Task force report

Adverse reactions to vaccines practice parameter 2012 update

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Key words: *Vaccine, immunization, adverse reaction, allergy, influenza vaccine, egg allergy*

Abbreviations used

AAAAI:	American Academy of Allergy, Asthma & Immunology
AAP:	American Academy of Pediatrics
ACAAI:	American College of Allergy, Asthma & Immunology
CDC:	US Centers for Disease Control and Prevention
DNR:	Dry natural rubber
DTaP:	Diphtheria and tetanus toxoids and acellular pertussis vaccine
DTP:	Diphtheria and tetanus toxoids and whole-cell pertussis vaccine
GBS:	Guillain-Barré syndrome
JTFPP:	Joint Task Force on Practice Parameters
LAIV:	Live attenuated influenza vaccine
MMR:	Measles, mumps, and rubella vaccine
Td:	Tetanus and diphtheria
Tdap:	Tetanus, diphtheria toxoids, and acellular pertussis
TIV:	Trivalent influenza vaccine
VAERS:	Vaccine Adverse Event Reporting System

These parameters were developed by the Joint Task Force on Practice Parameters (JTFPP), representing the American Academy of Allergy, Asthma & Immunology (AAAAI); the American College of Allergy, Asthma & Immunology (ACAAI); and the Joint Council of Allergy, Asthma & Immunology.

The AAAAI and ACAAI have jointly accepted responsibility for establishing "Adverse reactions to vaccines practice parameter 2012 update." This is a complete and comprehensive document at the current time. The medical environment is a changing environment, and not all recommendations will be appropriate for all patients. Because this document incorporates the efforts of many participants, no single individual, including those who served on the JTFPP, is authorized to provide an official AAAAI or ACAAI interpretation of these practice parameters. Any request for information about or an interpretation of these practice parameters by the AAAAI or ACAAI should be directed to the Executive Offices of the AAAAI, the ACAAI, and the Joint Council of Allergy, Asthma & Immunology.

The JTFPP understands that the cost of diagnostic tests and therapeutic agents is an important concern that might appropriately influence the workup and treatment chosen for a given patient. The emphasis of our primary recommendations regarding a medication can vary, for example, depending on third-party payer issues and product patent expiration dates. However, because a given test or agent's cost is so widely variable and there is a paucity of pharmacoeconomic data, the JTFPP generally does not consider cost when formulating practice parameter recommendations. In extraordinary circumstances, when the cost benefit of an intervention is prohibitive as supported by pharmacoeconomic data, commentary might be provided.

These parameters are not designed for use by pharmaceutical companies in drug promotion.

The Joint Task Force is committed to ensuring that the practice parameters are based on the best scientific evidence that is free of commercial bias. To this end, the parameter development process includes multiple layers of rigorous review. These layers include the work group convened to draft the parameter, the task force reviewers, and peer review by members of each sponsoring society. Although the Task Force has the final responsibility for the content of the documents submitted for publication, each reviewer's comment will be discussed, and reviewers will receive written responses to comments when appropriate.

To preserve the greatest transparency regarding potential conflicts of interest, all members of the Joint Task Force and the Practice Parameters Work Groups will complete a standard potential conflict of interest disclosure form, which will be available for external review by the sponsoring organization and any other interested individual. In addition, before confirming the selection of a work group chairperson, the Joint Task Force

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will discuss and resolve all relevant potential conflicts of interest associated with this selection. Finally, all members of parameter work groups will be provided a written statement regarding the importance of ensuring that the parameter development process is free of commercial bias.

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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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CLASSIFICATION OF RECOMMENDATIONS AND EVIDENCE

Category of evidence:	
Ia	Evidence from meta-analysis of randomized controlled trials
Ib	Evidence from at least 1 randomized controlled trial
IIa	Evidence from at least 1 controlled study without randomization
IIb	Evidence from at least 1 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 from category I evidence
C	Directly based on category III evidence or extrapolated from category I or II evidence
D	Directly based on category IV evidence or extrapolated from category I, II, or III evidence
E	Based on consensus of the Joint Task Force on Practice Parameters

ABSTRACT

Mild local reactions and fever after vaccinations are common and do not contraindicate future doses. Anaphylactic reactions to vaccines are rare and should be evaluated with skin tests to the vaccine and its components. If the skin test results are negative, subsequent doses can be administered in the usual manner but under observation. If the skin test results are positive and the patient requires subsequent doses, the vaccine can be administered in graded doses under observation. Some nonanaphylactic reactions to vaccines might also require evaluation, but only a few are contraindications to future doses. Pregnant women and persons who are immune compromised should generally not receive live vaccines. Purported long-term sequelae of vaccination, such as autism, are not supported by epidemiologic studies. Patients with egg allergy of any severity should receive annual influenza vaccinations because studies have demonstrated a very low rate of reactions. Studies to date have evaluated the injectable trivalent influenza vaccine (TIV), and thus TIV, rather than the live attenuated influenza vaccine (LAIV), should be used for recipients with egg allergy. All influenza vaccines available in the United States contain low amounts of ovalbumin. Neither skin testing with the vaccine nor dividing the dose is required; however, the vaccine should be administered in a setting in which anaphylaxis can be recognized and treated.

EXECUTIVE SUMMARY

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 can cause an injection-site nodule, but this is not a contraindication to subsequent vaccination. Anaphylactic reactions to vaccines are estimated to occur at a rate of approximately 1 per million doses. There are approximately 220 million doses of vaccines distributed in the United States each year. All serious events occurring after vaccine administration should be reported to the Vaccine Adverse Event Reporting System (VAERS), even if it is not certain that the vaccine was the causal agent. Measuring levels of IgG antibodies to the immunizing agents in a vaccine suspected of causing a serious adverse reaction to determine whether they are at protective levels can help determine whether subsequent doses are required. All suspected anaphylactic reactions to vaccines should ideally be evaluated in an attempt to determine the culprit allergen. IgE-mediated reactions to vaccines are more often caused by additive or residual vaccine components, such as gelatin, rather than the microbial immunizing agent itself. 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 to determine the responsible component of the vaccine. If the intradermal skin test result is negative, the chance that the patient has IgE antibodies to any vaccine constituent is negligible, and the vaccine can be administered in the usual manner. Nonetheless, it is prudent in a patient with a history suggestive of an anaphylactic reaction to administer the vaccine under observation with epinephrine and other treatment available. In a patient with a history and skin test results consistent with an IgE-mediated reaction to a vaccine who requires 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. Some nonanaphylactic reactions to vaccines might also require evaluation, but only a few are absolute contraindications to future doses. 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. 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. 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.

