 2 had positive skin tests. Most of these reactions were non-anaphylactic and all but one resolved without treatment. Epinephrine was not indicated for the treatment of

any of these reactions.

6. Management of Egg Protein Allergy

Patients with suspected egg-allergy who are considering vaccines containing egg protein should be updated on the available literature describing differing opinions of vaccine manufacturers, the AAP, and various investigators. They should be guided about the risks and benefits of the choices they intend to make. Preimmunization screening for egg allergy is not a feasible option because of the very low risk of anaphylaxis and a relatively high prevalence of self-reported food allergies in the general vaccinee population.²¹⁾

The 2003 *Red Book*⁶⁾ recommends the following procedure to test an egg-sensitive person with the egg-protein containing vaccine (e.g., yellow fever vaccine) before a full dose is administered:

- Scratch, prick or puncture test: A drop of 1 : 10 dilution of the vaccine in physiologic saline is applied at the site of a superficial scratch, prick, or puncture on the anterior forearm. Positive (histamine) and negative (physiologic saline) skin controls should be documented for a valid test interpretation. The test is read after 15 ~ 20 minutes. A positive test result is a wheal 3 mm larger than that of the saline control, usually with surrounding erythema. A negative prick test warrants further intradermal testing.

- Intradermal test: A dose of 0.02 ml of a 1 : 100 dilution of the vaccine in physiologic saline is injected intradermally with concurrent positive and negative skin controls. A wheal ≥ 5 mm larger than negative control with surrounding erythema is considered a positive reaction.

The vaccine may be safely administered if these test results are negative. If these tests are positive, a desensitization protocol is recommended for immunization depending on the subject's risk from the disease. An example of one such protocol involving subcutaneous administration of successive doses of vaccine at 15- to 20-minute intervals is mentioned below:

1. 0.05 ml of 1 : 10 dilution
2. 0.05 ml of full strength vaccine
3. 0.10 ml of full strength vaccine
4. 0.15 ml of full strength vaccine

5. 0.20 ml of full strength vaccine

A practical approach to influenza vaccination in patients with histories of or confirmed egg allergy is summarized in Fig. 1. In all cases, a history of adverse reactions to egg or prior influenza vaccination should be sought before administering the vaccine. Egg allergy can be ruled out if an individual presently ingests eggs or complete portions of egg-containing products without any reaction. Certain diseases, e.g., Guillain-Barre syndrome, are contraindications for influenza vaccination. Trained personnel and necessary resuscitation equipment should be available during these skin test and desensitization procedures.

7. Gelatin

Gelatin is partially hydrolyzed collagen of bovine or porcine origin. It has been used as a heat stabilizer in many vaccines.²²⁾ Measles, mumps, rubella, influenza, varicella, and yellow fever vaccines contain the highest concentrations of gelatin; smaller concentrations are found in certain brands of diphtheria, tetanus and, acellular pertussis combination vaccines (DTaP). Immediate hypersensitivity reactions to gelatin-containing vaccines are mediated by gelatin-specific IgE, whereas delayed reactions are associated with activation of gelatin-specific T-lymphocytes. It is not clear how long this sensitization to gelatin persists after vaccination.²³⁾

8. Hypersensitivity Reactions to Gelatin-Containing Vaccines

Kelso, et al (1993)²²⁾ first documented a case of anaphylactic reaction following administration of MMR II that was subsequently traced to the gelatin component of the vaccine (gelatin content 14.5 mg per 0.5 ml dose). This was followed by several Japanese reports which observed a similar association in an unusually high proportion of patients. Sakaguchi, et al^{24,25)} documented anti-gelatin IgE antibodies in 24 of 26 children with systemic immediate reactions to measles vaccination. Seven of these subjects also had allergic signs and symptoms on ingestion of gelatin-containing foods (2 had a history of such reactions prior to measles vaccination, and 5 noted reactions after vaccination). All of the controls lacked anti-gelatin IgE. Subsequent studies from Japan suggested that immediate and delayed allergic reactions after other gelatin-containing

