

Evaluating children with suspected allergic reactions to vaccines for infectious diseases

Fabrizio Franceschini, M.D.,¹ Paolo Bottau, M.D.,² Silvia Caimmi, M.D.,³ Fabio Cardinale, M.D.,⁴ Giuseppe Crisafulli, Ph.D.,⁵ Lucia Liotti, M.D.,⁶ Guido Pellegrini, M.D.,⁷ Diego Peroni, M.D.,⁸ Francesca Saretta, Ph.D.,⁹ Carla Mastroilli, M.D.,¹⁰ and Carlo Caffarelli, M.D.¹⁰

ABSTRACT

Background: Vaccines often contain potentially allergenic material in addition to pathogen-specific immunogens that may induce allergic reactions. Parents and physicians often suspect that adverse reactions to vaccines are allergic in etiology. The concern that some of the substances contained in vaccines may trigger an anaphylactic reaction may lead to a low vaccination adherence with emergence of infectious disease epidemics.

Objective: To provide practical suggestions for managing children suspected to have an allergic reaction to a vaccine.

Methods: Information was obtained from a search of guidelines and relevant studies on allergic reactions to vaccines for infectious diseases.

Results: True allergic reactions elicited by a vaccine are rare. Skin testing to the vaccine and to its components may identify the triggering agent. Graded dosing desensitization is helpful in children sensitized to the offending vaccine.

Conclusion: All children with a suspected allergic reaction to a vaccine should be carefully evaluated by routine allergy tests. When it is necessary, further immunization should be given under strict medical surveillance, which ensures that every child can safely complete the vaccination schedule.

(Allergy Asthma Proc 39:177–183, 2018; doi: 10.2500/aap.2018.39.4128)

Vaccinations are recognized as one of the most important public health interventions and the reason for the disappearance, or dramatic decrease, of many severe infectious diseases. It, therefore, is imperative, whenever an allergic reaction to a vaccine is believed to have occurred, that the adverse reaction is evaluated so that further immunization can be safely given. Possible allergic reactions to vaccines are events that can cause anxiety and concern in parents and sometimes can even lead to an interruption of the vaccine schedule. Only a small percentage of these reactions is related to vaccine hypersensitivity and, even in cases of true allergy, most children can continue the vaccination schedule, providing that the subsequent vaccine administration is performed by expert medical personnel.

A literature search of peer-reviewed journal articles on hypersensitivity reactions to vaccines was undertaken by using Medline. Identified relevant articles were discussed and a we reached a consensus. A summary of the principal guidelines^{1–6} and relevant studies that provide the evidence on allergic reactions to vaccines for infectious diseases was included within this report. Suggestions for a practical approach for the assessment and management of children with suspected allergic reaction to a vaccine were also provided.

The suspicion of vaccine-associated allergic reaction is supported by knowledge of previous studies^{1–6} that show increased risk or a clear association of a specific allergic reaction in vaccinated groups. However, the lack of such studies does not mean that the vaccine cannot induce an allergic reaction. The diagnosis is based on clinical manifestations, an onset of an allergic reaction usually within minutes to hours after vaccine administration, and laboratory test results that demonstrate the relationship.¹

It is compulsory that any physician who administers a vaccine that causes an allergic reaction files a written report of the observed reaction with a detailed description of the type of vaccine, composition, dose, and interval time between vaccine administration and symptoms. Although a definite diagnosis may theoretically be proved by vaccine challenge, this can be ethically unacceptable in practice. This decision should be based on clinical judgment that considers the individual patient

From the ¹UOC Pediatria, Azienda Ospedaliero—Universitaria “Ospedali Riuniti,” Ancona, Italy, ²UOC Pediatria, Ospedale di Imola, Italy, ³Clinica Pediatrica—Fondazione IRCCS—Policlinico San Matteo, Pavia, Italy, ⁴UOC di Pediatria, Azienda Ospedaliera—Universitaria “Consortiale-Policlinico,” Ospedale Pediatrico Giovanni XXIII, Bari, Italy, ⁵UO Allergologia, Dipartimento di Pediatria, Università di Messina, Messina, Italy, ⁶UOC di Pediatria, Ospedale di Senigallia, Italy, ⁷UOC di Pediatria, Ospedale Città di Sesto San Giovanni, ASST Nord Milano, Sesto San Giovanni, Italy, ⁸Clinica Pediatrica, Università di Pisa, Pisa, Italy, ⁹UOC di Pediatria, Ospedale di Palmanova, AAS2 Bassa Friulana-Isonza, Palmanova, Italy, and ¹⁰Clinica Pediatrica, Dipartimento di Medicina e Chirurgia, Università di Parma, Parma, Italy

No external funding sources reported

The authors have no conflicts of interest to declare pertaining to this article

Address correspondence to Carlo Caffarelli, M.D., Clinica Pediatrica, Dipartimento di Medicina e Chirurgia, Università di Parma, Via Gramsci 14, 43123 Parma, Italy

E-mail address: carlo.caffarelli@unipr.it

Copyright © 2018, OceanSide Publications, Inc., U.S.A.