Patients with egg allergy should receive influenza vaccinations (TIV) because the risks of vaccinating are outweighed by the risks of not vaccinating. Persons with a history of suspected egg allergy should be evaluated by an allergist to determine the status of their egg allergy, but this should not delay their influenza vaccination. A growing number of studies suggest that influenza vaccines can be safely administered even to patients with a history of anaphylaxis to egg ingestion. Skin testing (prick, intradermal, or both) with the influenza vaccine itself in subjects with egg allergy (but without a history of reacting to the vaccine itself) does not reliably identify patients who are at increased risk of reacting to the vaccine and is not recommended. Influenza vaccine can be administered as a single dose to patients with egg allergy. Patients with egg allergy should receive influenza vaccines in a setting in which clinicians experienced in recognizing and treating anaphylaxis and equipment to manage anaphylaxis are immediately available and should be observed for 30 minutes after vaccination. Patients with egg allergy with a history of only hives after egg ingestion can receive influenza vaccine in a primary care provider's office provided the appropriate personnel and equipment are available, whereas those with a history of more severe reactions to egg ingestion should receive their vaccine in an allergist's office. All influenza vaccines available in the United States contain low amounts of ovalbumin. Although the intranasally administered LAIV contains a low amount of ovalbumin, all published studies to date have evaluated the injectable TIV, and thus TIV rather than LAIV should be used for recipients with egg

allergy. Only for patients with a history of allergic reaction to influenza vaccine itself is additional evaluation appropriate, including skin testing with the vaccine and vaccine ingredients. For patients with positive skin test results, the vaccine can be administered in multiple divided doses or can be withheld.

PREFACE

This practice parameter provides a practical, peer-reviewed, evidence-based guide for evaluation and management of patients with suspected allergic or other adverse reactions to vaccines. It also addresses patients with preexisting allergies or other health conditions that might preclude or alter vaccination. It contains updates since the first publication in 2009.

The practice parameter offers both general and vaccine-specific recommendations for (1) skin testing to vaccines and components, (2) serum specific IgE antibody testing, (3) serologic testing for protective antibody responses to vaccines, (4) vaccine administration, and (5) avoidance. The guidelines should prove useful for not only specialists in allergy and immunology but also other physicians. Most patients who avoid vaccination because of allergy concerns will be able to receive their appropriate vaccinations if this practice parameter is followed.

This parameter emphasizes 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. **Recommendations regarding the administration of influenza vaccine to recipients with egg allergy are specifically addressed in an addendum at the end of this practice parameter.**

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 might unnecessarily be advised to avoid subsequent immunization, which could 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 an apparent allergic or other serious adverse reaction after receiving a vaccine warrant evaluation by an allergist/immunologist. Also, patients with preexisting health conditions that might predispose to adverse reactions to vaccines could benefit from such an evaluation. In most cases, a risk-benefit analysis will favor subsequent immunization (Fig 1).

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 can 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 positive patch test result for thimerosal can 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 220 million doses of vaccines distributed in the United States each year. (B)

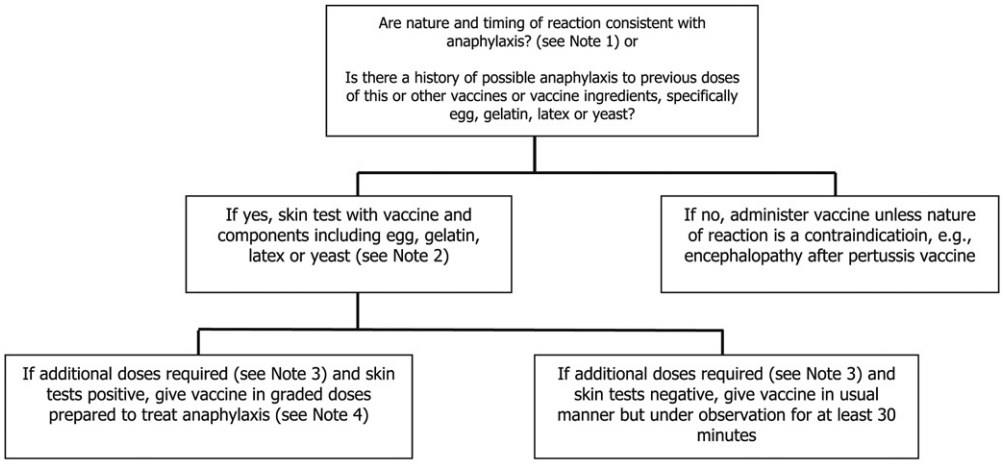
Anaphylaxis after vaccination is rare. The Vaccine Safety Datalink reviewed the diagnostic codes from medical encounters after the administration of more than 7.5 million doses of vaccines and estimated the risk of anaphylaxis to be 0.65 to 1.53 per million doses.[25] The US Centers for Disease Control and Prevention (CDC) estimates that there were 220,717,119 doses of all vaccines distributed in the United States in 2009, although not all doses are administered (John Iskander, CDC, written communication, July 20, 2011). Thus there are calculated to be approximately 140 to 340 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 VAERS was established by the CDC and the US Food and Drug Administration.[27] The 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 antibodies to the immunizing agents in a vaccine suspected of causing a serious adverse reaction to determine whether they are at protective levels can help determine whether subsequent doses are required. (B)

In a patient who has experienced an apparent adverse reaction to a 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 whether it is at a level associated with protection from disease. Such levels have been established for some but not all vaccines (Table I),[11,29-35] and many are available from diagnostic laboratories. If serologic evidence of immunity is documented, consideration can be given to withholding additional doses, although the magnitude and duration of immunity might be less than if all doses were received.[36,37] 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.



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.)
- Gastrointestinal: 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 egg, gelatin, latex 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 ingredient skin tests/ in vitro tests:

- Prick tests with commercial extracts of egg (influenza and yellow fever vaccines) or *Saccharomyces cerevisiae* yeast (Hepatitis B vaccine and Quadrivalent 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) or in vitro assay for specific IgE antibody. Vaccines that contain gelatin: influenza (some brands), measles, mumps, rabies (some brands), rubella, varicella, yellow fever, zoster
- In vitro assay for specific IgE antibody to latex. Vaccines that contain latex in packaging: http://www.cdc.gov/vaccines/pubs/pinkbook/downloads/appendices/B/latex-table.pdf

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, 0.1 ml of full strength, 0.15 ml of full strength, 0.2 ml of full strength.

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

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 might leave patients inadequately immunized if they unnecessarily avoid vaccines to which they are not allergic or if the vaccine could be administered safely despite the allergy. In addition, not knowing the particular constituent of a vaccine to which the patient is allergic might pose a risk with future doses of other vaccines that contain the same ingredient.

