Practice Parameter

Adverse reactions to vaccines

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TABLE OF CONTENTS

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PREFACE

This practice parameter provides a practical, peer-reviewed, evidence-based guide for evaluation and management of patients with suspected allergy to vaccines. This document contains detailed and specific guidelines not found in previously published reviews.

The practice parameter offers both general and vaccine-specific recommendations for skin testing to vaccines and components, serum specific IgE in vitro antibody testing, serologic testing for protective antibody responses to vaccines, vaccine administration, and avoidance. The guidelines should prove useful for primary care physicians and specialists in allergy and immunology. More importantly, most patients who avoid vaccination because of allergy concerns will be able to receive their appropriate vaccinations if this practice parameter is followed.

The 2 key points of the practice parameter are that (1) patients with suspected allergy to vaccines or vaccine components should be evaluated by an allergist/immunologist and (2) most patients with suspected allergy to vaccines can receive vaccination safely. With the recent worldwide con-

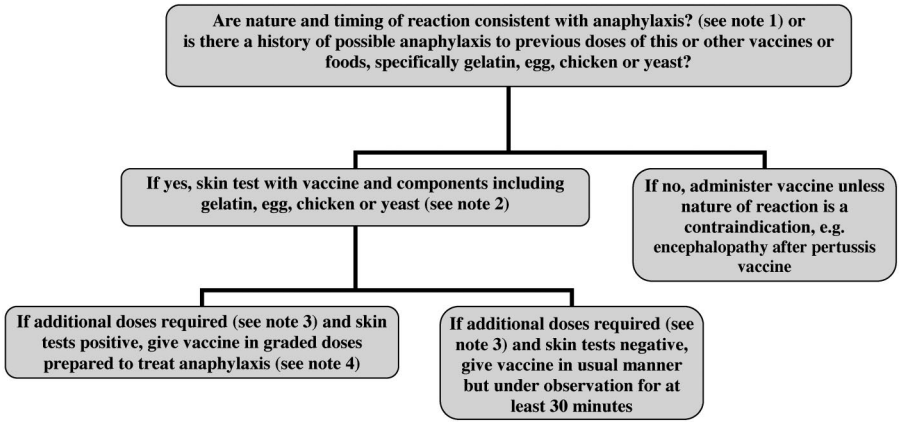

Figure 1. Suggested approach to suspected adverse reactions to a vaccine.

Note 1. Are nature and timing of reaction consistent with anaphylaxis?

Probable Anaphylactic Reaction: reaction occurring within 4 hours of vaccine administration to include signs and/or symptoms from more than 1 of the following systems:

- **Dermatologic: urticaria, flushing, angioedema, pruritus**
- **Respiratory: rhinoconjunctivitis (red, watery, itchy eyes, stuffy, runny, itchy nose, sneezing), upper airway edema (change in voice, difficulty swallowing, difficulty breathing), bronchospasm/asthma (cough, wheeze, shortness of breath, chest tightness)**
- **Cardiovascular: hypotension, tachycardia, palpitations, light-headedness, loss of consciousness (Note: hypotension or loss of consciousness with pallor and bradycardia is much more likely a vasovagal reaction.)**
- **GI: cramping, nausea, vomiting, diarrhea**

Possible Anaphylactic Reaction:

Signs and/or symptoms from only 1 system (as above)

Signs and/or symptoms from more than 1 system (as above) but occurring more than 4 hours after vaccination

Note 2. Skin tests with vaccine and components including gelatin, egg, chicken and/or yeast

Vaccine skin tests:

- **Prick test with full strength vaccine (consider dilution if history of life-threatening reaction)**
- **If prick test with full strength vaccine negative, intradermal test with 0.02 cc vaccine 1:100**
- **Note: Vaccine skin tests may cause false (or clinically irrelevant) positive reactions**

Vaccine component/food skin tests:

- **Prick tests with commercial extracts of whole egg or egg white (influenza and yellow fever vaccines), chicken (yellow fever vaccine) or *Saccharomyces cerevisiae* yeast (Hepatitis B vaccine and Human Papillomavirus vaccine)**
- **Prick test with sugared gelatin (e.g. Jell-O®: dissolve 1 teaspoon (5 grams) of gelatin powder in 5 cc normal saline) Vaccines that contain gelatin: DTaP (some brands), influenza (some brands), Japanese encephalitis, measles, mumps, rabies (some brands), rubella, varicella, yellow fever, zoster**

Note 3. If fewer than the recommended number of doses received, consider measuring level of IgG antibodies to immunizing agent. If at a level associated with protection from disease, consider withholding additional doses although magnitude and duration of immunity may be less than if all doses received.

Note 4. Vaccine administration in graded doses:

For a vaccine where usual dose is 0.5 ml, administer graded doses of vaccine at 15 minute intervals: 0.05 ml of 1:10 dilution, 0.05 ml of full strength, 0.10 ml of full strength, 0.15 ml of full strength, 0.20 ml of full strength. For influenza vaccine in egg-allergic patients, if the egg protein content of the vaccine is known to be $\leq$ 1.2 μgm/mL, administer 10% of the dose, followed in 30 minutes by the remaining 90%, or as a single dose.

cerns about H1N1 influenza, interest in the health benefits of vaccination is greater than ever. Our hope is that this publication will result in safe vaccination for patients with suspected allergy to vaccines.

Immunization is perhaps the greatest public health achievement of all time,[1] having significantly reduced the morbidity and mortality of many infectious diseases.[2] Routine immunization of children, adolescents, and adults provides substantial protection from a large number of infectious diseases. The current vaccination schedules for children and adults are available at www.cdc.gov/vaccines/recs/schedules.[3–5] Patients who have experienced adverse reactions to vaccines may unnecessarily be advised to avoid subsequent immunization, which may have important adverse personal and population health consequences.[6–10] Although there are some adverse reactions to vaccines that constitute absolute contraindications to administration of future doses, most such reactions do not preclude subsequent immunization.[11] Patients who have experienced some ill effect after receiving a vaccine warrant evaluation by an allergist/immunologist. In most cases, a risk-benefit analysis will favor subsequent immunization (Figure 1).

