HHS Public Access

Author manuscript

J Allergy Clin Immunol. Author manuscript; available in PMC 2019 July 01.

Published in final edited form as:

J Allergy Clin Immunol. 2018 February ; 141(2): 463–472. doi:10.1016/j.jaci.2017.12.971.

Vaccine-associated hypersensitivity

Michael M. McNeil, MD, MPH and **Frank DeStefano, MD, MPH**

Immunization Safety Office, Centers for Disease Control and Prevention.

Abstract

Vaccine-associated hypersensitivity reactions are not infrequent; however, serious acute-onset, presumably IgE–mediated or IgG and complement-mediated anaphylactic or serious delayed-onset T cell–mediated systemic reactions are considered extremely rare. Hypersensitivity can occur because of either the active vaccine component (antigen) or one of the other components. Postvaccination acute-onset hypersensitivity reactions include self-limited localized adverse events and, rarely, systemic reactions ranging from urticaria/angioedema to full-blown anaphylaxis with multisystem involvement. Risk of anaphylaxis after all vaccines is estimated to be 1.31 (95% CI, 0.90–1.84) per million vaccine doses, respectively. Serious hypersensitivity reactions after influenza vaccines are particularly important because of the large number of persons vaccinated annually. Influenza vaccines are unique in requiring annual changes in the vaccines' antigenic composition to match the predicted circulating influenza strains. Recently, novel influenza vaccine types were introduced in the United States (recombinant vaccines, some with higher antigen content and a new adjuvanted vaccine). Providers should be aware of changing recommendations on the basis of recent published evidence for persons with a history of egg allergy to receive annual influenza vaccination. Further research is needed to elucidate the pathophysiology and risk factors for reported vaccine-associated adverse events. Further research is also needed to determine whether repeated annual inactivated influenza vaccination, the number of vaccine antigens administered at the same time, and the current timing of routine infant vaccinations are optimal for overall population well-being.

Keywords

Acute; delayed; hypersensitivity; immunologically mediated; mast cell; IgE mediated; T cell mediated; allergy; anaphylaxis; postvaccination; vaccine safety

Vaccines have been recognized as one of the most effective public health interventions.[1] Routine immunization has resulted in major reductions in vaccine-preventable infectious disease and death. The Advisory Committee on Immunization Practices (ACIP) recommends an immunization schedule for the United States in which children receive 10 vaccines to protect against 16 diseases before the age of 2 years.[2] Although vaccination

Corresponding author: Michael M. McNeil, MD, MPH, Immunization Safety Office, Centers for Disease Control and Prevention, 1825 Century Center Blvd, MS-D26, Atlanta, GA 30345. mmm2@cdc.gov.

Disclaimer

The findings and conclusions of this report are those of the authors and do not necessarily represent the official position of the Centers for Disease Control and Prevention.

programs have as their main goal the protection of the person vaccinated, in some cases the protective effect extends to nonvaccinated persons, producing herd immunity (ie, resistance to the circulation of contagious disease in a population that results if a sufficiently high proportion of subjects are immune to the disease, especially through vaccination).[3]

Vaccine-associated hypersensitivity reactions are not infrequent. Fortunately, most reported vaccine-associated adverse reactions are not serious, and many are not immunologically mediated or even reproducible on re-exposure.[4] Serious anaphylactic or cutaneous adverse reactions do occur but are extremely rare. Evaluation of immunization-associated, potentially immunologically mediated hypersensitivity is important to help determine the mechanism or mechanisms of the reaction. If acute hypersensitivity is confirmed, it allows future exposure to the needed vaccine through desensitization or in split doses if low risk (one tenth of the dose and then nine tenths of the dose). Patients erroneously labeled as "vaccine intolerant" might be inadequately immunized and experience preventable disease. Careful review of the timing of the adverse reaction and the clinical nature of the reaction, along with appropriate testing for IgE–mediated allergy, mast cell activation, vaccine-specific IgG and complement activation, and T cell–mediated delayed-type hypersensitivity can in most cases allow safe re-exposure to the implicated vaccine when needed in the future.