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

Gelatin is added to many vaccines (Table II) as a stabilizer and has been shown to be responsible for many anaphylactic reactions to measles, mumps, and rubella vaccine (MMR), varicella vaccine, and Japanese encephalitis vaccine.[38-41] Although MMR and varicella vaccines in the United States still contain gelatin, vaccine manufacturers in Japan and Germany removed gelatin or changed to a less allergenic gelatin, with a resultant decrease in allergic reactions.[42,43] A new Japanese encephalitis vaccine does not contain gelatin.[44] A history of allergy to the ingestion of gelatin should be sought before the administration of any gelatin-containing vaccine. A negative history, however, might not exclude an allergic reaction to gelatin injected with the vaccine.[39] Gelatin used in vaccines is of either bovine or porcine origin, which are extensively cross-reactive.[38,39,45] Some patients sensitized to beef or pork meat are also sensitized to beef or pork gelatin, which might place them at risk for reactions to gelatin-containing vaccines.[45]

Measles and mumps vaccines and one type of rabies vaccine are grown in chick embryo fibroblast cultures and contain negligible or no egg protein.[46,47] Measles or MMR vaccines can be administered to children with egg allergy without adverse reactions[48,49] and can be given to such patients without skin

TABLE I. Levels of antibody associated with protection from vaccine-preventable diseases

Vaccine	Protective level of IgG antibody ≥
Diphtheria	0.1 IU/mL[11]
Haemophilus influenzae b	0.15 μg/mL[29]
Hepatitis A	10 mIU/mL[30]
Hepatitis B Surface Antibody	10 mIU/mL[31]
Measles (Rubeola)	120 PRN titer[32]
Polio types 1, 2, and 3	1:8 neutralizing antibody titer[33]
Rabies	0.5 IU VNA/mL[34]
Rubella	10 IU/mL[35]
Tetanus	0.1 IU/mL[11]
Yellow fever	0.7 IU/mL[29]

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

TABLE II. Gelatin content of vaccines, 2011

Vaccine	Gelatin content
Influenza (Fluzone, Sanofi Pasteur)	250 μg per 0.5 mL dose
Influenza (FluMist, MedImmune Vaccines, Gaithersburg, Md)	2,000 μg per 0.2 mL dose
Measles, mumps, rubella (ATTENUVAX, MERUVAXII, MMRII, MUMPSVAX; Merck, Whitehouse Station, NJ)	14,500 μg per 0.5 mL dose
Measles, mumps, rubella, varicella (ProQuad, Merck)	11,000 μg per 0.5 mL dose
Rabies (RabAvert; Novartis, Emeryville, Calif)	12,000 μg per 1.0 mL dose
Typhoid vaccine live oral Ty21a (VIVOTIF, Berna, Coral Gables, Flo)	Capsule
Varicella (VARIVAX, Merck)	12,500 μg per 0.5 mL dose
Yellow fever (YF-VAX, Sanofi Pasteur)	7,500 μg per 0.5 mL dose
Zoster (ZOSTAVAX, Merck)	15,580 μg per 0.65 mL dose

testing.[50] Egg protein is present in higher amounts in yellow fever and influenza vaccines[46] and could, in theory, cause reactions in recipients with egg allergy. However, numerous studies have demonstrated that injectable influenza vaccine can be safely administered even to patients with severe egg allergy with appropriate precautions,[51-59] likely because of the very low amount of egg protein (ovalbumin) contained in recent years' vaccines.[60-62] **Recommendations regarding the administration of influenza vaccine to recipients with egg allergy are specifically addressed in an addendum at the end of this practice parameter**.

If patients have a history of reaction to the influenza vaccine itself, as opposed to a history of a reaction to the ingestion of eggs, evaluation as per Fig 1 is appropriate. 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 having egg allergy.[63] Thus the clinical history might not identify all persons allergic to egg proteins present in influenza or yellow fever vaccines. Chicken proteins other than those found in chicken egg might be present in yellow fever vaccine and could be responsible for reactions in recipients with chicken allergy.[64]

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.[65] Quadrivalent human papillomavirus vaccine (HPV4) might also contain residual yeast protein.[12]

The "rubber" in vaccine vial stoppers or syringe plungers can be either dry natural rubber (DNR) latex or synthetic rubber. Those made with DNR pose a theoretic risk to the patient who is allergic to latex. There is one report of an anaphylactic reaction in a patient with latex allergy after hepatitis B vaccine, which was attributed to rubber in the stopper.[66] 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 might have been due to other components.[67] The latex content of vaccine packaging is provided in Table III and is updated at www.cdc.gov/vaccines/pubs/pinkbook/pink-appendx.htm.[68]

There is a single report of an immediate-type allergic reaction to a vaccination that was attributed to neomycin.[69] 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 might have been caused by thimerosal in a vaccine.[70]

However rare, if a patient provides 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.

A recent publication described 8 children with anaphylaxis within 1 hour of receiving diphtheria, tetanus, and pertussis vaccines (diphtheria and tetanus toxoids and acellular pertussis vaccine [DTaP] or tetanus toxoid, reduced diphtheria toxoid, and acellular pertussis [Tdap]).[71] Six had histories of past allergic reactions to cow's milk, and all had very high levels of milk-specific serum IgE. These vaccines might contain trace (nanogram) quantities of residual casein from the medium in which they are produced. The results of this report require further investigation.[72] Anaphylactic reactions to DTaP or Tdap vaccines are rare, and the majority of patients with cow's milk allergy tolerate them without reaction. It is recommended that all patients, including those with milk allergy, continue to receive these vaccines on schedule[71,72] but perhaps with some additional observation after vaccination in those with very high levels of milk sensitivity.

Table IV 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.[12,73]

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)

Skin testing with vaccine should be performed to determine whether the vaccine was responsible for a patient's apparent allergic reaction.[36,37] The vaccine should first be tested by using the prick method. If the past vaccine reaction was life-threatening, it is appropriate to use dilute vaccine for the skin prick test; in all other cases, full-strength vaccine should be used for the skin prick test. If the full-strength skin prick test result is negative, with appropriate positive and negative controls, an intradermal test with the vaccine diluted 1:100 should be performed,[74] 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 can

TABLE III. Latex in vaccine packaging*

Vaccine	Latex?
Anthrax (BioThrax)	YES–Vial
Comvax	YES–Vial
DTaP	
Daptacel	NO
Infanrix	YES–Syringe NO–Vial
Tripedia	YES–Vial
DT (generic)	YES–Vial
Hib	
Hiberix	YES–Syringe tip cap
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
Cervarix	YES–Syringe NO–Vial
Influenza	
Fluarix	YES–Syringe tip cap
Fluvirin	YES–Syringe tip cap
Fluzone	YES–Syringe tip cap
Fluzone High-Dose	YES–Syringe tip cap
Fluzone Intraderml	NO
FluLaval	NO
Afluria	NO
Agriflu	YES–Syringe tip cap
FluMist	NO
Japanese encephalitis (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
Menveo	NO
Pediarix	YES–Syringe NO–Vial
Pentacel	NO
Pneumococcal	
Pneumovax 23	NO
Prevnar 13	NO
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 YES–Syringe
Generic	YES–Vial YES–Syringe
Tdap	
Adacel	YES–Syringe tip cap NO–Vial
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
Zoster (Shingles) (Zostavax)	NO

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, diphtheria toxoids, and acellular pertussis (adult/adolescent formulation).