Table 1 Postvaccination anaphylaxis rate in children

Study	No. Doses	Study Period	Country	Anaphylaxis Incidence (per million doses)
McNeil <i>et al.</i> , ¹⁰ 2016	12,403,201	2009–2011	U.S.	1.45
Oberle <i>et al.</i> , ¹¹ 2016	19,243,519	2008–2010	Germany	0.11
Cheng <i>et al.</i> , ¹² 2015	3,203,951	2007–2013	Australia	8.42
Mahajan <i>et al.</i> , ¹³ 2015	3,937,876	2013	Australia	0.25
Galindo <i>et al.</i> , ¹⁴ 2012	45,237,532	1999–2008	Cuba	0.04
Lawrence <i>et al.</i> , ¹⁵ 2008	3,702,124	2007	Australia	0.54
Bohlke <i>et al.</i> , ¹⁶ 2003	7,644,049	1991–1997	U.S.	0.65

and the disease in question. The severity of reaction, the results of laboratory tests, and the importance of the specific immunization should be assessed. For example, it may be reasonable for tetanus or measles but unreasonable for influenza or rabies.

CLINICAL MANIFESTATIONS

Symptoms consistent with an allergic reaction after vaccine administration can be immediate or delayed in onset.

Immediate Allergic Reactions

Immediate allergic reactions to vaccines are rare, with a frequency of 1 per 50,000–1,000,000 doses.^{7,8} These reactions can take many forms and require the exclusion of several differential diagnoses. Immediate-type reactions usually occur within a few hours after vaccination and are mostly mediated by immunoglobulin E (IgE). They may occasionally occur without any history of allergy. No fatal postvaccine reaction has been definitely proved, but the possibility of severe allergic reactions underlines the importance of prompt assistance in any setting.⁹

Anaphylactic Reactions. Postvaccination anaphylaxis is rare, and the incidence varies greatly among studies (Table 1).^{10–16} The highest rate of anaphylactic reactions has been reported with rabies vaccine; measles, mumps, rubella, varicella vaccine; measles, mumps, rubella (MMR) vaccine; varicella vaccine; and human papilloma virus (HPV) vaccine.^{10,16,17} Anaphylactic reactions typically develop within a few minutes up to 1 hour after vaccination.¹⁰ Anaphylaxis may recur after 5–24 hours of symptom resolution (biphasic reactions).¹⁰ Anaphylaxis is defined as a systemic and severe allergic reaction, potentially fatal, whose diagnosis relies on clinical criteria. Criteria developed by the National Institutes of Allergy and Infectious Diseases and Food Allergy and Anaphylaxis Network¹⁸ could not be suitable for vaccine-related anaphylaxis because the diagnostic certainty is unclear. Furthermore, a reaction is called “anaphylactic” when it is elicited by a “known or probable allergen” that,

in most cases of a reaction to vaccine, could not be defined at the time of the reaction. Therefore, more accurate criteria for case definitions of anaphylaxis to vaccines were proposed by the Brighton Collaboration Working Group.² They define anaphylaxis as the involvement of at least two organs and provide a combination of major and minor criteria for classifying increasing levels of diagnostic certainty.² In practice, it is difficult to apply the Brighton criteria because most vaccinators do not adequately document all symptoms of the reaction or they use terms different than those required.³

Other Immediate Allergic Reactions. Other immediate IgE-mediated reactions can occur up to 4 hours after vaccination. Urticaria is the most frequent manifestation and occurs four times more frequently than anaphylaxis after influenza vaccine.¹⁹ The rate of postvaccination urticaria has been found to vary from 0.3% for rabies vaccine²⁰ to 3.9 per 10,000 doses for diphtheria, tetanus, pertussis vaccine.²¹ Generalized urticaria with severe itching occurs in 90% of reactions, usually within 30 minutes and subsides after a few hours. Other skin reactions include erythema, isolated pruritus, angioedema, especially involving the face and lips. Respiratory symptoms, such as rhinoconjunctivitis, sensation of throat closure, dyspnea, and wheezing, are less commonly reported. Vomiting and diarrhea after an influenza vaccine have been rarely reported.^{22,23} Cardiovascular (tachycardia, hypotension, shock) and neurologic (psychic and sensorial impairment, seizures, dizziness, incontinence, loss of consciousness) symptoms are not usually isolated. If immediate allergic reactions to vaccines appear without other symptoms, a diagnosis should be addressed toward other vaccine-associated adverse events with a more frequent onset, which are listed in Table 2.^{4,24–30}