Table 2. Differences between the types of gelatin used in the stabilizer formulation in live virus vaccines²¹⁾

Vaccine	Animal source ^a origin and manufacturer	Extent of hydrolysis	Gelatin mg/0.5 ml dose
Measles and mumps monovalent vaccines (Japan) used before 1998	Bovine (Haemacel, Behringwerke, Frankfurt, Germany)	Hydrolyzed gelatin and, in part, native/intact gelatin	1.5–10 mg*
Measles and mumps monovalent vaccines (Japan) used since September 1998	Porcine modified (Prionex, Pentapharm, Basel, Switzerland)	Hydrolyzed gelatin only (20,000 Da)	1 mg
MMR II (Merck) in use since 1979	Porcine (Sol-U-Pro by Dyna-Gel Inc, Calumet, IL)	Highly hydrolyzed gelatin (average size of gelatin peptide fragments = 2,000–3,000 Da)	14.5 mg

*Vaccines by 4 manufacturers used different amounts of gelatin.
Gelatin-Containing Vaccines

vaccines (against varicella and Japanese encephalitis) may have been associated with pre-vaccination sensitization to gelatin.^{26,27)} Nakayama, et al²⁸⁾ suggested that usage of gelatin-containing diphtheria-tetanus-acellular pertussis (DTaP) vaccines before immunization with live virus vaccines might be a potential source of gelatin sensitization.

A recent retrospective case-control study²¹⁾ comparing self-reported allergy histories and IgE antibody levels in people with and without reported symptoms of immediate hypersensitivity after MMR vaccination was undertaken at the Mayo Clinic. The purpose of this study was to determine if there was an association with gelatin sensitization in subjects who reported anaphylaxis after receiving measles or MMR vaccines. None of the 22 test subjects had a history of food allergy to gelatin. Six out of these 22 subjects (27%) tested positive for anti-gelatin IgE, whereas none of the 27 controls did. Their findings support the hypothesis that anaphylaxis after MMR vaccines can sometimes be attributed to hypersensitivity to gelatin.

9. Gelatin Sensitization

The prevalence of anti-gelatin IgE antibodies (Pharmacia CAP radioallergosorbent test, Pharmacia, Uppsala, Sweden) in patients with reported anaphylaxis to the above vaccines has varied between 14–28 percent in US and Finnish populations.²⁹⁾ These results are quite different from those

from the Japanese studies where most of the children with immediate-type reaction to measles, mumps, rubella, and varicella single-antigen vaccines in Japan had positive results of IgE tests on the CAP system (86%, 92%, 100%, and 90%, respectively).³⁰⁾ This has been explained by the differences in the type of gelatin used as a part of vaccine stabilizer formulation in live virus vaccines in these countries (Table 2). MMR II gelatin of porcine origin is highly hydrolyzed and has very low molecular weight. By contrast, the bovine gelatin added to the single-antigen measles, mumps, and rubella vaccines produced in Japan in the mid-1990s was only partially hydrolyzed and contained a small amount of high molecular weight gelatin. After these reports, the Japanese manufacturers have changed their live measles and mumps vaccines beginning September 1998. They now use a hydrolyzed, modified porcine gelatin (Prionex, Pentapharm) that has a lower binding affinity for antigelatin IgE than bovine gelatin. They also stopped using gelatin in DTaP vaccines in February 1999. Interestingly, they have noted a decrease in the incidence of allergic reactions to these vaccines after these modifications which has been attributed to both the modifications in the stabilizer formulation for the measles and mumps monovalent vaccines, and the discontinuation of gelatin-containing DTaP vaccines in Japan.^{21,31)} In the United States, two DTaP vaccines (Acel-Imune, Tripedia) became