*"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. In these cases providers should be prepared to treat patients who are having an allergic reaction. For latex allergies other than anaphylactic allergies (eg, a history of contact allergy to latex gloves), vaccines supplied in vials or syringes that contain dry natural rubber or rubber latex might be administered" (Advisory Committee on Immunization Practices General Recommendations on Immunization, 2011). The table is accurate, to the best of our knowledge, as of May 2011. If in doubt, check the package insert for the vaccine in question.

occur. Likewise, a false-negative response might also be seen. Some patients known to have IgE antibodies to various vaccines by means of *in vitro* testing or skin testing have nonetheless received the vaccines in the usual manner without reaction.[52,75-78] Although these findings complicate the interpretation of vaccine skin test results, if the test result is positive in a patient with a history of an allergic reaction to the vaccine, the patient must be treated with caution. The suggested approach to patients with apparent immediate-type allergic reactions to vaccines and negative or positive vaccine skin test results are described in Summary Statements 8 and 9, respectively. Intradermal skin tests with some vaccines, such as tetanus toxoid, can also induce delayed-type hypersensitivity responses.[79]

If the suspect vaccine contains egg (influenza and yellow fever), gelatin (Table II), latex (Table III), or *Saccharomyces cerevisiae* (baker's or brewer's) yeast (hepatitis B vaccine and quadrivalent human papillomavirus vaccine), the patient should also be skin tested for these allergens.[36,37] Egg 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 skin prick test solution, recognizing that this is not a standardized, validated, US

TABLE IV. Excipients included in US vaccines by vaccine*

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†
DTaP/Hib (TriHIBit)	Aluminum potassium sulfate, ammonium sulfate, bovine extract, formaldehyde or formalin, gelatin, polysorbate 80, sucrose, thimerosal†
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, BSA, 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 (multi-dose) or thimerosal† (single-dose)
DT (Massachusetts)	Aluminum hydroxide, formaldehyde or formalin
Hib (ACTHib)	Ammonium sulfate, formaldehyde or formalin, sucrose
Hib (Hiberix)	Formaldehyde or formalin, lactose
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,† 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,† vitamins, yeast protein
Human papillomavirus (HPV) (Cerverix)	3-O-desacyl-4′-monophosphoryl lipid A (MPL), aluminum hydroxide, amino acids, insect cell protein, mineral salts, sodium dihydrogen phosphate dihydrate, vitamins
Human papillomavirus (HPV) (Gardasil)	Amino Acids, amorphous aluminum hydroxyphosphate sulfate, carbohydrates, L-histidine, mineral salts, polysorbate 80, sodium borate, vitamins, yeast protein
Influenza (Afluria)	β-propiolactone, calcium chloride, neomycin, ovalbumin, polymyxin B, potassium chloride, potassium phosphate, sodium phosphate, sodium taurodeoxycholate
Influenza (Agriflu)	Cetyltrimethylammonium bromide (CTAB), egg protein, formaldehyde or formalin, kanamycin, neomycin sulfate, polysorbate 80
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†
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 nonylphenol (Triton N-101, Octoxynol 9), thimerosal (multidose containers), thimerosal† (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 (Ixiaro)	Aluminum hydroxide, BSA, formaldehyde, protamine sulfate, sodium metabisulphite
Meningococcal (Menactra)	Formaldehyde or formalin, phosphate buffers
Meningococcal (Menomune)	Lactose, thimerosal (10-dose vials only)
Meningococcal (Menveo)	Amino acid, formaldehyde or formalin, yeast
MMR (MMR-II)	Amino acid, bovine albumin or serum, chick embryo fibroblasts, human serum albumin, gelatin, glutamate, neomycin, phosphate buffers, sorbitol, sucrose, vitamins
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

(Continued)

TABLE IV. *(Continued)*

Vaccine	Contains
Pneumococcal (Pneumovax)	Bovine protein, phenol
Pneumococcal (Prevnar)	Aluminum phosphate, amino acid, soy peptone, yeast extract
Pneumococcal (Prevnar 13)	Aluminum phosphate, amino acid, polysorbate 80, soy peptone, succinate buffer, 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, FBS, 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 bicarbonate, 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†
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

(Continued)

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).

*Vaccine excipient and media summary, part 2. Includes vaccine ingredients (eg, adjuvants and preservatives), as well as 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 individual products' package inserts and Grabenstein JD. ImmunoFacts: vaccines & immunologic drugs. St Louis (MO): Wolters Kluwer Health, Inc; 2009. All reasonable efforts have been made to ensure the accuracy of this information, but manufacturers can change product contents before that information is reflected here.

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

Food and Drug Administration–approved method. *In vitro* assays for specific IgE antibody are also commercially available for egg, gelatin, latex, and yeast. There are no commercially available immediate-type skin test reagents or serum specific IgE tests for neomycin or thimerosal.

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. Nonetheless, in a patient with a history suggestive of an anaphylactic reaction, it is prudent to administer the vaccine under observation, with epinephrine and other treatments available. (B)

Intradermal skin tests are recommended for the evaluation of suspected anaphylaxis to a vaccine. Formal performance parameters (eg, positive and negative predictive values) for intradermal skin testing to confirm or exclude allergy to a vaccine or vaccine component have not been established.[79] 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 there are reports of patients receiving the vaccines uneventfully despite positive skin test results.[78] Dilutions of vaccines of 1:100 have been demonstrated to be nonirritating.[74] 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 given the vaccine in the usual manner but observed for at least 30 minutes afterward.[36,37]

Summary Statement 9: In a patient with a history and skin test results consistent with an IgE-mediated reaction to a vaccine who requires 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 might still be administered, if necessary, in graded doses (Table V).[50,80-82] If the full vaccine dose is normally a volume of 0.5 mL, the patient is first given 0.05 mL of a 1:10 dilution and then given full-strength vaccine (at 15-minute intervals) at doses of 0.05, 0.1, 0.15, and finally 0.2 mL, for a cumulative dose of 0.5 mL.