Delayed Allergic Reactions

Local delayed allergic reactions are observed more commonly than a systemic reaction (13% versus 0.2%).^{31,32} An inflammatory response to aluminum is frequently associated with itching nodules, which

Table 2 Differential diagnosis of immediate allergic reactions to vaccines

Immediate local reaction
Breath-holding spells
Panic attacks
Vasovagal reactions
Hypotonic hyporesponsive episode
Oculorespiratory syndrome
Anaphylaxis triggered by other allergens
Bradykinin-mediated angioedema

could persist for months, or with granuloma at the injection site.³³ These reactions should be differentiated from other delayed hypersensitivity reactions that are characterized by pain, erythema, and swelling at injection sites. The onset of an allergic reaction usually occurs within 2–8 hours after vaccination, with a peak after 12–36 hours and resolution in a few days.³⁴ Delayed allergic reactions are caused by hyperimmunization related to high levels of antibodies (Arthus reaction), and they are caused by a localized immune-complex-mediated mechanism. A history of a high number of previous injections and elevated protective antibody titers are risk factors. The most frequently involved vaccines are diphtheria, tetanus, pertussis vaccine in childhood and pneumococcal polysaccharides vaccine in adulthood.

Generalized delayed allergic reactions, in most cases, are characterized by macular-papular exanthema; arthralgia, arthritis, hematologic, renal, and gastrointestinal involvement are rarely observed. Due to the unavailability of standardized allergy tests, the cause-effect relation is frequently unclear.⁴ However, these are mild reactions and do not contraindicate additional doses of vaccine. Severe delayed reactions to vaccine have rarely been described (e.g., Steven-Johnson syndrome, toxic epidermolysis).^{35,36} IgE antibodies to galactose- α -1,3-galactose (α -gal) trigger delayed urticaria, abdominal symptoms, or anaphylaxis to red meat that occurs 3 to 6 hours after ingestion; α -gal has been detected in bovine gelatin, and IgE to α -gal is associated with antigelatin IgE and gelatin anaphylaxis.³⁷ Contrasting data were provided on the safety of zoster vaccine that contains gelatin in patients with an allergy to α -gal.^{38,39}

IN VIVO AND IN VITRO TESTS

In patients with a history of adverse events consistent with an immediate allergic reaction to a vaccine, the first step is to verify whether there is a hypersensitivity to the vaccine and/or one of the vaccine components. Performing allergy testing is recommended before continuing with further vaccinations. This approach is also advisable when patients do not require

additional doses of a vaccine. A definitive diagnosis is necessary to establish preventive measures to avoid future adverse reactions to vaccine components. The allergy workup should be initiated with vaccine skin tests.^{40–43} Skin tests should be performed, if possible, with the same batch of the vaccine that caused the allergic reaction with positive (histamine) and negative (normal saline solution or solvent) controls. First, a skin-prick test should be performed with undiluted vaccine. In patients with anaphylaxis, a skin-prick test with the vaccine at a concentration of 1:10 is recommended.⁵ If skin-prick test results are negative, then intradermal tests should follow with a 1:100 dilution. An intradermal test with a 1:10 dilution has been reported to provoke irritant responses, especially for MMR, influenza, and varicella vaccines, and may lead to false-positive reactions^{5,40}; therefore, this test has no value.

Skin tests and measurement of serum-specific IgE antibodies to some of the potentially allergenic components of the suspected vaccines should also be performed (Table 3).^{40–43} Constituents include residuals of culture media used for growing organisms such as yeasts (hepatitis B, quadrivalent HPV vaccine, pneumococcal conjugate vaccine [PCV], typhoid fever vaccine), egg (MMR, influenza, yellow fever, rabies), cow's milk proteins (oral polio vaccine; diphtheria, tetanus, acellular pertussis vaccine; typhoid fever vaccine).^{44,45} Studies on large populations found that MMR vaccine^{46–50} and influenza vaccine^{51–53} are well tolerated in children with egg allergy. The amount of egg proteins in influenza vaccine is below the level that induces allergic reactions.^{54,55} Accordingly, the content in egg protein of MMR and influenza vaccine is considered to be safe for children with egg allergy.⁵⁶

Vaccines for diphtheria-tetanus-pertussis, MMR, influenza, varicella, yellow fever, zoster, rabies, typhoid fever contain gelatin as a stabilizer.⁶ Skin-prick tests to both bovine and porcine gelatin should be performed by using a solution that contains 1 teaspoon of sugared gelatin powder in 5 mL of saline solution.⁴ MMR and zoster vaccines contain both gelatin and bovine calf serum contaminated by α -gal.^{38,39} In patients who react to such vaccines, specific IgE to α -gal should be determined. Delayed allergic reactions have rarely been associated with antimicrobial drugs (neomycin) and adjuvants (aluminum hydroxide and phosphate). Contaminants, such as latex contained in vaccine rubber stoppers and in syringes, may rarely elicit immediate reactions.^{4,54} Thimerosal, a preservative contained in influenza vaccine, has been sporadically reported to cause maculo-papular rash.⁵⁷ There is no evidence that IgE tests to neomycin, aluminum hydroxide and phosphate, and thimerosal have diagnostic value.