CLASSIFICATION OF RECOMMENDATIONS AND EVIDENCE

Category of evidence

Ia Evidence from meta-analysis of randomized controlled trials
Ib Evidence from at least one randomized controlled trial
IIa Evidence from at least one controlled study without randomization
IIb Evidence from at least one other type of quasiexperimental study
III Evidence from nonexperimental descriptive studies, such as comparative studies
IV Evidence from expert committee reports or opinions or clinical experience of respected authorities or both

Strength of recommendation

A Directly based on category I evidence
B Directly based on category II evidence or extrapolated recommendation from category I evidence
C Directly based on category III evidence or extrapolated recommendation from category I or II evidence
D Directly based on category IV evidence or extrapolated recommendation from category I, II, or III evidence

SUMMARY STATEMENTS

Summary Statement 1. Mild local reactions and constitutional symptoms, such as fever, after vaccinations are common and do not contraindicate future doses. Rarely, delayed-type hypersensitivity to a vaccine constituent may cause an injection site nodule, but this is not a contraindication to subsequent vaccination. (C)

Local, injection site reactions (swelling, redness, and/or soreness) and constitutional symptoms, especially fever, are common after the administration of most vaccines and are not contraindications to subsequent vaccination.[11] Neomycin is contained in several vaccines.[12] For those reporting a delayed-type hypersensitivity contact dermatitis to neomycin, the only anticipated reaction is a small, temporary papule at the injection site,[13,14] and this is not a contraindication to subsequent vaccination.[11] Delayed-type hypersensitivity to thimerosal has also been reported.[15] Although patients with a

Table 1. Levels of Antibody Associated With Protection From Vaccine-Preventable Diseases

Vaccine	Protective level of IgG antibody ≥
Diphtheria	0.1 IU/mL[11]
Haemophilus influenzae type B	0.15 μg/mL[29]
Hepatitis A	10 mIU/mL[30]
Hepatitis B surface antibody	10 mIU/mL[31]
Measles (rubeola)	120 mIU/mL (PRN titer)[32]
Polio (inactivated)	1:8 neutralizing antibody titer[33]
Rabies	0.5 IU/mL (VNA titer)[34]
Rubella	10 IU/mL[80]
Tetanus	0.1 IU/mL[11]
Yellow fever	0.7 IU/mL[29]

Abbreviations: IU, international units; mIU, milli-international units; PRN, plaque reduction neutralization; VNA, virus-neutralizing antibodies.

Table 2. Gelatin Content of Vaccines 2008

Vaccine	Gelatin content
DTaP (Tripedia/TriHIBit; Sanofi Pasteur, Swiftwater, Pennsylvania)	28 μg per 0.5-mL dose[a]
Influenza (Fluzone; Sanofi Pasteur)	250 μg per 0.5-mL dose[b]
Influenza (FluMist; Medimmune Vaccines, Gaithersburg, Maryland)	2000 μg per 0.2-mL dose[b]
Japanese Encephalitis (JE-VAX; Sanofi Pasteur)	500 μg per 1.0-mL dose[b]
Measles, Mumps, Rubella (ATTENUVAX, MERUVAXII, MMRII, MUMPSVAX; Merck, Whitehouse Station, New Jersey)	14,500 μg per 0.5-mL dose[b]
Measles, mumps, rubella, varicella (ProQuad; Merck)	11,000 μg per 0.5-mL dose[b]
Rabies (RabAvert; Novartis, Emeryville, California)	12,000 μg per 1.0-mL dose[b]
Typhoid Vaccine Live Oral Ty21a (VIVOTIF; Berna, Coral Gables, Florida)	Capsule[b]
Varicella (VARIVAX; Oka/Merck)	12,500 μg per 0.5-mL dose[b]
Yellow Fever (YF-VAX; Sanofi Pasteur)	7,500 μg per 0.5-mL dose[a]
Zoster (ZOSTAVAX; Oka/Merck)	15,580 μg per 0.65-mL dose[b]

[a] Sanofi Pasteur, oral communication, September 4, 2009.
[b] Package inserts.

Table 3. Egg Content of Vaccines

Vaccine	Grown in	Egg protein content	Approach in egg allergic patient
Measles and mumps	Chick embryo fibroblast cell cultures	Picograms to nanograms	Administer in usual manner[44–46]
Purified chick embryo rabies	Chick embryo fibroblast cell cultures	Picograms to nanograms	Administer in usual manner[109]
Influenza (killed injected and live attenuated nasal)	Chick extraembryonic allantoic fluid	Micrograms	Skin test with egg and vaccine before administration[48,110]
Yellow fever	Chick embryos	Micrograms	Skin test with egg and vaccine before administration[67]

positive patch test result for thimerosal may have large local reactions to vaccination with thimerosal-containing vaccines,[16,17] most such patients do not.[15,18–20] Neither a history of such reactions nor a positive patch test result to thimerosal is a contraindication to future vaccination.[11] There is a single case report of a generalized pruritic maculopapular rash attributed to thimerosal in an influenza vaccine.[21] Aluminum-containing vaccines[12] rarely cause persistent nodules at the injection site, possibly because of delayed hypersensitivity or other immune responses to aluminum.[22–24]

Summary Statement 2. Anaphylactic reactions to vaccines are estimated to occur at a rate of approximately 1 per million doses. There are approximately 235 million doses of vaccines administered in the United States each year. (B)

Anaphylaxis after vaccination is rare. The Vaccine Safety Datalink reviewed the diagnosis codes from medical encounters after the administration of more than 7.5 million doses of vaccines and estimated the risk of anaphylaxis to be 0.65 million to 1.53 per million doses.[25] The Centers for Disease Control and Prevention (CDC) estimates that there were 235,705,179 doses of all vaccines distributed in the United States in 2007 (Angela Calugar, CDC, written communication, December 19, 2008). Thus, there are approximately 150 to 350 cases of vaccine-induced anaphylaxis in the United States annually. Fatalities from vaccine-induced anaphylaxis are exceedingly rare.[26]

Summary Statement 3. All serious events occurring after vaccine administration should be reported to the Vaccine Adverse Event Reporting System, even if it is not certain that the vaccine was causal. (C)

In 1990, the Vaccine Adverse Event Reporting System (VAERS) was established by the CDC and Food and Drug Administration (FDA).[27] VAERS relies on reporting by health care professionals and parents or patients, and all serious events after vaccination should be reported.[28] These reports of suspected associations between vaccine administration and adverse events can then be evaluated for strength of potential causality.