Table 3. Amounts of gelatin in vaccines licensed in the United States*

Vaccine type	Vaccine name (Manufacturer)	Amount (μ g) of gelatin per dose
DTaP	Tripedia (Aventis Pasteur, Lyon, France)	28
Influenza	Fluzone (Aventis Pasteur, Lyon, France)	250
Japanese encephalitis	JE-VAX (Aventis Pasteur, Lyon, France)	500
Measles	Attenuvax (Merck, West Point, PA)	14,500
Measles and rubella	MRVAX II (Merck, West Point, PA)	14,500
Measles, mumps, and rubella	MMR II (Merck, West Point, PA)	14,500
Mumps	Mumpsavax (Merck, West Point, PA)	14,500
Mumps and rubella	Biavax II (Merck, West Point, PA)	14,500
Rabies	Rabavert (Chiron Corporation, Emeryville, CA)	12,000
Rubella	Meruvax II (Merck, West Point, PA)	14,500
Varicella	Varivax (Merck, West Point, PA)	12,500
Yellow fever	YF-VAX (Aventis Pasteur, Lyon, France)	7,500

The oral typhoid vaccine by Vivotif (Berna) contains gelatin in the capsule shell. Adapted from Pool, et al, 2002.²¹⁾

used widely for the primary immunizations in 1997. The gelatin content of these vaccines is similar to the Japanese DTaP vaccines used in mid-90s but no increase in the incidence of gelatin sensitization has been observed.³²⁾

Sensitization from dietary gelatin has also been considered.^{23,33)} People with a history of food allergy to gelatin rarely develop anaphylaxis after receiving gelatin-containing vaccines. Skin testing prior to the administration of a gelatin-containing vaccine may be considered, but there are no protocols or reported experience available. Because gelatin used in the United States as a vaccine stabilizer usually is porcine, and food gelatins may be derived solely from bovine sources, a negative food history itself does not exclude the possibility of an immunization reaction. Documented allergy to gelatin-containing foods is very rare in the United States compared to Japan. Differences between foods traditionally preferred in Japanese and Western cultures may play a role in prevaccine sensitization to gelatin. Some investigators have also suggested that genetics might play a role in gelatin allergy.

The amounts of gelatin in the currently licensed US vaccines are shown in Table 3.

10. Management of gelatin hypersensitivity

A thorough literature review did not reveal any official recommendations for skin testing or desensitization to gelatin. Using gelatin-free DTaP appears desirable in order

to prevent unnecessary gelatin sensitization.³²⁾ Removal of gelatin from all DTaP vaccines and modification of gelatin used in measles, mumps, and rubella vaccines has dramatically diminished the incidence of vaccine-related anaphylaxis in Japan.

Almost one fourth of patients with reported anaphylaxis after MMR seem to have hypersensitivity to gelatin in the vaccine. These subjects may be at a higher risk of developing anaphylaxis to subsequent doses of other gelatin-containing vaccines and therefore, warrant an allergy evaluation before such immunization.²¹⁾

11. Thimerosal

Thimerosal is an ethyl mercury-containing preservative that has been used since 1930s as an additive to biologics and vaccines to prevent their contamination by bacteria and fungi. Vaccines that contain thimerosal include some DTaP and Hib products, DT, dT, one hepatitis B product, all influenza vaccines, meningococcal vaccine, one pneumococcal vaccine, and one rabies vaccine. None of the live-virus vaccines contains thimerosal. A listing of thimerosal content of currently licensed vaccines in US is shown in Table 4.

The prevalence of thimerosal hypersensitivity has been variously reported to range from 1 ~ 26%.³⁴⁾ It is seen more often in countries where mercury-containing solutions are used widely as a skin antiseptic.³⁵⁾ People with allergic contact conjunctivitis, dyshidrotic eczema and subjects