Table 3 In vivo and in vitro tests for assessing allergic reactions to a vaccine

Vaccine	Skin Test Material	Specific IgE
DTaP, Td, Tdap	DTaP, Td, Tdap, tetanus toxoid, gelatin, milk proteins	Gelatin, milk proteins
Hepatitis B	Hepatitis B, yeast	Yeast
HPV	HPV, yeast (one type)	Yeast (one type)
Influenza	Influenza, egg, gelatin#	Egg, gelatin#
JEV	JEV, protamine	Protamine
MMR	MMR, measles, mumps, rubella, egg, gelatin	Egg, gelatin, α -gal
OPV	OPV, milk	Milk
PCV13	PCV13, DTaP, yeast	Yeast
Rabies	Yellow fever, egg (one type), gelatin	Egg (one type), gelatin
TBE	TBE, protamine	Protamine
Typhoid fever (oral)	Typhoid fever, gelatin, yeast, milk	Gelatin, yeast, milk gelatin, α -gal
Varicella/zoster	Varicella/zoster, gelatin	Egg, gelatin
Yellow fever	Yellow fever, egg, gelatin	
Hepatitis A, HiB, MCV, IPV, PPSV23, rotavirus	Vaccine given before reaction	

IgE = Immunoglobulin E; DTaP = pediatric diphtheria, tetanus, acellular pertussis vaccine; Td = tetanus, diphtheria vaccine (older children and adults); Tdap = tetanus, diphtheria, acellular pertussis vaccine (older children and adults); HPV = human papilloma vaccine; JEV = Japanese encephalitis vaccine; MMR = measles, mumps, rubella vaccine; α -gal = galactose- α -1,3-galactose; OPV = oral polio vaccine; PCV13 = pneumococcal conjugate vaccine; TBE = tick-borne encephalitis vaccine; HiB = haemophilus influenzae type B vaccine; MCV = meningococcal conjugate vaccine; IPV = inactivated polio vaccine; PPSV23 = pneumococcal polysaccharides vaccine.

#Gelatin is present only in the live attenuated influenza vaccines.

In some vaccines, capsule polysaccharides are conjugated to carrier proteins that may trigger an allergic reaction to increase immune response. PCV13 is conjugated to a nontoxic diphtheria mutant toxin (CRM 197). *Haemophilus influenzae* type b vaccine with tetanus toxoids and MCV with tetanus toxoid or CRM 197⁵⁸. The carrier protein CRM 197 in PCV13 has been found to trigger anaphylaxis in an infant.⁵⁸ In some cases, allergic reactions are directly correlated with vaccine antigens. Heptavalent PCV can induce an IgE-mediated sensitization against pneumococcal polysaccharides and may cause anaphylaxis after a PCV23 injection. In these cases, a prick-by-prick test with vaccine (nondiluted), followed by an intradermal test 1/100 can provide good diagnostic reliability.⁵⁹ In patients with a suspicion of a delayed allergic reaction to a vaccine, no allergy workup is usually necessary. When a vaccine induces a local delayed reaction, patch testing may be considered.

MANAGEMENT OF SUBSEQUENT VACCINATIONS

Because immediate reactions to a vaccine are unlikely to be IgE mediated when *in vivo* and *in vitro* allergy test results are negative, the clinical history must be considered. If anaphylaxis occurred, then a

two-step vaccination is suggested by using a first dose with 10% of the total dose and, after 60 minutes, a second dose with the remaining vaccine,⁶⁰ followed by a 60-minute observation period. Alternatively, the whole vaccine dose can be given, followed by a 60-minute observation period.⁴¹ If allergy test results are positive, then the child must be considered as allergic to that specific vaccine and some recommendations are required (Fig. 1).

If the child had a positive allergy test result to a vaccine component and if a similar vaccine without that specific allergenic component is available, then that vaccine should be administered as usual in an outpatient setting by following general recommendations. If no vaccine that lacks the specific allergenic component is available or if the child had a positive allergy test result to the vaccine but not to its components, then levels of IgG antibodies to the immunizing agent should be measured to verify if immunity has already been achieved.^{4,61} If this is the case, then an additional dose is not required. However, it is mandatory to periodically measure levels of IgG antibody titers to determine that protective levels are maintained over time.