In this report we review the types of immunologically mediated hypersensitivity that can occur after vaccination, the components in vaccines implicated in these reactions, and the incidence of serious acute-onset and delayed-onset reactions and highlight recent important research advances. The interested reader is referred to excellent recent reviews of allergic outcomes and clinical guidance on treatment of these outcomes.[5–10]

ALLERGIC REACTIONS TO VACCINES

Immunologically mediated allergic reactions are either acute in onset or delayed.[6] The majority of acute-onset reactions are type I hypersensitivity reactions mediated by preformed IgE antibodies against a vaccine component. The importance of distinguishing acute-onset IgE-mediated reactions is that they can manifest as severe life-threatening anaphylaxis in the patient and require more careful evaluation. Typically, these reactions occur within minutes of exposure to the relevant allergen, and most normally occur within 4 hours; possible exceptions might include delayed-onset reactions to rabies and Japanese encephalitis vaccines.[9] The most common symptoms of acute-onset IgE-mediated hypersensitivity range from urticaria to angioedema to anaphylaxis.

Anaphylaxis can occur after exposure to allergens from a variety of sources, including food, venom, drugs, and immunizations. Anaphylaxis is a rare, severe, life-threatening allergic reaction with a rapid onset that involves multiple organ systems and can progress rapidly. Symptoms and signs of anaphylaxis can include but are not limited to generalized urticaria; wheezing; swelling of the mouth, tongue, and throat; difficulty breathing; vomiting; diarrhea; hypotension; decreased level of consciousness; and shock.[6–10]

Urticaria characterized by wheals (hives) accompanied by an itching or burning sensation resolves generally within 24 hours. Urticaria can result from immunologic and nonimmunologic mast cell activation. Although allergic triggers, such as stinging insects, foods, and medications (including vaccines), are commonly considered and sometimes confirmed as the cause of acute urticaria, several studies have identified infections (urinary tract and upper respiratory tract) as a cause with rates as high as 81%, whereas others have found foods, food additives, and infections also to be common, with rates of 11% to 13% each.[11]

Angioedema is a potentially life-threatening adverse event with less well-circumscribed edema than urticaria and mainly involves the deeper subcutaneous tissues, often of the face, oropharynx, or both; tissue involvement is painful rather than pruritic and tends to fade more slowly, usually within 24 to 48 hours.[12] Although urticaria and angioedema are considered typical manifestations of immediate-type reactions, they can also occur with delayed reactions. In a delayed reaction these might be the result of non–IgE–mediated processes, such as complement activation, by immune complexes (type 3 hypersensitivity or an Arthus reaction) or other less-well defined mechanisms, including T cell–mediated processes or, less likely, late activation of the IgE system.[5]

Delayed-type reactions occur commonly within hours or days after exposure, although symptom onset can be delayed up to 2 to 3 weeks. The most common signs of delayed-type reactions are rashes (ie, various morphologic forms of maculopapular eruptions).[4] Some delayed reactions might not be immunologically mediated. Persistent hard nodules at the injection site can involve nonspecific inflammation or irritant reactions usually induced by adjuvants, such as aluminum, and do not necessarily reflect immunologic hypersensitivity to vaccine constituents.[13,14] Large local vaccine reactions secondary to T–cell infiltration are often associated with prolonged and very effective immunity. Delayed reactions are often self-limiting conditions that do not contraindicate administration of future doses (eg, booster doses) of the same vaccine.

VACCINE COMPONENTS KNOWN TO CAUSE ALLERGIC REACTIONS

Vaccines, similar to other drugs, have the potential to cause allergic reactions. Vaccines contain an active component (the antigen) and additional components. Vaccine antigens can comprise whole organisms or parts of organisms, inactivated toxins (toxoids), or both that induce protective immune responses. Vaccine antigens themselves rarely, if ever, are the cause of hypersensitivity reactions. Rather, hypersensitivity reactions after vaccination are usually due to individual vaccine components, such as egg protein, gelatin, and potentially other additives. The manufacturer's package insert for each of the currently available US vaccines can be found on the US Food and Drug Administration (FDA)'s Web site at http://www.fda.gov/BiologicsBloodVaccines/Vaccines/ApprovedProducts/ucm093833.htm, and these contain a description of that vaccine's manufacturing process, including the amount and purpose of each excipient substance. Many of these components are present in small amounts that are usually insufficient to induce allergic reactions in most patients with possible hypersensitivity to the component. However, patients with unusually high levels of

IgE antibody can theoretically react to very small amounts of these antigens and experience severe reactions, including anaphylaxis.