Table 4. Thimerosal content of some vaccines licensed in the United States

Vaccine	Brand name	Manufacturer	Thimerosal concentration*	Mercury $\mu\text{g}/0.5 \text{ ml}$
Anthrax	Anthrax vaccine	BioPort Corporation	0	0
DTaP	Tripedia	Aventis Pasteur	Trace ($<0.3 \mu\text{g}$)	Trace ($<0.3 \mu\text{g}$)
	Infanrix	GlaxoSmithKline	0	0
DTwP	All Products		0.01%	25
DT	All Products		0.01%	25
Td	All Products		0.01%	25
TT	All Products		0.01%	25
Hib	ActHIB/OmniHIB	Aventis Pasteur	0	0
	TriHIBit	Aventis Pasteur	Trace ($<0.3 \mu\text{g}$)	Trace ($<0.3 \mu\text{g}$)
	Hib TITER	Wyeth-Ayerst	0.01%	25
		Singledose	Wyeth-Ayerst	0
	Pedvax HIB liquid	Merck	0	0
	Comvax	Merck	0	0
Hepatitis A	Havrix	GlaxoSmithKline	0	0
	Vaqta adult/pediatric	Merck	0	0
Hepatitis B	Engerix-B	GlaxoSmithKline	Trace ($<0.3 \mu\text{g}$)	Trace ($<0.3 \mu\text{g}$)
	Recombivax HB preservative free	Merck	0	0
	Recombivax HB preservative free	Merck	0.005%	12.5
Hep A-B	Twinrix	GlaxoSmithKline	0	0
Influenza	All U.S. products		0.01%	25
IPV	IIPOL	Aventis Pasteur	0	0
Lyme	LYMERix	GlaxoSmithKline	0	0
Meningococcal	MENOMUNE- A/C/Y/W-135	Aventis Pasteur	Trace ($<0.3 \mu\text{g}$)	Trace ($<0.3 \mu\text{g}$)
MMR	M-M-R II	Merck	0	0
Measles	Attenuvax	Merck	0	0
Pneumococcal	Prenar	Wyeth-Ayerst	0	0
	Pnu-Imune 23	Wyeth-Ayerst	0.01%	25
	Pneumovax 23	Merck	0	0
Rabies	RabAvert	Chiron	0	0
	IMOVAX	Aventis Pasteur	0	0
Typhoid	Vivotif Berna	Berna	0	0
Typhoid Fever	Typhim Vi	Aventis Pasteur	0	0
	Typhoid vaccine	Wyeth-Ayerst	0	0
Varicella	Varivax	Merck	0	0
Yellow Fever	YF-VAX	Aventis Pasteur	0	0

*Adapted from Institute for Vaccine Safety website <http://www.vaccinesafety.edu>

treated with immunotherapy vaccines containing thimerosal have also been shown to have an increased prevalence of thimerosal hypersensitivity.^{36,37)}

Thimerosal exposure most often results in a mild, local, delayed-type inflammation or eczema.³⁶⁾ Despite a high

prevalence of contact hypersensitivity to thimerosal, it is generally quite safe, with only rare cases of systemic reactions such as generalized eczema or urticaria.^{34,38)}

Mercury-allergic subjects are also able to tolerate thimerosal in vaccines with only mild, local reactions reported in 0 ~

20% of cases.^{34,36)} No cases of anaphylaxis have been attributed to thimerosal. A recent review³⁵⁾ found no evidence of systemic adverse effects from thimerosal in vaccines. Thimerosal-free vaccines are now available for all routine childhood immunizations. We have discussed the historical background leading to the recommendation of thimerosal free vaccines elsewhere.⁵⁾

12. Antibiotic-Induced Allergic Reactions

It is difficult to prove a causal relationship between suspected hypersensitivity reactions in persons with known allergies who receive vaccines containing trace amounts of antibiotics.⁶⁾ The usual antibiotics found in trace amounts in some vaccine products include neomycin, streptomycin, polymyxin B, and chlortetracycline. None of the currently recommended vaccine products contains penicillin or its derivatives. Neomycin is the most common antibiotic that is associated with adverse reactions to vaccines.⁶⁾ It is present in trace amounts in live-virus measles, mumps, rubella (singly or combined as MMR), and varicella vaccines. Approximately 1% of the general population manifests allergy to neomycin, usually as a delayed-type contact dermatitis.