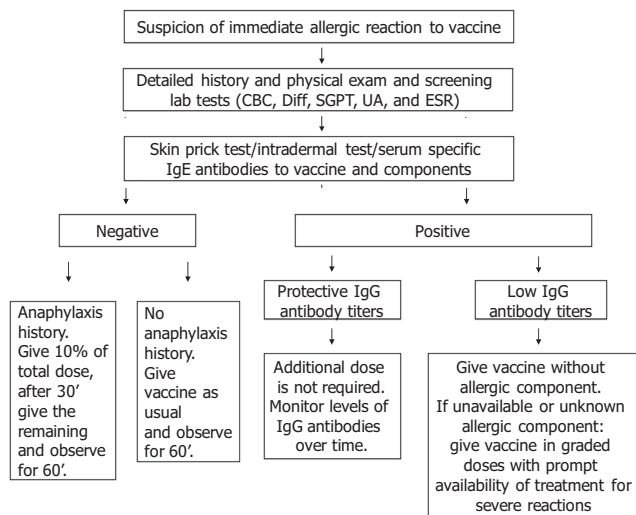


Figure 1. An algorithm for the management of a suspected immediate reaction to a vaccine. CBC = Complete blood test; Diff = blood differential test or white blood cell count; SGPT = serum glutamic-pyruvic transaminase; UA = urine analysis; ESR = erythrocyte sedimentation rate.

If there is no available vaccine that lacks the component to which the child is allergic or if the child had a positive allergy test result to the vaccine but not to its components and IgG antibody titers are not protective, and clinical judgment based on the individual patient and the disease in question recommend vaccination, vaccination should be performed with a graded-dose protocol.⁴ This procedure consists in increasing doses of vaccine every 15–30 minutes or more if the previous reaction was observed in a longer interval.^{8,62} There are several protocols that differ in the initial dilution. The more diluted, the more numerous are the doses needed to complete the vaccination. In general, every dose is 2–10-fold greater than the previous one.^{63–67} Kelso *et al.*⁴ indicated administering graded doses of vaccine with a 0.5 dose every 15 minutes as follows: 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, and 0.2 mL of full strength. When the vaccine dose is 1 mL, the 0.5 mL that remains could be given in one shot after 15 minutes. The graded-dose protocol should be performed in a monitored setting under close supervision of experienced personnel and with prompt availability of materials and support for treating severe reactions. However, only minor local reactions have been reported.⁶⁷ With a down-scaling or a widening of the interval, it is usually possible to complete the procedure despite these reactions and avoid more severe reactions.⁷ All local reactions and nonsevere generalized delayed allergic reactions are not a contraindication to further vaccinations.

ALLERGIC REACTIONS TO COMBINATION OR MULTIPLE VACCINES

The approach is more intricate and time consuming when an allergic reaction occurs after administration of multiple vaccines or a multivalent vaccine that is common in a single pediatric vaccination visit. Patients should be skin tested to all suspected vaccines because each vaccine, or more than one, may be a potential culprit. This requires that skin testing should be performed not only with the combination vaccines but also separately with each individual vaccine contained in a multivalent vaccine, if commercially available. Vaccine should be skin tested, as described above. After skin testing, it is prudent to separately give the next doses of potentially implicated vaccines to reduce the risk and to document the cause of the reaction if another reaction occurs. Therefore, children with negative skin test results to the vaccines should receive each vaccine or combined vaccine on different days (Fig. 1).

If the skin testing result to a vaccine is positive, and, after assessing the risk and benefits, it is necessary to give the vaccine (Fig. 1), each individual vaccine may be administered by using a graded-dose protocol in a single visit. Separating vaccines causes concern because children may be at risk for acquiring the preventable disease for a period of time. So, it may be reasonable to start with a vaccine that prevents diseases for which the risk of exposure is elevated in the particular region. However, when taking into account the likelihood of reactogenicity, it could be important to start with pertussis and hepatitis B vaccines and continue from there. Another issue is that an increased number of vaccination visits may severely elevate costs (loss of work days, transport) for the family and the likelihood of a lack of adherence to the vaccination schedule. Therefore, it is suggested that vaccines should be given during the shortest possible period of time.

CONCLUSION

Allergic reactions to vaccines rarely occur but potentially are severe. A prompt and correct diagnosis is essential to assure a safe vaccine administration. All children with a suspected allergic reaction to a vaccine should be carefully evaluated by an allergist because it is mandatory to assess risks and consequences of further vaccine doses, and to provide indications on how a satisfactory vaccination schedule should be completed.