MICROBIAL ANTIGENS

Rarely, hypersensitivity to the microbial component itself has been implicated in patients with systemic allergic reactions after immunizations (eg, hypersensitivity to tetanus and diphtheria toxoids, pneumococcus, or Bordetella pertussis antigens).[15] Delayed urticaria, angioedema, or both and nonspecific skin rashes have been reported frequently (5% to 13%) in patients receiving these vaccines.[4] However, comprehensive allergy testing to confirm an immune-mediated allergic reaction was not performed in the great majority of these reports.

EGG

Acute-onset hypersensitivity reactions or anaphylaxis are uncommon and occur principally among persons with histories of allergies to egg or other substances.[4] Egg allergy is the most frequent food allergy among children, and sensitization reactions occur most frequently before 5 years of age. Egg allergy might be the cause of hypersensitivity reactions to vaccines.[16] Certain commonly used vaccines contain small amounts of residual egg protein (ovalbumin) from the vaccine manufacturing process. Ovalbumin concentrations are not usually reported and can vary among vaccine brands and batches.[17] Concentrations are usually higher in vaccines cultured on embryonated chicken eggs (influenza, yellow fever, and rabies) and lower for vaccines cultured on fibroblasts of chicken embryos (measles, mumps, and rubella vaccine [MMR; Merck, Whitehouse Station, NJ]). Most studies to evaluate the safety of vaccines containing egg proteins in patients with egg allergy have assessed the influenza vaccines.[4,17]

INFLUENZA VACCINE AND EGG ALLERGY

Until recently, propagation of the virus in embryonated eggs was integral for the preparation of influenza vaccines, resulting in small amounts of residual ovalbumin in these vaccines. After ACIP's 2010 recommendation for universal annual influenza vaccination of all persons older than 6 months, the total number of influenza vaccine doses distributed in the United States has steadily increased and reached approximately 146 million in the 2016–2017 season (https://www.cdc.gov/flu/professionals/vaccination/vaccinesupply-2016.htm).

Egg allergy has been a longstanding concern with influenza vaccination. Egg allergy can be confirmed by a consistent medical history of adverse reactions to egg-containing foods plus skin and/or blood testing for IgE directed against egg proteins. Studies to date have indicated that severe allergic reactions to the currently available egg-based influenza vaccines in persons with egg allergy are rare, and consequently, ACIP has modified its recommendations for this patient group. The current 2017–2018 recommendations for vaccination of patients with egg allergies state that most can receive any licensed and recommended age-appropriate influenza vaccine and no longer have to be monitored for 30 minutes after receiving the vaccine.[18] Patients with severe egg allergies should be vaccinated in a medical setting and supervised by a health care provider who is able to recognize and manage severe allergic

conditions. This current official US Centers for Disease Control and Prevention guidance is slightly more restrictive than 2017 season's guidance from the American Academy of Pediatrics Committee on Infectious Diseases, which states that because the rate of anaphylaxis after inactivated influenza vaccine (IIV) administration is not greater in recipients with egg allergy than those without egg allergy or from other universally recommended vaccines, all children with egg allergy of any severity can receive influenza vaccine without any additional precautions beyond those recommended for any vaccine.[19] The American Academy of Pediatrics Committee on Infectious Diseases guidance also states that standard vaccination practice for all vaccines in children should include the ability to respond to rare acute hypersensitivity reactions.[19]

GELATIN

Gelatin is an animal protein used widely in foods and medications. Gelatin of either bovine or porcine origin is added to both live and inactivated vaccines as a stabilizing agent. Formerly, allergic reactions after gelatin-containing live MMR vaccine were considered rare and possibly caused by either egg protein or antibiotics; however, in 1993, Kelso et al[20] reported a patient with an anaphylactic reaction after administration of MMR who had antibodies to gelatin. Subsequently, reports from Japan and some European countries implicated this and other gelatin-containing vaccines. The exact mechanism for these patients to become sensitized to gelatin is unknown.

In the United States Pool et al[21] conducted a retrospective case-control study identifying anaphylaxis reports after MMR to the Vaccine Adverse Event Reporting System (VAERS) and interviewing and obtaining sera from these patients. Sera from these patients were tested for IgE antibodies to gelatin, whole egg, and vaccine viral antigens. Control subjects received MMR vaccine uneventfully. They found that none of the interviewed patients had a history of food allergy to gelatin, and 27% of case patients had positive results for anti-gelatin IgE, whereas none of the control subjects did.