Summary Statement 4. Measuring levels of IgG antibody to the immunizing agent in a vaccine suspected of causing a serious adverse reaction to determine if they are at protective levels can help determine whether or not subsequent doses are required. (B)

In a patient who has experienced an apparent adverse reaction to vaccine yet has received fewer than the recommended number of doses, the level of IgG antibodies to the immunizing agent can be measured to see if it is at a level associated with protection from disease. Such levels have been established for some, but not all, vaccines (Table 1)[11,29–34] and are available from many diagnostic laboratories. If so, consideration can be given to withholding additional doses, although the magnitude and duration of immunity may be less than if all doses were received.[35,36] Even if the recommended number of doses has already been received or if protective antibody levels have already been achieved, evaluation of the reaction, including skin testing if indicated, should be undertaken as discussed herein.

Summary Statement 5. All suspected anaphylactic reactions to vaccines should ideally be evaluated in an attempt to determine the culprit allergen. (B)

When a patient experiences an apparently IgE-mediated reaction after an immunization, the patient is often labeled as being "allergic" to the vaccine and advised against receiving future doses without further investigation. However, this approach should be avoided because it may leave patients inadequately immunized if they unnecessarily avoid vaccines to which they are not allergic or if the vaccine could be administered safely despite their allergy. In addition, not knowing the particular constituent of a vaccine to which the patient is allergic may pose a risk with future vaccinations that contain the same ingredient.

Summary Statement 6. IgE-mediated reactions to vaccines are more often caused by vaccine components, such as gelatin or egg protein, rather than the immunizing agent itself. (B)

Gelatin is added to many vaccines (Table 2) as a stabilizer and has been shown to be responsible for many anaphylactic reactions to MMR, varicella, and Japanese encephalitis vaccines.[37–40] Vaccine manufacturers in Japan and Germany removed gelatin or changed to a less allergenic gelatin with a resultant decrease in allergic reactions.[41,42] A history of allergy to the ingestion of gelatin should be sought before the administration of any gelatin-containing vaccine. A negative history, however, may not exclude an allergic reaction to gelatin injected with the vaccine.[38] Gelatin used in vaccines is of either bovine or porcine origin, which are extensively

cross-reactive.[37,38] There are no published reports of patients allergic to both gelatin and beef or pork meat.

Measles and mumps vaccines and 1 type of rabies vaccine are grown in chick embryo fibroblast cultures and contain negligible or no egg protein (Table 3).[43] Measles or MMR vaccines can be administered to egg allergic children without adverse reactions[44,45] and can be given to such patients without skin testing.[46] Egg protein is present in higher amounts in yellow fever and influenza vaccines[12] (Table 3) and may cause reactions in egg allergic recipients. Administration of influenza vaccine containing 1.2 μg/mL of egg protein has been safely administered to egg allergic patients, initially in a 2-dose protocol (10% of the dose followed in 30 minutes by the remaining 90% of the dose) and later as a single dose.[47] However, the influenza vaccine is newly made every year, and there are variable amounts of egg protein present in any given years' vaccine (as high as 42 μg/mL of egg protein).[48] Whether this is sufficient to cause a reaction in an egg allergic patient is also not known but may pose a risk. Patients can be allergic to heat-labile egg proteins in raw egg and, because they tolerate the ingestion of cooked egg, do not think of themselves as being egg allergic.[49] Thus, the clinical history may not identify all persons allergic to egg proteins present in influenza or yellow fever vaccines. Chicken proteins other than those found in chicken egg may be present in yellow fever vaccine and may be responsible for reactions in chicken allergic recipients.[50]

Hepatitis B vaccines are grown in *Saccharomyces cerevisiae* (baker's yeast or brewer's yeast) and contain residual yeast protein,[12] but adverse reactions to these, if any, appear to be rare.[51] Human papillomavirus vaccine may also contain residual yeast protein.[52]

The rubber in vaccine vial stoppers or syringe plungers may be either dry natural rubber (DNR) latex or synthetic rubber. Those made with DNR pose a theoretical risk to the patient who is latex allergic. There is 1 report of an anaphylactic reaction in a latex allergic patient after hepatitis B vaccine attributed to rubber in the stopper.[53] A review of more than 160,000 VAERS reports found only 28 cases of possible immediate-type allergic reactions after receiving a DNR-containing vaccine, and these may have been due to other components.[54] The latex content of vaccine packaging is provided in Table 4 and is updated at www.cdc.gov/vaccines/pubs/pinkbook/pink-appendx.htm.[55]

There is a single report of an immediate-type allergic reaction to a vaccination that was attributed to neomycin.[56] However, the patient had a maculopapular (not urticarial) rash to the topical application of neomycin, and no testing for IgE to neomycin was performed. There is a single case report of an immediate-type reaction that may have been caused by thimerosal in a vaccine.[57]

However rare, if a patient gives a history of an immediate-type reaction to yeast, latex, neomycin, or thimerosal, it is appropriate to investigate with immediate-type skin testing before immunization with a vaccine containing these constituents.

Table 5 lists vaccine excipients by vaccine. Updated lists of vaccine excipients by vaccine and by excipient are available at www.cdc.gov/vaccines/pubs/pinkbook/pink-appendx.htm.[12,58]

Summary Statement 7. Patients who have had an apparent anaphylactic reaction after immunization should undergo immediate-type allergy skin testing to help confirm that the reaction was IgE mediated and determine the responsible component of the vaccine. (B)

To determine whether a vaccine was responsible for a patient's apparent allergic reaction, skin testing with the vaccine should be performed.[35,36] The vaccine should first be tested by the prick method. Full-strength vaccine can be used unless the history of the reaction was truly life-threatening, in which case beginning even the prick test with dilute vaccine is appropriate. If the full-strength prick test result is negative, with appropriate positive and negative controls, an intradermal test with the vaccine diluted 1:100 should be performed,[59] again with appropriate controls.