REFERENCES

1. Halsey NA, Edwards KM, Dekker CL, et al. Algorithm to assess causality after individual adverse events following immunizations. *Vaccine*. 2012; 30:5791–5798.
2. Ruggeberg JU, Gold MS, Bayas JM, et al. Anaphylaxis: case definition and guidelines for data collection, analysis, and pre-

- sentation of immunization safety data. *Vaccine*. 2007; 25:5675–5684.
3. Gold MS, Gidudu J, Erlewyn-Lajeunesse M, Law B, and Brighton Collaboration Working Group on Anaphylaxis. Can the Brighton Collaboration case definitions be used to improve the quality of Adverse Event Following Immunization (AEFI) reporting? Anaphylaxis as a case study. *Vaccine*. 2010; 28:4487–4498.
4. Kelso JM, Greenhawt MJ, Li JT, et al. Adverse reactions to vaccines practice parameters 2012 update. *J Allergy Clin Immunol*. 2012; 130:25–43.
5. Wood RA, Berger M, Dreskin SC, et al. An algorithm for treatment of patients with hypersensitivity reactions after vaccines. *Pediatrics*. 2008; 122:e771–e777.
6. Dreskin SC, Halsey NA, Kelso JM, et al. International Consensus (ICON): allergic reactions to vaccines. *World Allergy Organ J*. 2016; 9:32.
7. Wood RA. Allergic reaction to vaccines. *Pediatr Allergy Immunol*. 2013; 24:521–526.
8. Committee on Infectious Diseases American Academy of Pediatrics. Red book: 2015 Report of the committee on infectious diseases, 30th ed. Elk Grove Village, IL: American Academy of Pediatrics, 2015.
9. Caubet JC, Rudzeviciene O, Gomes E, Terreehorst I, Brockow K, Eigenmann PA. Managing a child with possible allergy to vaccine. *Pediatr Allergy Immunol*. 2014; 25:394–403.
10. McNeil MM, Weintraub ES, Duffy J, et al. Risk of anaphylaxis after vaccination in children and adults. *J Allergy Clin Immunol*. 2016; 137:868–878.
11. Oberle D, Pavel J, Rieck T, et al. Anaphylaxis after immunization of children and adolescents in Germany. *Pediatr Infect Dis J*. 2016; 35:535–541.
12. Cheng DR, Perrett KP, Choo S, Danchin M, Buttery JP, Crawford NW. Pediatric anaphylactic adverse events following immunization in Victoria, Australia from 2007 to 2013. *Vaccine*. 2015; 33:1602–1607.
13. Mahajan D, Dey A, Cook J, Harvey B, Menzies R, Macartney K. Surveillance of adverse events following immunisation in Australia annual report, 2013. *Commun Dis Intell Q Rep*. 2015; 39:E369–E386.
14. Galindo BM, Concepcion D, Galindo MA, Perez A, Saiz J. Vaccine-related adverse events in Cuban children, 1999–2008. *MEDICC Rev*. 2012; 14:38–43.
15. Lawrence G, Gold MS, Hill R, Deeks S, Glasswell A, McIntyre PB. Annual report: surveillance of adverse events following immunisation in Australia, 2007. *Commun Dis Intell Q Rep*. 2008; 32:371–387.
16. Bohlke K, Davis RL, Marcy SM, et al. Risk of anaphylaxis after vaccination of children and adolescents. *Pediatrics*. 2003; 112: 815–820.
17. Erlewyn-Lajeunesse M, Hunt LP, Heath PT, Finn A. Anaphylaxis as an adverse event following immunisation in the UK and Ireland. *Arch Dis Child*. 2012; 97:487–490.
18. Sampson HA, Munoz-Furlong A, Campbell RL, et al. Second symposium on the definition and management of anaphylaxis: summary report—Second National Institute of Allergy and Infectious Disease/Food Allergy and Anaphylaxis Network symposium. *J Allergy Clin Immunol*. 2006; 117:391–397.
19. Halsey NA, Griffioen M, Dreskin SC, et al. Immediate hypersensitivity reactions following monovalent 2009 pandemic influenza A (H1N1) vaccines: reports to VAERS. *Vaccine*. 2013; 31:6107–6112.
20. Majchrowicz H. Post-vaccination reactions to diploid rabies vaccine. *Przegl Epidemiol*. 1989; 43:259–262.