In the southeastern United States, galactose-a-1,3galactose (alpha-gal) sensitivity has emerged as a cause of red meat allergy that is causally linked to bites from the lone star tick.[22] Alpha-gal sensitivity often presents with delayed anaphylaxis (3–6 hours) after ingestion of red meat, with lesser degrees of reactivity to milk and gelatin. A recent report identified vaccine–induced anaphylaxis associated with alpha-gal allergy in a 63–year–old patient minutes after receiving varicella zoster virus immunization.[23] These authors caution that vaccines with higher gelatin content (MMR and varicella zoster virus) might pose a risk in such patients, especially because of their parenteral administration.

RESIDUAL MEDIA

Residual amounts of media used to grow organisms are often found in both inactivated and live vaccines, such as viruses grown in cell lines. No intact cells from these cell lines persist in live or inactivated vaccines, and purification removes most of the cellular material, but it is impossible to remove all traces of the components. Vaccines (antigens) that are recombinant proteins expressed in Saccharomyces cerevisiae (Baker's yeast) include

hepatitis B, human papillomavirus vaccines (quadrivalent human papillomavirus vaccine and nonavalent human papillomavirus vaccine), and one type of meningococcal conjugate vaccine (Men-veo; Novartis, Basel, Switzerland), and these contain yeast protein.

In a review of VAERS data from 1990–2004, DiMiceli et al[24] identified only 15 reports of probable or possible anaphylaxis after vaccination of patients with a reported history of yeast allergy. Of these, 11 received hepatitis B vaccine that contains trace amounts of yeast proteins. It is possible that sensitivity to yeast played a role in some of these cases' adverse reactions; however, because allergy testing was not performed in these subjects to confirm sensitivity to yeast, the role of other allergens in the vaccines cannot be ruled out. These data suggest that recombinant yeast-derived hepatitis B vaccine poses minimal risk of allergic reactions in yeast-sensitive patients. If a patient has a history of severe yeast reaction, allergist evaluation before hepatitis B and human papillomavirus vaccine administration is recommended.[24]

MILK

Milk proteins are used as stabilizers in tetanus, diphtheria, and acellular pertussis vaccines (diphtheria, tetanus, and acellular pertussis vaccine [DTaP] and tetanus, reduced diphtheria, and acellular pertussis vaccine [Tdap]), and these vaccines can contain nanogram quantities of bovine casein. Anaphylaxis to these vaccines is rare and can often be attributed to toxoid components. One report identified 8 children with severe cow's milk allergy who reacted with anaphylaxis to booster doses of the vaccines.[25] Because anaphylaxis is rare and many children with milk allergy tolerate the vaccines, continuing standard practice for DTaP vaccination for all children is recommended; however, caution is advised, administering booster doses in highly sensitive children with milk allergy.

ADJUVANTS

Adjuvants are incorporated into some vaccine formulations to enhance or direct the immune response of the vaccinated subject, specifically to boost T-cell immunity and increase helper T-cell function. Aluminum hydroxide and aluminum phosphate are the most common adjuvants used in vaccines. No immediate hypersensitivity reactions have been documented to these adjuvants; however, contact allergy and small granulomas or nodules with persistent urticaria at the site can occur after aluminum-containing vaccines. Follow-up 5 to 9 years after initial diagnosis in affected children revealed that the majority of children no longer had positive reactions to aluminum on contact allergy testing.[26] Larger recurrent nodules at the site of injection of aluminum-containing vaccines have been reported rarely.

An increased rate of anaphylaxis and other immediate hypersensitivity reactions was reported in Canada associated with adjuvant system 03 (AS03; trade name for a squalene-based adjuvant; GlaxoSmithKline, Research Triangle Park, NC) influenza A 2009 (H1N1) pandemic vaccine (influenza A [H1N1]pdm09) vaccine.[27] A case-control study revealed higher rates of food allergy in affected subjects, but no evidence that the reactions were due to the AS03 adjuvant has been provided.[28] Until recently, only nonadjuvanted influenza A(H1N1)pdm09 and seasonal influenza vaccines were used in the United States.