The usual dose of neomycin required to elicit a contact hypersensitivity response on skin testing is in the order of 100~1,000 μ g.³⁹⁾ Measles, mumps, rubella, MMR, varicella, and poliovirus vaccines contain $\leq 25 \mu$ g neomycin per dose, which is four times less than the minimal amount typically required to elicit an allergic skin response. Despite these facts, some neomycin- allergic subjects may experience a delayed-type local reaction 48~96 hours after administration of IPV, MMR, or varicella vaccines. These reactions typically consist of an erythematous, pruritic papule. This minor reaction is of little importance compared with the benefit of immunization and should not be considered a contraindication. However, neomycin-containing vaccines should be avoided in patients with a history of anaphylactic reaction to this antibiotic.

Skin testing in allergic individuals is not recommended²⁹⁾ and no desensitization protocols have been proposed. As previously noted, contact dermatitis to neomycin is relatively common and is not a contraindication to immunization with neomycin- containing vaccines.⁴⁰⁾

13. Latex Allergy

Latex is liquid sap from the commercial rubber tree. It is the naturally occurring impurities (e.g., plant proteins and peptides) in this product that are believed to be responsible for allergic reactions. These impurities are reduced but not eliminated when the crude product is processed to form natural rubber latex and dry natural rubber products. Natural rubber latex is used in the manufacturing of medical gloves, catheters etc. Dry natural rubber is used in the manufacturing of syringe plungers, vial stoppers and injection ports on intravascular tubing. The most common type of latex sensitivity is contact-type (type IV) hypersensitivity, usually as a result of prolonged contact with latex-containing gloves.⁴¹⁾ There are reports of injection procedure-associated latex allergies in diabetics. We were able to find only a single report of an allergic reaction following administration of hepatitis B vaccine to a patient with history of latex induced anaphylaxis.⁴⁰⁾ In clinical practice, patients reporting severe (anaphylactic) allergy to latex should not be injected with products (including vaccines) supplied in vials or syringes that contain natural rubber, unless the benefits of such administration clearly outweigh the risks of an allergic reaction to latex. For patients with non-anaphylactic allergies to latex (e.g., a history of contact allergy to latex gloves), vaccines supplied in vials or syringes that contain dry natural rubber or natural rubber latex can be administered.

14. Hypersensitivity to Other Vaccine Components

Measles and rabies vaccines contain human albumin. Because of effective donor screening and product manufacturing processes, the FDA believes the risk for transmission of any viral disease from albumin in these vaccines is rare. Reactions resembling serum sickness have been reported in approximately 6% of patients after a booster dose of human diploid rabies vaccine, probably due to sensitization to human albumin that had been altered chemically by the virus inactivating agent.

Japanese encephalitis virus vaccine has been associated with generalized urticaria and angioedema, sometimes with respiratory distress and hypotension occurring within

minutes to as long as 2 weeks after immunization. The pathogenesis of such reactions is not understood. Persons with a history of urticaria are at increased risk for such reactions.

Recombinant hepatitis B vaccine is derived from yeast cultures. The 2003 *Physicians' Desk Reference*⁷⁾ lists hypersensitivity to yeast as a contraindication to recombinant hepatitis B vaccine; however, no cases of anaphylaxis to hepatitis B vaccine have been attributed to yeast hypersensitivity.⁴²⁻⁴⁴⁾ Phenoxylethanol, used as a preservative in some DTP vaccines, has also been reported to cause generalized eczema in some instances.

15. Aluminum

Aluminum salts have been used since the 1930s to enhance immunogenicity of various vaccines, most notably diphtheria, tetanus, and pertussis toxoids. Subcutaneous nodules are relatively common after injection with an aluminum-adsorbed vaccine but usually resolve within a few weeks to months.³⁶⁾ Rarely, subcutaneous nodules from aluminum injection become pruritic and painful and can last for years, requiring surgical removal. Histologically, the persistent nodules show retained aluminum and inflammatory cells consistent with a hypersensitivity reaction.^{36,45,46)} Individuals with such nodules have a higher incidence of contact allergy to aluminum compared to the general population.^{40,47)} No reports of anaphylaxis have been attributed specifically to aluminum.