As with any skin test reagent, and particularly with materials not standardized for skin testing such as vaccines, false-positive (irritant) results and clinically irrelevant positive results may occur. Likewise, false-negative response may also be seen. Some patients known to have IgE antibodies to various vaccines by in vitro testing or skin testing have nonetheless received the vaccines in the usual manner without reaction.[47,60–63] Although these findings complicate the interpretation of vaccine skin tests, if the test result is positive in a patient with a history of an allergic reaction to the vaccine, the patient must be assumed to be allergic. Intradermal skin tests with some vaccines, such as tetanus toxoid, can also induce delayed-type hypersensitivity responses.[64]

If the suspect vaccine contains gelatin (Table 2), egg (influenza and yellow fever), chicken (yellow fever), or yeast (hepatitis B vaccine and human papillomavirus vaccine), the patient should also be skin tested for these allergens.[35,36] Egg, chicken, and yeast extracts for skin testing are commercially available. Gelatin can be prepared by dissolving 1 teaspoon (5 g) of any sugared gelatin powder (for example, Jell-O) in 5 mL of normal saline to create a prick skin test solution, recognizing that this is not a standardized, validated, FDA-approved method. In vitro assays for specific IgE antibody are also commercially available for these foods, including gelatin.

Summary Statement 8. If the intradermal skin test result is negative, the chance that the patient has IgE antibody to any vaccine constituent is negligible, and the vaccine can be administered in the usual manner. It is prudent, nonetheless, in a patient with a history suggestive of an anaphylactic reaction to administer the vaccine under observation with epinephrine and other treatment available. (B)

Although there are no formal studies to evaluate the positive and negative predictive values for intradermal skin test results in patients who have had apparent allergic reactions to vaccines, the approach is almost certainly sufficiently sensitive to identify patients with IgE-mediated reactions to some

Table 4. Latex in Vaccine Packaging[a]

Vaccine	Latex
Anthrax (BioThrax)	Yes–vial
Comvax	Yes–vial
DTaP	
Daptacel	Yes–vial
Infanrix	Yes–syringe
	No–vial
Tripedia	Yes–vial
DT (generic)	Yes–vial
Hib	
HibTITER	Yes–vial
PedvaxHIB	Yes–vial
ActHIB	Yes–diluent vial
	No–lyophilized vaccine vial
Hepatitis A	
Havrix	Yes–syringe
	No–vial
Vaqta	Yes–vial
	Yes–syringe
Hepatitis B	
Engerix-B	Yes–syringe
	No–vial
Recombivax HB	Yes–vial
HPV (Gardasil)	No
Influenza	
Fluarix	Yes–syringe
Fluvirin	No
Fluzone	No
FluLaval	No
Afluria	No
FluMist	No
Japanese encephalitis	
JE-Vax	No
Ixiaro	No
Kinrix	Yes–syringe
	No–vial
MMR (M-M-R II)	No
MMRV (ProQuad)	No
Measles (Attenuvax)	No
Mumps (Mumpsvax)	No
Rubella (Meruvax II)	No
Meningococcal	
Menomune	Yes–vial
Menactra	Yes–vial
	No–syringe
Pediarix	Yes–syringe
	No–vial
Pentacel	No
Pneumococcal	
Pneumovax 23	No
Prevnar	Yes–syringe, before lot D46873
	No–syringe, lot D46873 and after
Polio (IPOL)	Yes–syringe
	No–vial
Rabies	
Imovax Rabies	No
RabAvert	No
Rotavirus	
RotaTeq	No
Rotarix	Yes–applicator
	No–vial and transfer adapter
Td	
Decavac	No–vial
	No–syringe
Generic	Yes–vial
	Yes–syringe
Tdap	
Adacel	No
Boostrix	Yes–syringe
	No–vial
TriHIBit	Yes–vial
Twinrix	Yes–syringe
	No–vial
Typhoid	
Typhim Vi	No
Vivotif Berna	NA
Varicella (Varivax)	No
Vaccinia (smallpox) (ACAM2000)	No
Yellow fever (YF-Vax)	Yes–vial

Abbreviations: DT, diphtheria and tetanus toxoids (pediatric formulation); DTaP, diphtheria and tetanus toxoids and acellular pertussis (pediatric formulation); Hib, *Haemophilus influenzae* type B; HPV, human papillomavirus; MMRV, measles, mumps, rubella and varicella; NA, not applicable; Td, tetanus and diphtheria toxoids (adult/adolescent formulation); Tdap, tetanus and diphtheria toxoids and acellular pertussis (adult/adolescent formulation).

[a] "If a person reports a severe (anaphylactic) allergy to latex, vaccines supplied in vials or syringes that contain natural rubber should not be administered unless the benefit of vaccination outweighs the risk for a potential allergic reaction. For latex allergies other than anaphylactic allergies (e.g., a history of contact allergy to latex gloves), vaccines supplied in vials or syringes that contain dry natural rubber or rubber latex can be administered." (Advisory Committee on Immunization Practices General Recommendations on Immunization, 2006). This table is accurate, to the best of our knowledge, as of June 2009. If in doubt, check the package insert for the vaccine in question.

vaccine component. Intradermal skin tests are recommended when increased sensitivity is required for the evaluation of anaphylaxis.[64] There are no reports of patients with negative intradermal skin test results to a vaccine reacting to subsequent administration of that vaccine. As with any diagnostic test, the increased sensitivity of intradermal testing likely comes with some loss of specificity. Thus, although there are reports of patients being safely administered the vaccines after negative intradermal skin test results,[47,65] there are also reports of patients with positive skin test results nonetheless receiving the vaccines uneventfully.[47,63] Dilutions of vaccines of 1:100 have been demonstrated to be nonirritating.[59] Thus, if the skin test results to the vaccine and its ingredients are negative, particularly at the intradermal level (with the vaccine diluted 1:100), then it is unlikely that the patient has IgE antibody to any component of the vaccine, and they can be