Beginning with the 2016–2017 season, a new FDA licensed seasonal influenza vaccine (Fluad; Seqirus, Holly Springs, NC) containing the oil-in-water emulsion of squalene adjuvant (MF59) was approved for adults 65 years of age and older.[29] This vaccine has been licensed in European countries for many years and has been evaluated in elderly subjects in both clinical trials and postmarketing surveillance programs.[30] Although the vaccine is transiently more reactogenic than unadjuvanted influenza vaccine, the occurrence of allergic-type responses, such as urticarial rash, allergic bronchospasm, or systemic anaphylaxis, occur extremely rarely.[30–33]

ANTIMICROBIALS

Gentamicin, tetracycline, neomycin, streptomycin, and polymixin B are used during the production process for vaccines to prevent bacterial or fungal growth. Although most of these antimicrobials are removed during the purification process, trace amounts can be present in some vaccines.[34] These antimicrobial agents can cause contact or, rarely, systemic hypersensitivity reactions when used in clinical settings for disease therapy (eg, treatment of an infection). However, allergic reactions associated with trace amounts present in vaccines have not been well documented.

PRESERVATIVES

Thimerosal, 2-phenoxyethanol, and phenol are used in multidose vials of vaccines to prevent bacterial growth. Thimerosal in vaccines has been associated with contact allergy and rarely with systemic allergic reactions.[35] Thimerosal was used in several vaccines in the United States until 2001 but was removed as a preservative in vaccines used in young children as a precautionary measure because of theoretical concerns about mercury toxicity. Some multidose vials of inactivated influenza vaccines contain thimerosal, and trace amounts can be found in some other vaccines.[34] The majority of persons do not experience reactions to thimerosal administered as a vaccine component, even when patch or intradermal tests for thimerosal indicate hypersensitivity. A local or delayed-onset hypersensitivity reaction to thimerosal is not a contraindication to receipt of a vaccine that contains thimerosal.[36] In addition to vaccines, 2-phenoxyethanol is used in cosmetics, ophthalmic solutions, and antiseptics. There have been reports of contact dermatitis caused by 2-phenoxyethanol.[37] In Japan a 2011–2012 spike in reports of influenza vaccine–associated anaphylaxis was linked to a 2-phenoxyethanol containing vaccine from a single manufacturer, and a follow-up investigation implicated a possible role of the preservative in the enhancement of these IgE–mediated reactions.[38] However, these investigators were unable to identify a possible specific immunologic mechanism for these cases of influenza vaccine-associated anaphylaxis. Phenol is widely used in mouthwashes, throat lozenges, and throat sprays. Currently, phenol is a preservative in 3 US licensed vaccines, pneumococcal vaccine polyvalent (Pneumovax23; Merck), typhoid Vi polysaccharide vaccine (Typhim Vi;Sanofi Pasteur), and smallpox (vaccinia) vaccine live (ACAM2000; Emergent BioSolutions, Gaithersburg, Md), each of which contains 0.25% phenol. Phenol has not been associated with reports of immediate hypersensitivity reactions.[5] With the exception of Nagao et al,[38] the evidence to suggest these preservatives can trigger allergic reactions, mainly delayed-

onset contact dermatitis and maculo-papular rash, has been limited to several single-case reports.[4]

EXTRINSIC SUBSTANCES

With high-level large surface area mucosal membrane exposures, water-soluble proteins in natural latex products can cause immediate-onset hypersensitivity reactions, including anaphylaxis. Natural latex is also present in the rubber stoppers of some vaccine vials and on the plungers in some prefilled syringes. There are rare reports of acute-onset hypersensitivity reactions in this situation, but in most instances specific studies to determine that latex was the cause of the reaction have not been performed.[39] Nevertheless, patients with severe latex allergy should avoid vaccines packaged with latex-containing stoppers and syringe plungers, if possible.[36] Alternative vaccines without risk of exposure to natural latex might be available. Synthetic rubber, which is not allergenic, has replaced natural latex in most products. The manufacturer's package insert provides information on vaccines that contain natural latex in the packaging, and these can be accessed on the FDA's Web site at http://www.fda.gov/BiologicsBloodVaccines/Vaccines/ApprovedProducts/ucm093833.htm.