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

TABLE V. Administration of vaccines in graded doses

For a vaccine in which the full normal dose volume is 0.5 mL, give the following doses at 15-minute intervals as tolerated*:
0.05 mL 1:10 dilution
0.05 mL full-strength
0.1 mL full-strength
0.15 mL full-strength
0.2 mL full-strength

*Must be done under direct medical supervision prepared with emergency medications and equipment to promptly treat an anaphylactic reaction should it occur. Observe for at least 30 minutes afterward.

immediately available to promptly treat an anaphylactic reaction should it occur.[79] Such challenges can be performed in an office or hospital setting with or without an intravenous line in place, depending on the severity of the original reaction to the vaccine and the patient's medical condition.[79]

As above, for patients with a history of a suspected allergic reaction to the influenza vaccine itself, evaluation as per Fig 1 is appropriate. This differs from the approach to patients with a history of reactions to the ingestion of egg but no history of a reaction to influenza vaccination. **Recommendations regarding the administration of influenza vaccine to recipients with egg allergy are specifically addressed in an addendum at the end of this practice parameter**.

Summary Statement 10: Some nonanaphylactic reactions to vaccines might also require evaluation, but only a few are absolute contraindications to future doses. (B)

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

The "swine flu" influenza vaccine administered in 1976 was associated with an increased risk for Guillain-Barré syndrome (GBS), which was estimated at 1 additional case per 100,000 vaccinations (over the annual background rate of 1 to 2 cases per 100,000 adults).[83] 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.[83,84] A low level of GBS cases continues to be reported in temporal association with previous influenza infection[85,86] and with influenza and other vaccines.[87,88] Specific attention was paid to the potential for GBS after the 2009 pandemic influenza A (H1N1) vaccine campaign, and no increased rate was found.[89,90] Persons with GBS within 6 weeks of influenza vaccination should avoid subsequent immunization with influenza vaccines.[83] However, patients 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.[83]

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.[32,50,91] 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.[92,93] For reasons that are not clear, when the MMR is given in a combination vaccine with varicella (ie, measles, mumps, rubella, and varicella vaccine), there is a 2-fold higher risk of febrile seizures than if the MMR and varicella vaccines are given as separate injections at the same visit (one additional febrile seizure per 2500 children vaccinated).[94] This increased risk exists only for the first dose of the vaccines, which is typically given between 12 and 15 months of age, and not for the second dose, which is typically given between 4 and 6 years of age. For this reason, the preferred strategy is to administer the MMR and varicella vaccines as separate injections at the same visit for the first dose and combined as measles, mumps, rubella, and varicella vaccine for the second dose.[94] Recipients of the MMR vaccine can also have thrombocytopenia, which is usually without any significant clinical consequence but can rarely cause hemorrhage.[26,91,95,96] The rate of thrombocytopenia is much higher with the measles disease itself.[91] Rubella vaccine can cause acute arthritis in approximately 15% of adult women who receive the vaccine.[35,97] This might represent a direct infection of the joints by the vaccine virus but has a questionable association with chronic arthritis.[35,97] Rubella vaccine can also cause transient arthralgia in children. 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 quite 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] The estimated additional risk of this event attributed to the vaccine is 0 to 10 per million doses of diphtheria and tetanus toxoids and whole-cell pertussis (DTP) vaccine.[91] This can have permanent neurologic sequelae and is an absolute contraindication to further pertussis vaccination (including acellular pertussis).[11] Pertussis vaccine can cause less severe apparent neurologic events, including febrile seizures,[92] inconsolable crying,[50] and hypotonic-hyporesponsive episodes.[98] 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.[11,91,99] 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 DTP to the DTaP.[34,50,99-103]

About 5% of immunizations with tetanus toxoid–containing vaccines cause large local swelling at the injection site.[104,105] This probably represents an Arthus reaction in patients with preexisting IgG anti-tetanus antibodies from prior immunizations who then receive a large injection of antigen in the vaccine. These reactions can cause discomfort but are not serious. Because of increasing rates of pertussis in adolescents and adults, new vaccines were recommended in 2006 for those 11 to 64 years of age to provide not only booster doses for tetanus and diphtheria (Td) but also pertussis (Tdap).[104,106] The recommended interval between doses of Td had been 10 years, with shorter intervals thought to be associated with increased rates of Arthus reactions. However, in a recent study the rate of Tdap injection-site reactions was the same in patients who had received Td less than 2 years previously or more than 2 years previously.[107] Another study found no higher rates of injection-site reactions whether a Tdap-containing vaccine was administered 1 month after a Td-containing vaccine or placebo.[108] Thus with the pertussis disease burden continuing to be substantial, it is now recommended that Tdap be given to all adolescents and adults (including those ≥65 years of age), regardless of the interval since the last Td.[109]

Tetanus toxoid also has some potential association with GBS and with a rare local neurologic event called brachial neuritis, which involves shoulder pain followed by weakness.[26] However, neither GBS nor brachial neuritis is a contraindication to the receipt of additional doses of tetanus-containing vaccines.[104]

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 are more generalized in another 3%.[110] The rash typically appears within 3 weeks of vaccination.[111] The disease caused by coincident natural exposure might be difficult to distinguish from vaccine-induced varicella, and most rashes are due to wild-type virus.[111] A zoster-type rash can rarely appear after a varicella vaccination and might contain either vaccine-strain or wild-type virus.[112,113] As with MMR vaccine described above, varicella vaccine can cause a late-onset fever and rarely febrile seizures, again without long-term sequelae. 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,[114] and humoral and cellular immune responses to the vaccine are similar in children with and without atopic dermatitis.[115]

A serious adverse effect of yellow fever vaccine is encephalitis.[116] 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 6 months; it should only be given to those younger than 9 months if their risk from the disease is very high.[117] The yellow fever vaccine has recently been associated with a very severe multisystem illness in adults with features that are strikingly similar to those of yellow fever disease itself.[117] This adverse reaction, now termed yellow fever vaccine–associated viscerotropic disease, has occurred exclusively in first-time vaccine recipients and has a 65% mortality rate.[117] Most yellow fever vaccine–associated viscerotropic disease has occurred in patients who are not known to be immunocompromised; however, a history of a thymus disorder and age 60 years or greater have been identified as risk factors, making these a contraindication and a precaution, respectively.[117] 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 in which the disease is endemic. An inactivated, and thus presumably safer, vaccine is being developed.[118]

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 theoretic risk of transmitting the live agent to the fetus, pregnant women should not receive live vaccines, such as MMR, varicella vaccine, or LAIV.[119] 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.[119] Hepatitis B vaccine and tetanus and diphtheria vaccines should also be administered to pregnant women if they would otherwise be indicated.[119]

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 VI) are generally contraindicated in patients with immune suppression, specifically those with severe humoral or cellular immune deficiency.[11,50,120] This includes patients with X-linked agammaglobulinemia, common variable immune deficiency, severe combined immune deficiency, severe HIV infection, leukemia, lymphoma, or 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, and readers are referred to other published guidelines for details.[11,50,120,121]