Table 5. Excipients Included in US Vaccines, by Vaccine[a]

Vaccine	Contains
Anthrax (BioThrax)	Aluminum hydroxide, amino acids, benzethonium chloride, formaldehyde or formalin, inorganic salts and sugars, vitamins
BCG (Tice)	Asparagine, citric acid, lactose, glycerin, iron ammonium citrate, magnesium sulfate, potassium phosphate
DTaP (Daptacel)	Aluminum phosphate, ammonium sulfate, Casamino acid, dimethyl-β-cyclodextrin, formaldehyde or formalin, glutaraldehyde, 2-phenoxyethanol
DTaP (Infanrix)	Aluminum hydroxide, bovine extract, formaldehyde or formalin, glutaraldehyde, 2-phenoxyethanol, polysorbate 80
DTaP (Tripedia)	Aluminum potassium sulfate, ammonium sulfate, bovine extract, formaldehyde or formalin, gelatin, polysorbate 80, sodium phosphate, thimerosal[b]
DTaP/Hib (TriHIBit)	Aluminum potassium sulfate, ammonium sulfate, bovine extract, formaldehyde or formalin, gelatin, polysorbate 80, sucrose, thimerosal[b]
DTaP-IPV (Kinrix)	Aluminum hydroxide, bovine extract, formaldehyde, lactalbumin hydrolysate, monkey kidney tissue, neomycin sulfate, polymyxin B, polysorbate 80
DTaP-Hep B-IPV (Pediarix)	Aluminum hydroxide, aluminum phosphate, bovine protein, lactalbumin hydrolysate, formaldehyde or formalin, glutaraldehyde, monkey kidney tissue, neomycin, 2-phenoxyethanol, polymyxin B, polysorbate 80, yeast protein
DtaP-IPV/Hib (Pentacel)	Aluminum phosphate, bovine serum albumin, formaldehyde, glutaraldehyde, MRC-5 DNA and cellular protein, neomycin, polymyxin B sulfate, polysorbate 80, 2-phenoxyethanol
DT (sanofi)	Aluminum potassium sulfate, bovine extract, formaldehyde or formalin, thimerosal (multidose) or thimerosal[b] (single dose)
DT (Massachusetts)	Aluminum hydroxide, formaldehyde or formalin
Hib (ACTHib)	Ammonium sulfate, formaldehyde or formalin, sucrose
Hib (PedvaxHib)	Aluminum hydroxyphosphate sulfate
Hib/Hep B (Comvax)	Amino acids, aluminum hydroxyphosphate sulfate, dextrose, formaldehyde or formalin, mineral salts, sodium borate, soy peptone, yeast protein
Hep A (Havrix)	Aluminum hydroxide, amino acids, formaldehyde or formalin, MRC-5 cellular protein, neomycin sulfate, 2-phenoxyethanol, phosphate buffers, polysorbate
Hep A (Vaqta)	Aluminum hydroxyphosphate sulfate, bovine albumin or serum, DNA, formaldehyde or formalin, MRC-5 cellular protein, sodium borate
Hep B (Engerix-B)	Aluminum hydroxide, phosphate buffers, thimerosal,[b] yeast protein
Hep B (Recombivax)	Aluminum hydroxyphosphate sulfate, amino acids, dextrose, formaldehyde or formalin, mineral salts, potassium aluminum sulfate, soy peptone, yeast protein
Hep A/Hep B (Twinrix)	Aluminum hydroxide, aluminum phosphate, amino acids, dextrose, formaldehyde or formalin, inorganic salts, MRC-5 cellular protein, neomycin sulfate, 2-phenoxyethanol, phosphate buffers, polysorbate 20, thimerosal,[b] vitamins, yeast protein
HPV (Gardasil)	Amino acids, amorphous aluminum hydroxyphosphate sulfate, carbohydrates, L-histidine, mineral salts, polysorbate 80, sodium borate, vitamins
Influenza (Afluria)	β-Propiolactone, calcium chloride, neomycin, ovalbumin, Polymyxin B, potassium chloride, potassium phosphate, sodium phosphate, sodium taurodeoxycholate.
Influenza (Fluarix)	Egg albumin (ovalbumin), egg protein, formaldehyde or formalin, gentamicin, hydrocortisone, octoxynol-10, α-tocopheryl hydrogen succinate, polysorbate 80, sodium deoxycholate, sodium phosphate, thimerosal[b]
Influenza (Flulaval)	Egg albumin (ovalbumin), egg protein, formaldehyde or formalin, sodium deoxycholate, phosphate buffers, thimerosal
Influenza (Fluvirin)	β-Propiolactone, egg protein, neomycin, polymyxin B, polyoxyethylene 9–10 nonyl phenol (triton N-101, octoxynol 9), thimerosal (multidose containers), thimerosal[b] (single-dose syringes)
Influenza (Fluzone)	Egg Protein, Formaldehyde or Formalin, Gelatin, Octoxinol-9 (Triton X-100), Thimerosal (multidose containers)
Influenza (FluMist)	Chick kidney cells, egg protein, gentamicin sulfate, monosodium glutamate, sucrose phosphate glutamate buffer
IPV (Ipol)	Calf serum protein, formaldehyde or formalin, monkey kidney tissue, neomycin, 2-phenoxyethanol, polymyxin b, streptomycin
Japanese Encephalitis (JE-Vax)	Formaldehyde or formalin, gelatin, mouse serum protein, polysorbate 80, thimerosal
Japanese Encephalitis (Ixiaro)	Aluminum hydroxide, bovine serum albumin, formaldehyde, protamine sulfate, sodium metabisulfite
Meningococcal (Menactra)	Formaldehyde or formalin, phosphate buffers
Meningococcal (Menomune)	Lactose, thimerosal (10-dose vials only)
MMR (MMR-II)	Amino acid, bovine albumin or serum, chick embryo fibroblasts, human serum albumin, gelatin, glutamate, neomycin, phosphate buffers, sorbitol, sucrose, vitamins

Continued

Table 5. (Continued)