21. Jackson LA, Carste BA, Malais D, Froeschle J. Retrospective population-based assessment of medically attended injection site reactions, seizures, allergic responses and febrile episodes after acellular pertussis vaccine combined with diphtheria and tetanus toxoids. *Pediatr Infect Dis J*. 2002; 21:781–786.
22. Baxter R, Toback SL, Sifakis F, et al. A postmarketing evaluation of the safety of Ann Arbor strain live attenuated influenza vaccine in children 5 through 17 years of age. *Vaccine*. 2012; 30:2989–2998.
23. Glanz JM, Newcomer SR, Hambidge SJ, et al. Safety of trivalent inactivated influenza vaccine in children aged 24 to 59 months in the vaccine safety datalink. *Arch Pediatr Adolesc Med*. 2011; 165:749–755.
24. Goldman RD. Breath-holding spells in infants. *Can Fam Physician*. 2015; 61:149–150.
25. Kearney CA, Albano AM, Eisen AR, Allan WD, Barlow DH. The phenomenology of panic disorder in youngsters: an empirical study of a clinical sample. *J Anxiety Disord*. 1997; 11:49–62.
26. Kroger AT, Atkinson WL, Marcuse EK, et al. General recommendations on immunization: recommendations of the Advisory Committee on Immunization Practices (ACIP). *MMWR Recomm Rep*. 2006; 55:1–48.
27. Barbaud A, Deschildre A, Waton G, Raison-Peyron N, Trechot P. Hypersensitivity to vaccines: an update. *Eur J Dermatol*. 2013; 23:135–141.
28. Buettcher M, Heininger U, Braun M, et al. Hypotonic-hyporesponsive episode (HHE) as an adverse event following immunization in early childhood: case definition and guidelines for data collection, analysis, and presentation. *Vaccine*. 2007; 25: 5875–5881.
29. Orr P. Supplementary statement for the 2002–2003 influenza season: update on oculo-respiratory syndrome in association with influenza vaccination. *Can Commun Dis Rep*. 2002; 28:1.
30. Al-Dabbagh M, Lapphra K, Scheifele DW, et al. Elevated inflammatory mediators in adults with oculo-respiratory syndrome following influenza immunization: a public health agency of Canada/Canadian Institutes of Health Research Influenza Research Network Study. *Clin Vaccine Immunol*. 2013; 20:1108–1114.
31. Alves RR, Gaspar A, Ferreira MB. Allergic reactions to vaccines. *Eur Ann Allergy Clin Immunol*. 2007; 39:269–277.
32. O'Hagan DT, Rappuoli R. The safety of vaccines. *Drug Discov Today*. 2004; 9:846–854.
33. Bergfors E, Trollfors B, Inerot A. Unexpectedly high incidence of persistent itching nodules and delayed hypersensitivity to aluminium in children after the use of adsorbed vaccines from a single manufacturer. *Vaccine*. 2003; 22:64–69.
34. Bellanti JA, Fishman HJ, Wientzen RL. Adverse reactions to vaccines. *Immunol Allergy Clin North Am*. 1987; 7:423–445.
35. Christou EM, Wargon O. Stevens-Johnson syndrome after varicella vaccination. *Med J Aust*. 2012; 196:240–241.
36. Chopra A, Drage LA, Hanson EM, Touchet NL. Stevens-Johnson syndrome after immunization with smallpox, anthrax, and tetanus vaccines. *Mayo Clin Proc*. 2004; 79:1193–1196.
37. Mullins RJ, James H, Platts-Mills TA, Commins S. Relationship between red meat allergy and sensitization to gelatin and galactose- α 1,3-galactose. *J Allergy Clin Immunol*. 2012; 129:1334–1342.e1.
38. Stone CA Jr, Hemler JA, Commins SP, et al. Anaphylaxis after zoster vaccine: Implicating alpha-gal allergy as a possible mechanism. *J Allergy Clin Immunol*. 2017; 139:1710–1713.e2.
39. Pinson ML, Waibel KH. Safe administration of a gelatin-containing vaccine in an adult with galactose- α 1,3-galactose allergy. *Vaccine*. 2015; 33:1231–1232.
40. Wood RA, Setse R, Halsey N. Irritant skin test reactions to common vaccines. *J Allergy Clin Immunol*. 2007; 120:478–481.
41. Fritsche PJ, Helbling A, Ballmer-Weber BK. Vaccine hypersensitivity—update and overview. *Swiss Med Wkly*. 2010; 140: 238–246.