TABLE VI. Live versus killed vaccines

Live vaccines	Killed vaccines
Bacille Calmette-Guerin (BCG)	Diphtheria, tetanus, 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 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 the long-term consequences of particular vaccines or of vaccination in general. There have been claims that receiving childhood vaccinations increases the likelihood of atopic disease, autism, diabetes, or multiple sclerosis. The associations have all been extensively evaluated by using many appropriate research methods and epidemiologic studies, and no relationship between vaccinations and any of these outcomes has been demonstrated in these studies.[122-127] There has been particular concern about thimerosal, which was previously used as a preservative in vaccines. Although studies have not supported any adverse effect from thimerosal exposure in vaccines,[128-130] 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.[50]

ADDENDUM

Administering influenza vaccine to recipients with egg allergy

Influenza vaccines are grown on embryonated chicken eggs, leading to concern that residual egg protein (ovalbumin) could

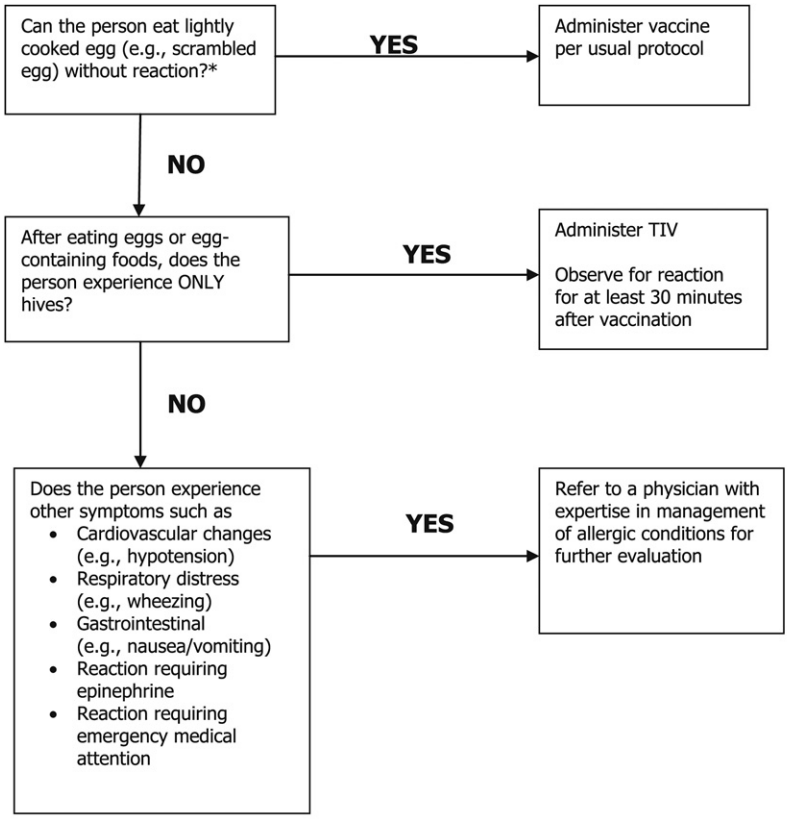


FIG 2. Recommendations regarding influenza vaccination for persons who report allergy to eggs. Advisory Committee on Immunization Practices (ACIP), 2011-2012 influenza season.

provoke an allergic reaction in a recipient with egg allergy. However, all studies to date have suggested that the risk of such reactions is very low.[52-58] This addendum to the practice parameter update reflects changes to recommendations for administration of TIV to patients with egg allergy based on several studies completed since the original focused practice parameter was published in January 2011[131] and is consistent with new guidelines from the US Centers for Disease Control and Prevention's (CDC) Advisory Committee on Immunization Practices[51] (Fig 2) and the Committee on Infectious Diseases (Red Book committee) of the American Academy of Pediatrics (AAP).[132] Immunization of such patients provides them the substantial protection that the vaccine provides against the morbidity and mortality associated with influenza disease.

The areas of residual uncertainty in the original parameter[131] stemmed from the fact that relatively few studies had investigated the safety of administering TIV to patients with a history of a severe reaction to the ingestion of egg and concern about the amount of residual ovalbumin in some vaccines. Studies published in the past year offer further data supporting the safety of influenza vaccine in even patients with severe egg allergy[56-58] and offer reassurance about the ovalbumin content of the vaccines.[62] This parameter offers evidence-based guidance on how to evaluate patients with egg allergy before influenza vaccination and how to administer the vaccine to such patients.

Summary statements

Summary Statement 14: Patients with egg allergy should receive influenza vaccinations (TIV) because the risks of vaccinating are outweighed by the risks of not vaccinating. (A)

There are now 7 published studies (6 from the past 2 years) reporting on vaccination of patients with egg allergy with TIV.[52-58] The details of these studies are summarized in Table VII. More than 1600 patients (mostly children) with egg allergy have been vaccinated without any serious reactions. Zero percent to 6.3% of vaccinations have involved reactions confined to the skin (eg, hives). Zero percent to 4.8% of vaccinations have involved mild respiratory or gastrointestinal symptoms. No reactions have involved symptoms of hypotension. None of these reactions required treatment with epinephrine. One study included an additional 3640 patients with reported but not proved egg allergy given influenza vaccine; 1.2% had skin reactions and 0.7% had respiratory reactions, including 2 who were given epinephrine, although the authors concluded that these were not anaphylactic reactions.[54] Of note, in those studies that included control subjects without egg allergy, similar rates of reactions between the 2 groups are reported, indicating that not all adverse reactions to influenza vaccine are related to egg allergy.[52,54,55,57]

Between 86,494 and 544,909 (average 294,128) persons are hospitalized each year in the United States because of influenza, including an average of 21,156 hospitalizations in children less than 5 years of age.[133] Three thousand three hundred forty-nine to

TABLE VII. Published studies involving TIV and H1N1 vaccine administration to patients with egg allergy