Vaccine	Contains
MMRV (ProQuad)	Bovine albumin or serum, gelatin, human serum albumin, monosodium L-glutamate, MRC-5 Cellular Protein, Neomycin, Sodium Phosphate Dibasic, Sodium Bicarbonate, Sorbitol, Sucrose, Potassium Phosphate Monobasic, Potassium Chloride, Potassium Phosphate Dibasic
Pneumococcal (Pneumovax)	Bovine protein, phenol
Pneumococcal (Prevnar)	Aluminum phosphate, amino acid, soy peptone, yeast extract
Rabies (Imovax)	Human serum albumin, β-propiolactone, MRC-5 cellular protein, neomycin, phenol red (phenolsulfonphthalein), vitamins
Rabies (RabAvert)	Amphotericin B, β-propiolactone, bovine albumin or serum, chicken protein, chlortetracycline, egg albumin (ovalbumin), EDTA, neomycin, potassium glutamate
Rotavirus (RotaTeq)	Cell culture media, fetal bovine serum, sodium citrate, sodium phosphate monobasic monohydrate, sodium hydroxide sucrose, polysorbate 80
Rotavirus (Rotarix)	Amino acids, calcium carbonate, calcium chloride, D-glucose, dextran, ferric (III) nitrate, L-cystine, L-tyrosine, magnesium sulfate, phenol red, potassium chloride, sodium hydrogenocarbonate, sodium phosphate, sodium L-glutamine, sodium pyruvate, sorbitol, sucrose, vitamins, xanthan
Td (Decavac)	Aluminum potassium sulfate, bovine extract, formaldehyde or formalin, 2-phenoxyethanol, peptone, thimerosal[b]
Td (Massachusetts)	Aluminum hydroxide, aluminum phosphate, formaldehyde or formalin, thimerosal (some multidose containers)
Tdap (Adacel)	Aluminum phosphate, formaldehyde or formalin, glutaraldehyde, 2-phenoxyethanol
Tdap (Boostrix)	Aluminum hydroxide, bovine extract, formaldehyde or formalin, glutaraldehyde, polysorbate 80
Typhoid (inactivated - Typhim Vi)	Disodium phosphate, monosodium phosphate, phenol, polydimethylsiloxane, hexadecyltrimethylammonium bromide
Typhoid (oral - Ty21a)	Amino acids, ascorbic acid, bovine protein, casein, dextrose, galactose, gelatin, lactose, magnesium stearate, sucrose, yeast extract
Vaccinia (ACAM2000)	Glycerin, human serum albumin, mannitol, monkey kidney cells, neomycin, phenol, polymyxin B
Varicella (Varivax)	Bovine albumin or serum, EDTA, gelatin, monosodium L-glutamate, MRC-5 DNA and cellular protein, neomycin, potassium chloride, potassium phosphate monobasic, sodium phosphate monobasic, sucrose
Yellow fever (YF-Vax)	Egg protein, gelatin, sorbitol
Zoster (Zostavax)	Bovine calf serum, hydrolyzed porcine gelatin, monosodium L-glutamate, MRC-5 DNA and cellular protein, neomycin, potassium phosphate monobasic, potassium chloride, sodium phosphate dibasic, sucrose

Abbreviations: DT, diphtheria and tetanus toxoids (pediatric formulation); DTaP, diphtheria and tetanus toxoids and acellular pertussis (pediatric formulation); Hep A, hepatitis A; Hep B, hepatitis B; Hib, *Haemophilus influenzae* type B; HPV, human papillomavirus; IPV, inactivated poliovirus; MMRV, measles, mumps, rubella and varicella; Td, tetanus-diphtheria toxoids (adult/adolescent formulation); Tdap, tetanus and diphtheria toxoids and acellular pertussis (adult/adolescent formulation).

[a] Vaccine Excipient & Media Summary, Part 2. Includes vaccine ingredients (eg, adjuvants and preservatives) and substances used during the manufacturing process, including vaccine-production media, that are removed from the final product and present only in trace quantities. In addition to the substances listed, most vaccines contain sodium chloride (table salt). Adapted from Grabenstein JD. *ImmunoFacts: Vaccines & Immunologic Drugs.* St. Louis, MO: Wolters Kluwer Health; 2009 and individual product package inserts. All reasonable efforts have been made to ensure the accuracy of this information, but manufacturers may change product contents before that information is reflected here.

[b] The product should be considered equivalent to thimerosal-free products. This vaccine may contain trace amounts (<0.3 μg) of mercury left after postproduction thimerosal removal, but these amounts have no biological effect.

given the vaccine in the usual manner but observed for at least 30 minutes afterward.[35,36]

Summary Statement 9. In patients with histories and skin tests results consistent with an IgE-mediated reaction to a vaccine, who require additional doses of the suspect vaccine or other vaccines with common ingredients, consideration can be given to administering the vaccine in graded doses under observation. (C)

If vaccine or vaccine component skin test results are positive, the vaccine may still be administered, if necessary, in graded doses (Table 6).[46,66,67] For a vaccine where the full normal dose volume is 0.5 mL, the patient is first given 0.05 mL of a 1:10 dilution and then given (at 15-minute intervals), 0.05 mL of full-strength vaccine, with subsequent doses of 0.1 mL, 0.15 mL, and finally 0.2 mL for a cumulative dose of 0.5 mL. This or similar protocols have been used successfully for the administration of egg-containing vaccines to egg allergic recipients[66] and with other vaccines as well.[50,68]

This procedure in a patient who is presumed to be allergic to the vaccine being administered needs to be performed under direct medical supervision with emergency medications and equipment to promptly treat an anaphylactic reaction should it occur.[64] Whether such challenges are undertaken in the office vs hospital or with or without an

Table 6. Administration of Vaccines in Graded Doses

For a vaccine for which the full normal-dose volume is 0.5 mL, give the following doses at 15-minute intervals as tolerated[a]	For influenza vaccine in egg allergic patients, if the egg protein content of the vaccine is known to be ≤1.2 μg/mL administer as follows[b]
0.05 mL, 1:10 dilution	In 2 doses: 10% of the dose (0.025 mL or 0.05 mL) followed in 30 minutes by the remaining 90% of the dose (0.225 mL or 0.45 mL) or
0.05 mL, full strength	In a single dose (0.25 mL or 0.5 mL)
0.1 mL, full strength	
0.15 mL, full strength	
0.2 mL, full strength	

[a] Must be done under direct medical supervision with emergency medications and equipment to promptly treat an anaphylactic reaction should it occur.