42. Gruber C, Nilsson L, Björkstén B. Do early childhood immunizations influence the development of and do they cause allergic reactions? *Pediatr Allergy Immunol*. 2001; 12:296–311.
43. Bernstein IL, Li JT, Bernstein DI, et al. Allergy diagnostic testing: an updated practice parameter. *Ann Allergy Asthma Immunol*. 2008; 100(suppl. 3):S1–S148.
44. Kattan JD, Konstantinou GN, Cox AL, et al. Anaphylaxis to diphtheria, tetanus, and pertussis vaccines among children with cow's milk allergy. *J Allergy Clin Immunol*. 2011; 128:215–218.
45. Parisi CA, Smaldini PL, Gervasoni ME, Maspero JF, and Docena GH. Hypersensitivity reactions to the Sabin vaccine in children with cow's milk allergy. *Clin Exp Allergy*. 2013; 43:249–254.
46. Goodyear-Smith F, Wong F, Petousis-Harris H, Wilson E, Turner N. Follow-up of MMR vaccination status in children referred to a pediatric immunization clinic on account of egg allergy. *Hum Vaccin*. 2005; 1:118–122.
47. Erlewyn-Lajeunesse M, Manek R, Lingam R, Finn A, Emond A. Anaphylaxis following single component measles and rubella immunisation. *Arch Dis Child*. 2008; 93:974–975.
48. Govindaraj P, Alfaham M, Davies C, Tuthill D. Decline of hospital admissions for MMR vaccinations in children with egg allergy. *Arch Dis Child*. 2009; 94:914–915.
49. Cronin J, Scorr A, Russell S, McCoy S, Walsh S, O'Sullivan R. A review of a paediatric emergency department vaccination programme for patients at risk of allergy/anaphylaxis. *Acta Paediatr*. 2012; 101:941–945.
50. Andersen DV, Jørgensen IM. MMR vaccination of children with egg allergy is safe. *Dan Med J*. 2013; 60:A4573.
51. Erlewyn-Lajeunesse M, Lucas JS, Warner JO. Influenza immunization in egg allergy: an update for the 2011–2012 season. *Clin Exp Allergy*. 2011; 41:1367–1370.
52. Des Roches A, Paradis L, Gagnon R, et al. Egg-allergic patients can be safely vaccinated against influenza. *J Allergy Clin Immunol*. 2012; 130:1213–1216.e1.
53. Gagnon R, Primeau MN, Des Roches A, et al. Safe vaccination of patients with egg allergy with an adjuvanted pandemic H1N1 vaccine. *J Allergy Clin Immunol*. 2010; 126:317–323.
54. Schuster JE, Sawyer MH, O'Leary S, Kimberlin B. Update from the Advisory Committee on Immunization Practices. *J Pediatr Infect Dis Soc*. 2016; 5:101–104.
55. Grohskopf LA, Sokolow LZ, Broder KR, et al. Prevention and Control of Seasonal Influenza with Vaccines: Recommendations of the Advisory Committee on Immunization Practices—United States, 2017–18 Influenza Season. *MMWR Recomm Rep*. 2017; 66:1–20.
56. Franceschini F, Bottau P, Caimmi S, et al. Vaccination in children with allergy to non active vaccine components. *Clin Trasl Med*. 2015; 4:3.
57. Lee-Wong M, Resnick D, Chong K. A generalized reaction to thimerosal from an influenza vaccine. *Ann Allergy Asthma Immunol*. 2005; 94:90–94.
58. Arroabarren E, Anda M, Sanz ML. Anaphylaxis to pneumococcal vaccine; CRM (197): Novel cause of vaccine allergy. *Pediatr Allergy Immunol*. 2016; 27:433–437.
59. Ponvert C, Scheinmann P, de Blic J. Anaphylaxis to the 23-valent pneumococcal vaccine: a second explored case by means of immediate-reading skin tests with pneumococcal vaccines. *Vaccine*. 2010; 28:8256–8257.
60. Nilsson L, Brockow K, Alm J, et al. Vaccination and allergy: EAACI position paper, practical aspects. *Pediatr Allergy Immunol*. 2017; 28:628–640.
61. Mark A, Björkstén B, Granström M. Immunoglobulin E and G antibodies two years after a booster dose of an aluminum adsorbed or a fluid DT vaccine in relation to atopy. *Pediatr Allergy Immunol*. 1997; 8:83–87.
62. Madaan A, Maddox DE. Vaccine allergy: diagnosis and management. *Immunol Allergy Clin North Am*. 2003; 23:555–588.
63. Erlewyn-Lajeunesse M, Brathwaite N, Lucas JS, Warner JO, et al. Recommendations for the administration of influenza vaccine in children allergic to egg. *BMJ*. 2009; 339:b3680.
64. Rutkowski K, Ewan PW, Nasser SM. Administration of yellow fever vaccine in patients with egg allergy. *Int Arch Allergy Immunol*. 2012; 161:274–278.
65. Kang LW, Crawford N, Tang ML, et al. Hypersensitivity reactions to human papillomavirus vaccine in Australian school-girls: retrospective cohort study. *BMJ*. 2008; 337:a2642.
66. Carey AB, Meltzer EO. Diagnosis and “desensitization” in tetanus vaccine hypersensitivity. *Ann Allergy*. 1992; 69:336–338.
67. Atanaskovic-Markovic M, Nestorovic B. Desensitization to diphtheria, tetanus and pertussis vaccine. *Srp Arh Celok Lek*. 2003; 131:427–4231. □

Copyright of Allergy & Asthma Proceedings is the property of OceanSide Publications Inc. and its content may not be copied or emailed to multiple sites or posted to a listserv without the copyright holder's express written permission. However, users may print, download, or email articles for individual use.