Study	Year	Method	No. of subjects	Mean age (range [y])	Patients with history of anaphylaxis to egg ingestion	Vaccine (maximum ovalbumin content, μg per 0.5 mL dose)	Protocol*	No. (%) of systemic reactions (skin only)	No. (%) of systemic reactions (respiratory, cardiovascular, gastrointestinal, or other)	No. (%) treated with epinephrine
James et al[52]	1998	Prospective, controlled	83 with egg allergy	3 (1-46)	27	TIV (0.6)	Skin prick testing (vaccinated even if positive, n = 4); divided dose	2 (2.4)	4 (4.8) 1 mild throat itch/ cough/wheeze, 1 delayed emesis/mild cough/wheeze, 1 delayed fussiness, 1 mild URI symptoms	0
			124 control subjects	37.5 (1-78.5)			Single dose (1 with positive skin test result)	1 (0.8)	1 (0.8) delayed emesis	0
Chung et al[53]	2010	Retrospective	56 with egg allergy	6.2 (<18)	0	TIV (NR)	Skin prick testing; vaccine withheld if positive, divided dose if negative	1 (1.8)	1 (1.8) wheeze	0
			115 with egg allergy	3.9 (<18)	0		No skin testing; divided dose	2 (1.7)	2 (1.7) wheeze	0
Gagnon et al[54]	2010	Prospective, controlled	830 with egg allergy	NR (<2->12)	72	H1N1 (0.0075)	No skin testing, single dose if no history of anaphylaxis, divided dose if history of anaphylaxis	13 (1.6)	4 (0.5) 1 mild abdominal pain, 1 hoarse voice, 1 sensation of throat closure, and 1 wheezing	0
			393 control subjects	NR (<2->12)				6 (1.5)	6 (1.5) 1 emesis, 1 sensation of throat closure, 1 sneezing, 3 signs/ symptoms in >2 systems	0
		Prospective	3640 self-reported egg allergy	NR	NR			42 (1.2)	24 (0.7) 17 throat tingling/ tightening, 7 cough	2 (0.05) 1 dyspnea, 1 wheezing
Greenhawt et al[55]	2010	Prospective, controlled	105 with egg allergy	5.5 (0.4-20.4)	25	H1N1 (0.025)	Skin prick and intradermal testing; single dose if negative; divided dose if positive (n = 39)	3 (2.9)	0	0
			19 control subjects	6.3 (0.2-20.1)			Single dose	1 (5.3)	0	0
Owens et al[56]	2011	Retrospective	64 with egg allergy	NR	NR	TIV and H1N1 (0.7)	No skin testing, divided dose	4 (6.3)	0	0
Howe et al[57]	2011	Retrospective	135 with egg allergy	<3	14	TIV (0.54)	Skin prick testing; single dose if negative; divided dose if positive (n = 6)	4 (3.0)	1 (0.7) diarrhea	
		Prospective, controlled	69 with egg allergy	NR	13			2 (2.9)	0	0

(Continued)

TABLE VII. *(Continued)*

Study	Year	Method	No. of subjects	Mean age (range [y])	Patients with history of anaphylaxis to egg ingestion	Vaccine (maximum ovalbumin content, μg per 0.5 mL dose)	Protocol*	No. (%) of systemic reactions (skin only)	No. (%) of systemic reactions (respiratory, cardiovascular, gastrointestinal, or other)	No. (%) treated with epinephrine
			14 control subjects	NR				2 (14)	0	0
Webb et al[58]	2011	Retrospective	152 with egg allergy	3 (0.6-30)	34	TIV and H1N1 (0.7)	Skin prick testing; single dose if negative; divided dose if positive (n = 1)	0	0	0

NR, Not reported; *URI*, upper respiratory tract infection.
*Divide dose: 10% of dose administered, observe for 30 minutes, and, if no reaction, 90% of dose administered.

TABLE VIII. Ovalbumin content of injectable TIVs approved for the 2011-2012 season

Brand name	Manufacturer	Approved ages	Ovalbumin content (μg per 0.5 mL dose*)†
Afluria	CSL Biotherapies (Merck)	≥9 y	≤1
Fluarix	GlaxoSmithKline	≥3 y	≤0.05
FluLaval	ID Biomedical Corporation of Quebec (GlaxoSmithKline)	≥18 y	≤1
Fluvirin	Novartis	≥4 y	≤1
Fluzone	Sanofi Pasteur	≥6 mo	~0.1
Fluzone High-Dose	Sanofi Pasteur	≥65 y	~0.1

*Dose: 0.25 mL, 6-35 months; 0.5 mL, ≥3 years.
†Information in package inserts except Fluzone and Fluzone High-Dose from Sanofi Pasteur by telephone (1-800-822-2463) or e-mail (MIS.Emails@sanofipasteur.com).

48,614 (average 23,607) deaths occur each year in the United States as a result of influenza, including 57 to 197 (average, 124) children.[134] Many of these events could have been prevented by vaccination.[135] Higher influenza vaccine coverage rates, including among those who are or who think they are allergic to eggs, can reduce these preventable hospitalizations and deaths.

Summary Statement 15: Persons with a history of suspected egg allergy should be evaluated by an allergist to determine the status of their egg allergy, but this should not delay their influenza vaccination. (A)

Persons with a history of suspected egg allergy should be evaluated by an allergist.[136] The evaluation should include a detailed history of the nature and timing of prior suspected reactions to egg. If the clinical history is consistent with egg allergy, then skin prick testing to egg or specific *in vitro* IgE antibody testing for egg is indicated to confirm sensitization. With a convincing clinical history and evidence of specific IgE, the diagnosis can be confirmed, but in certain circumstances an oral food challenge to egg might be necessary or desired.[136] Influenza vaccine should not be withheld from those undergoing egg allergy evaluation or from those with confirmed egg allergy. Suspected egg allergy deserves evaluation, regardless of the influenza vaccination status.

Summary Statement 16: A growing number of studies suggest that influenza vaccines can be safely administered, even to patients with a history of anaphylaxis to egg ingestion. (B)

Most studies on influenza vaccine in patients with egg allergy have specifically included patients with histories of anaphylaxis to egg ingestion.[52,54,55,57,58] The number of such patients now collectively reported is 185, about 13% of the total population of patients with proved egg allergy studied. These patients with severe egg allergy have tolerated the vaccine without serious reactions, as is the case with patients with less severe egg allergy.

Summary Statement 17: Skin testing (prick, intradermal, or both) with the influenza vaccine itself in patients with egg allergy (but without a history of reacting to the vaccine itself) does not reliably identify patients who are at increased risk of reacting to the vaccine and is not recommended. (A)

In studies in which vaccine skin testing was done because of a history of egg allergy, vaccinated patients with skin test results had no reactions or no greater rate of reactions than subjects with negative skin test results.[52,53,55,57,58] In one study the vaccine was withheld from patients with positive prick or intradermal vaccine skin test results.[53] However, skin testing was later removed from the protocol; all patients were vaccinated, and the rate (low) of reactions (minor) was the same as when skin testing had been included in the protocol. The authors concluded that vaccine skin testing was unnecessary.[53]

Skin testing is of utility in evaluation of a patient with a history of an allergic reaction to the influenza vaccine itself and is addressed in another section of this parameter and below.