[b] Observe for at least 30 minutes afterward.

intravenous line in place depends on the severity of the original reaction to the vaccine and the patient's medical condition.[64]

For influenza vaccine in egg allergic patients, if the egg protein content of the vaccine is known to be 1.2 μg/mL or less, the vaccine can be administered in 2 doses (10% of the dose, followed in 30 minutes by the remaining 90%) or as a single dose, without prior vaccine skin testing,[47] although observation for at least 30 minutes afterward seems prudent (Table 6). Unfortunately, the specific egg protein content of any given year's influenza vaccines is not readily available.[47]

Because of the lot to lot variability in the egg protein content of egg-containing vaccines,[48] even if an egg allergic patient has a negative vaccine skin test response and is given the vaccine in the usual manner or has a positive vaccine skin test response and is given the vaccine in graded doses, if the patient needs to be given the vaccine again at a later time, the vaccine skin test, and graded challenge if necessary, would need to be repeated.

Summary Statement 10. Some more serious, and less common, reactions to vaccines require evaluation, but only a few are absolute contraindications to future doses. (B)

In addition to anaphylactic reactions (discussed herein), some vaccines are capable of causing other rare but serious reactions that might contraindicate the administration of future doses.[11]

There was a particular type of influenza vaccine, namely, swine flu vaccine administered in 1976, which was associated with an increased risk for Guillain-Barré syndrome (GBS), estimated at 1 additional case per 100,000 vaccinations (over the annual background rate of 10 to 20 cases per million adults).[69] In subsequent years, influenza vaccines have been carefully monitored for this possible adverse effect and have shown no consistent increased risk. If there is any increased risk, it is on the order of 1 per million.[69,70] A low level of GBS cases continues to be reported in temporal association with previous influenza infection[71] and with influenza and other vaccines.[72,73] Previous GBS raises the risk of a recurrence of GBS. Persons who developed GBS within 6 weeks of influenza vaccination should avoid subsequent immunization with influenza vaccines.[69] However, individuals with a history of GBS unrelated to influenza infection or vaccination who would benefit from immunization can be vaccinated, particularly if the influenza infection risk is high or if the infecting strain is resistant to antiviral therapy.[69] The live attenuated influenza vaccine is not recommended in persons with a history of GBS simply because it has not been studied for safety in such persons.[69]

Measles, mumps, and rubella (MMR) vaccines can cause adverse reactions related to the live viruses they contain. Transient rashes appear in as many as 5% of recipients of measles vaccine, and this probably represents vaccine-induced modified measles.[32] There is a late-onset fever occurring 5 to 12 days after vaccine administration in as many as 15% of recipients of the MMR vaccine.[32,46,74] As with any fever in young children, this increases the risk of febrile seizures; however, such seizures do not have any sort of long-term sequelae.[75,76] Recipients of the MMR vaccine can also have thrombocytopenia, which is usually without any significant clinical consequence, but can rarely cause hemorrhage.[26,74,77,78] The rate of thrombocytopenia is much higher with the disease itself.[74] Rubella vaccine can cause acute arthritis in approximately 15% of adult women who received the vaccine.[79,80] This may represent a direct infection of the joints by the vaccine virus but has a questionable association with chronic arthritis.[79,80] None of these events are contraindications to the administration of subsequent doses of MMR vaccine.[11]

The most serious adverse effect related to pertussis vaccine is termed *encephalopathy*. This term describes a specific and severe reaction characterized as an "acute, severe CNS [central nervous system] disorder occurring within 7 days following vaccination and generally consisting of major alterations in consciousness, unresponsiveness, generalized or focal seizures that persist more than a few hours, with failure to recover within 24 hours."[26] This event happens with an incidence that may actually be 0, meaning that it is not actually increased after vaccination, but to a maximum of 10 per million doses of diphtheria and tetanus toxoids and whole-cell pertussis (DTP) vaccine.[74] This can have permanent neurologic sequela and is an absolute contraindication to further pertussis vaccination.[11] Pertussis vaccine can cause less severe apparent neurologic events, including febrile seizures,[75] inconsolable crying,[46] and hypotonic-hyporesponsive episodes.[81] Although these are clearly concerning episodes for parents to witness, none of them result in permanent

sequelae, and none of them are contraindications to further doses of these vaccines.[11,74,82] Of note is the fact that all these serious and less serious neurologic events after pertussis-containing vaccines have been significantly reduced since changing from the diphtheria and tetanus toxoids and whole-cell pertussis vaccine (DTP) to the diphtheria and tetanus toxoids and acellular pertussis vaccine (DTaP).[46,82–87]

Tetanus toxoid often causes patients to develop a large local swelling.[88] This probably represents an Arthus reaction in patients with preexisting antitetanus antibodies from prior immunizations who then receive a large injection of antigen in the vaccine. These reactions may cause discomfort but are not serious. Tetanus toxoid also has some potential association with Guillain-Barre syndrome and with a rare local neurologic event called brachial neuritis, which involves shoulder pain followed by weakness.[26]

Varicella vaccine is another live virus immunization that can cause vaccine-induced illness, particularly the appearance of varicella lesions. These reactions occur at the injection site in approximately 3% of recipients and in another 3% are more generalized.[89] The disease due to coincident natural exposure may be difficult to distinguish from vaccine-induced varicella. A zoster-type rash may rarely appear after a varicella vaccination and may contain either vaccine-strain or wild-type virus.[90,91] Although varicella disease (chickenpox) itself can be more severe in children with atopic dermatitis, the varicella vaccine can be safely administered to children with atopic dermatitis without an increased risk of complications.[92]