16. Bacterial Antigens

During the manufacture of a bacterial vaccine, either killing the agent (e.g., *Bordetella pertussis*) or attenuating the organism (e.g., polio or measles virus) blunts the pathogenicity of the organism. In both instances, the organisms must retain antigenicity while losing pathogenicity. The injection of complete cellular vaccines even in the killed form results in the injection of a variety of cell-associated substances. Preparation of vaccines using fractionated cellular components presumably reduces this risk while offering development of long-lasting protection.⁴⁸⁾

Local swelling and erythema correlate positively with tetanus antibody titers before the booster, whereas pain and tenderness at injection site are more common if the tetanus

booster is absorbed to aluminum.²⁷⁾ Better purification of the bacterial toxin before detoxification with formaldehyde makes the vaccine less likely to cause an adverse reaction because there are fewer accessory antigens to elicit an IgE response.⁴⁹⁾

Although IgE formation to toxoids is very common, anaphylaxis is rare. Toxoid-specific IgE levels correspond more with local vaccination reactions than anaphylaxis. Specific IgE to bacterial toxoids are common even in subjects who do not react adversely to the vaccine. Further studies are necessary to determine the role of toxoid-specific IgE in vaccine-induced anaphylaxis.

17. Hypersensitivity to Nonviral Components of Rabies Vaccine

HDCV is made from the concentrated Pitman-Moore strain of rabies virus grown in an MRC5 human diploid cell culture. It contains trace contaminants of fetal calf serum (FCS) from the culture medium and human serum albumin (HSA), the latter as a stabilizer.^{3,50)} The virus is inactivated by β -propiolactone (BPL), a low-molecular-weight compound capable of chemically binding proteins such as HSA, FCS, and cell remnants of the MRC5 cells.³⁾

Systemic hypersensitivity occurs in approximately 6% of booster vaccinations with human diploid cell rabies vaccine (HDCV) and less frequently after primary vaccination.²¹⁾ Delayed, immune complex-like reactions are most common, although immediate reactions with wheezing, urticaria, and angioedema have also been reported.⁴⁷⁾ Symptoms usually resolve spontaneously in a few days or following treatment with antihistamines.^{47,50)} No life-threatening reactions have been reported. Vaccine reactors have been shown to develop significantly higher levels of rabies-specific IgG and increased IgG to BPL-HSA and BPL-FCS complexes. Biopsies of urticarial skin lesions reveal leukocytoclastic vasculitis with fibrin and C3 granular deposits with immunofluorescence. Both IgE and IgG to nonviral vaccine components are responsible for allergic reactions to rabies booster immunization. It has been hypothesized that IgE antibody increases vascular permeability, which in turn facilitates deposition of complement-activating IgG antibodies to BPL-FCS or BPL-HSA, producing urticarial vasculitis.⁵⁰⁾

Individuals at risk for rabies who require pre-exposure prophylaxis should have their antibody titer checked every 2 years after primary vaccination. Booster vaccination is indicated only if their serum antibody titer falls below 1 : 5.²¹⁾ A change in vaccine-manufacturing technique may reduce the incidence of hypersensitivity. Lower reactivity has been demonstrated with the use of rabies vaccine lacking HSA and when most of the BPL is removed prior to addition of gelatin as the stabilizer.⁵¹⁾

SUMMARY

Vaccines provide a safe and effective approach to prevent infectious and allergic diseases. Allergic reactions to vaccines and drug products have become an important feature of modern day practice. Most of these reactions are mild, but healthcare providers should be aware of the potential serious adverse reactions. The diagnosis of vaccine allergy is usually based on a detailed history and physical examination. Prevention, avoidance, the use of alternative agents, desensitization, and premedication remain the mainstays of therapy even as more refined diagnostic and management tools are being developed.

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