Summary Statement 18: Influenza vaccine can be administered as a single dose to patients with egg allergy. (B)

In those studies of influenza vaccine in patients with egg allergy that have divided the dose (first administering 10% and, if no reaction in 30 minutes, the administering the remaining 90%), the vast majority of patients ultimately tolerate the entire dose,[52-58] and studies administering the vaccine as a single dose also report no serious reactions.[54,55,57,58] The CDC and AAP have concluded that persons who have experienced only hives after exposure to egg should receive influenza vaccine and that in these patients vaccine skin testing and dividing the dose are no longer necessary or recommended.[51,132]

In those patients with a history of more severe reactions to egg ingestion, the CDC and AAP recommend that before receipt of vaccine, such persons should be referred to an allergy specialist.[51,132] Studies support the single-dose approach, even in these patients with severe egg allergy. Collectively from among these studies, 185 patients with a history of anaphylaxis to egg ingestion

have been vaccinated with TIV, with 119 receiving a divided dose and 66 receiving a single dose, all without serious reactions.[52,54,55,57,58]

Summary Statement 19: Patients with egg allergy should receive influenza vaccines in a setting in which clinicians experienced in recognizing and treating anaphylaxis and equipment to manage anaphylaxis are immediately available and should be observed for 30 minutes after vaccination. (A)

Given the possibility of allergic reactions to any vaccine, health care providers who administer vaccinations should have proper resuscitative equipment available in the office to manage anaphylaxis.[11] Although a large number of patients with egg allergy have been given the influenza vaccine in the published studies cited above, this cannot exclude a rare reaction. Thus although annual TIV vaccination is offered at many pharmacies and other nonmedical settings, patients with egg allergy should receive the vaccine in a medical setting with the personnel and equipment described above. Furthermore, patients with egg allergy receiving influenza vaccine should be observed for 30 minutes after vaccination. Most vaccine studies have used an observation period of 30 minutes,[53,55-58] and this interval is consistent with the observation period recommended after receiving subcutaneous allergen immunotherapy.[137]

Summary Statement 20: Patients with egg allergy with a history of only hives after egg ingestion can receive influenza vaccine in a primary care provider's office provided the appropriate personnel and equipment are available as per Summary Statement 19, whereas those with a history of more severe reactions to egg ingestion should receive their vaccine in an allergist's office. (C)

Studies done to date indicate that adverse reactions to influenza vaccine in recipients with egg allergy are rare and mild.[52-58] Nonetheless, the number of patients studied to date (approximately 5000) cannot exclude the possibility of a rare serious reaction. These studies have included relatively small numbers of patients with histories of severe egg allergy (approximately 200) who would presumably be at greater risk. Thus although patients with a history of mild reactions to egg ingestion (hives only) can receive their vaccine in a primary care provider's office, those with a history of more severe reactions (cardiovascular, respiratory, or gastrointestinal symptoms) should receive the influenza vaccine in an allergist's office. In both cases, personnel to recognize and equipment to treat anaphylaxis need to be immediately available, but the allergist's office affords additional expertise in this area should it be required.[51,132]

Summary Statement 21: All influenza vaccines available in the United States contain low amounts of ovalbumin. (A)

In many of the studies on administration of influenza vaccine to recipients with egg allergy, the egg protein (ovalbumin) content of the vaccine was reported.[52,54-58] Vaccines used have contained as much as a 0.7 μg per 0.5 mL dose without serious reactions, implying that at least that much is generally well tolerated.[56] Data pertaining to "safe" ovalbumin levels have been limited to analyzing lot content after a study has been completed rather than prospectively attempting to assess a dose-response relationship. Thus it is not known whether there is an amount of ovalbumin per dose that would be associated with a higher rate of reactions or more severe reactions.

Three of the 4 manufacturers of injectable influenza vaccines (CSL, King of Prussia, Pa; GlaxoSmithKline, Research Triangle Park, NC; and Novartis, Emeryville, Calif) report the maximum amount of ovalbumin per 0.5 mL dose in their package inserts. The other manufacturer, Sanofi Pasteur (Lyon, France), will provide the information on request by telephone (1-800-822-2463) or e-mail (MIS.Emails@sanofipasteur.com). All of the claimed amounts are less than 1 μg per 0.5 mL dose (Table VIII).

When the actual amount of ovalbumin in the vaccines has been measured in independent laboratories, the levels are usually much lower than the claimed amounts. Three groups have separately analyzed the ovalbumin content from the United States–approved influenza vaccines for both H1N1 (2009-2010 season) and TIV (both 2009-2010 and 2010-2011 seasons).[60-62] Ovalbumin content ranged from 0.008 to 0.71 μg per 0.5 mL dose.

Summary Statement 22: Although the intranasally administered LAIV contains a low amount of ovalbumin, all published studies to date have evaluated the injectable TIV, and thus TIV rather than LAIV should be used for recipients with egg allergy. (C)

The amount of ovalbumin in the intranasal LAIV is not stated in the package insert, but the manufacturer, MedImmune (Gaithersburg, Md), indicates by personal communication that the vaccine contains less than 0.24 μg per 0.2 mL dose. When the actual amount of ovalbumin in the vaccine has been measured in independent laboratories, it has been found to be very low, between 0.00013 to 0.0017 μg per 0.2 mL dose. This very low amount of ovalbumin is likely to be safe in patients with egg allergy; however, there are no published studies to date on exposure through the intranasal route. Given the large amount of data on the safety of injectable influenza vaccine in patients with egg allergy, TIV is recommended until ongoing studies on LAIV are published.[51,132]

Summary Statement 23: For patients with a history of allergic reaction to the influenza vaccine itself, additional evaluation is appropriate, including skin testing with the vaccine and vaccine ingredients. For patients with positive skin test results, the vaccine can be administered in multiple divided doses or can be withheld. (B)

The topic of this addendum is administration of influenza vaccine to recipients with egg allergy. This clinical situation is different than management of a patient with a history of an allergic reaction to the receipt of a prior dose of influenza vaccine itself. If a patient has had an apparent allergic reaction to any vaccine, they should be evaluated by an allergist to determine whether the reaction was IgE mediated and, if so, to determine the culprit allergen. This evaluation involves skin testing with the vaccine and with vaccine constituents. If such test results are positive, consideration can still be given to administering subsequent doses of the vaccine, if required, in multiple graded doses. This is specifically covered in a previous section of this parameter.

There has been a great deal of additional information published over the past year demonstrating the safety of influenza vaccination in patients with egg allergy. Health care providers should no longer withhold the vaccine from any patient with egg allergy. In an update to recommendations made in the last year, it is now considered safe for patients even with a history of a severe egg allergy to receive influenza vaccination. The vaccine can be administered as a single dose without any additional precautions beyond proper equipment and preparedness to observe and treat

potential postvaccination anaphylaxis. Patients with mild egg allergy (hives only) have the option to receive the vaccine at their primary care provider's office.

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