A serious adverse effect of yellow fever vaccine is encephalitis.[93] The risk for this complication is as high as 4 per 1000 infants, and for this reason the vaccine is relatively contraindicated in this age group. It should not be given to any infant younger than 4 months and to those younger than 9 months only if their risk from the disease is very high.[46] The yellow fever vaccine has recently been associated with a very severe illness in adults. There have been fatalities from multisystem disease with features strikingly similar to the disease yellow fever itself.[94–98] This has occurred in patients who are not known to be immunocompromised. The cause of these reactions is still unknown, but this vaccine should not be given to patients unless they are at risk of acquiring yellow fever, typically by traveling to an area where the disease is endemic.[99]

Table 7. Live vs Killed Vaccines

Live vaccines	Killed vaccines
Bacille Calmette-Guerin (BCG)	Diphtheria, tetanus and acellular pertussis (DTaP, Tdap)
Influenza (intranasal)	Diphtheria-tetanus (DT, Td)
Measles-mumps-rubella (MMR)	Hepatitis A
Oral poliovirus (OPV	Hepatitis B
Rotavirus	Hib conjugates
Typhoid (oral)	Human papillomavirus (HPV)
Vaccinia (smallpox)	Inactivated poliovirus (IPV)
Varicella	Influenza (injectable)
Yellow fever	Japanese encephalitis
Zoster	Meningococcal
	Meningococcal conjugate
	Pneumococcal
	Pneumococcal conjugate
	Rabies
	Typhoid (injectable)

Summary Statement 11. Pregnant women should not be vaccinated with live vaccines. However, pregnant women should be given inactivated influenza vaccine, as well as tetanus and hepatitis B vaccine if otherwise indicated. (B)

Because of a theoretical risk of transmitting the live agent to the fetus, pregnant women should not receive live vaccines such as MMR, varicella, or live attenuated influenza vaccine.[100] There is an increased risk of hospitalization from influenza in pregnancy, and therefore (inactivated) influenza vaccine is specifically indicated in women who will be pregnant during the influenza season.[100] Hepatitis B vaccine and tetanus and diphtheria vaccines should also be administered to pregnant women if they would otherwise be indicated.[100]

Summary Statement 12. In general, live vaccines should not be given to persons who are immune compromised because of a risk of generalized infection with the immunizing agent. (B)

Live vaccines (Table 7) are generally contraindicated in patients with immune suppression, specifically those with severe humoral or cellular immune deficiency.[11,46,101] This includes patients with X-linked agammaglobulinemia, common variable immune deficiency, severe combined immune deficiency, severe human immunodeficiency virus (HIV) infection, leukemia, lymphoma, other malignant neoplasms, or patients requiring treatment for these or other conditions with treatment modalities that impair immune responses, such as high-dose corticosteroids (2 weeks of daily treatment with prednisone, 20 mg or 2 mg/kg or equivalent per day). There are, however, exceptions even to this general rule that immune compromised patients should not receive live viral vaccines.[11,46,101] For example, the MMR vaccine should be given to HIV-infected children and adults if they have only mild or moderate disease. Similarly varicella vaccine should be given to mildly HIV-infected children.

Summary Statement 13. Specific vaccines or vaccination in general have been purported to have long-term consequences, including atopy, autism, and multiple sclerosis. Epidemiologic studies have not supported such associations. (B)

There are a number of controversies related to long-term consequences of particular vaccines or of vaccination in general. There have been claims that receiving childhood vaccinations increases the likelihood of developing atopic disease, autism, diabetes, or multiple sclerosis. The associations have all been extensively evaluated using many appropriate research methods and epidemiologic studies, and no relationship between vaccinations and any of these outcomes has been demonstrated in these studies.[102–106] There has been particular concern about thimerosal, which was previously used as a preservative in vaccines. Although studies have

failed to support any adverse effect from thimerosal exposure in vaccines,[107,108] all routinely recommended vaccines for infants and children in the United States are now available only as thimerosal-free formulations or contain only trace amounts of thimerosal, with the exception of some inactivated influenza vaccines. Inactivated influenza vaccine for pediatric use is available as a thimerosal preservative-containing formulation, a trace thimerosal-containing formulation, and a thimerosal-free formulation.[46]

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1. Practice parameters for the diagnosis and treatment of asthma. *J Allergy Clin Immunol.* 1995;96(suppl):S707-S870.

2. Practice parameters for allergy diagnostic testing. *Ann Allergy.* 1995;75:543–625.

3. Practice parameters for the diagnosis and management of immunodeficiency. *Ann Allergy.* 1996;76:282–294.

4. Practice parameters for allergen immunotherapy. *J Allergy Clin Immunol.* 1996;98:1001–1011.

5. Disease management of atopic dermatitis: a practice parameter. *Ann Allergy.* 1997;79197–211.

6. The diagnosis and management of anaphylaxis. *J Allergy Clin Immunol.* 1998;101(suppl):S465-S528.

7. Algorithm for the diagnosis and management of asthma: a practice parameter update. *Ann Allergy.* 1998;81:415–420.

8. Diagnosis and management of rhinitis: parameter documents of the Joint Task Force on Practice Parameters in Allergy, Asthma and Immunology. *Ann Allergy.* 1998; 81(suppl):S463-S518.

9. Parameters for the diagnosis and management of sinusitis. *J Allergy Clin Immunol.* 1998;102(suppl):S107-S144.

10. Stinging insect hypersensitivity: a practice parameter. *J Allergy Clin Immunol.* 1999;103:963–980.

11. Disease management of drug hypersensitivity: a practice parameter. *Ann Allergy.* 1999;83(suppl):S665-S700.

12. Diagnosis and management of urticaria: a practice parameter. *Ann Allergy.* 2000;85(suppl):S521-S544.

13. Allergen immunotherapy: a practice parameter. *Ann Allergy.* 2003;90(suppl):SI-S540.

14. Symptom severity assessment of allergic rhinitis: part I. *Ann Allergy.* 2003;91:105–114.

15. Disease management of atopic dermatitis: an updated practice parameter. *Ann Allergy.* 2004;93:S1-S21.

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These parameters are also available on the Internet at http://www.jcaai.org

The Joint Task Force has made a concerted effort to acknowledge all contributors to this parameter. If any contributors have been excluded inadvertently, the Task Force will ensure that appropriate recognition of such contributions is made subsequently.

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