CARRIER PROTEINS

In 2016, Arroabarren et al[40] were the first to report a case of anaphylaxis after pneumococcal conjugate vaccine (13-valent) administration. The subject was a healthy 12-month-old infant who had anaphylaxis after the fourth dose of the vaccine. The carrier protein CRM(197), a nontoxic mutant of diphtheria toxin, was suggested to be the trigger, with supportive evidence demonstrated by skin test and basophil activation test results. Although very infrequent, these proteins should be considered in patients with hypersensitivity to conjugated or combined vaccines containing carrier proteins. In these cases monocomponent vaccines or vaccines containing different carriers might be a safe alternative.

EPIDEMIOLOGY OF VACCINE-TRIGGERED ANAPHYLAXIS

Virtually all vaccines have the potential to trigger anaphylaxis. Recently, the Institute of Medicine concluded that epidemiologic and mechanistic evidence convincingly supports or favors a causal relationship between anaphylaxis and several childhood and adolescent vaccines, including MMR vaccine; varicella vaccine; influenza vaccine; hepatitis B vaccine; DTaP-containing vaccines; meningococcal vaccine; and human papillomavirus vaccine.[15] Evidence was determined to be inadequate for hepatitis A vaccine.[15] All of the previously discussed vaccine components also have the potential to cause anaphylaxis.

Brighton Collaboration case definition

Standard case definitions are crucial in epidemiologic studies, as well as clinical trials. In 2007, the Brighton Collaboration published a standardized case definition for anaphylaxis after vaccination.[41] In vaccine safety Brighton Collaboration definitions are generally accepted as the gold standard surveillance case definitions for post vaccination adverse events, including anaphylaxis. Other clinical algorithms to identify anaphylaxis regardless of

cause have been proposed, including the more specific Second National Institute of Allergy and Infectious Disease/Food Allergy and Anaphylaxis Network Symposium clinical criteria.[42]

Incidence of post vaccination anaphylaxis

The life-threatening nature of anaphylaxis and acceptance of a causal relationship with certain vaccines make estimation of the magnitude of the risk after vaccination an important priority. Current data are limited for quantifying the risk of anaphylaxis associated with vaccination in general or with specific vaccines. Large populations are needed to study such a rare exposure-disease association, and Table I[21,27,43–49] shows rates of post vaccination anaphylaxis reported in several recent studies[21,27,43–49]; only 2 of these were population-based studies,[43,44] both from the Vaccine Safety Datalink (VSD). The VSD is a collaboration between the US Centers for Disease Control and Prevention and several integrated health care systems across the United States.[50]

McNeil et al,[44] in a 3–year VSD study, identified 33 cases of anaphylaxis after administration of 25,173,965 vaccine doses, for an incidence rate of 1.31 (95% CI, 0.90–1.84) cases per million vaccine doses. Reproduced from this study, the incidence of vaccination-triggered anaphylaxis by age, sex, year, and vaccine type is shown in Table II,[44] and vaccine-specific incidence of anaphylaxis for influenza and certain other vaccines is shown in Table III.[44] Trivalent inactivated influenza vaccine (TIV) was the major contributor to the number of vaccine-triggered anaphylaxis cases, and the rate (1.35 [95% CI, 0.65–2.47] cases per million vaccine doses of TIV given alone) was similar to that for all vaccines. Anaphylaxis cases were identified in this study after several vaccines not included in the Institute of Medicine reports (influenza A[H1N1]pdm09 vaccine, T dap, pneumococcal polysaccharide vaccine [23-valent], hepatitis A vaccine, herpes zoster vaccine, and rabies vaccine).[44] There were no deaths among the cases, which was consistent with other recent reports.[27,45,48] That no infant or toddler cases were identified might have been due to difficulty making a diagnosis of anaphylaxis in these age groups and the possibility that anaphylaxis in children might present most often with respiratory features leading to diagnostic confusion with acute asthma.[51] The VSD study identified a female predominance among adults. Two studies using passive surveillance systems found reporting rates for anaphylaxis after the pandemic influenza A(H1N1)pdm09 monovalent vaccine were highest in women of childbearing age.[27,52] In general, anaphylaxis and immediate hypersensitivity, particularly drug allergy, occur more frequently in women of childbearing age.[53–57] Sex-specific differences in innate, humoral, and cell-mediated immune responses to vaccination have also been reported.[58–60] In addition, sex differences in adverse events (fever, pain, and inflammation) after immunization have been noted for several vaccines, including influenza[61,62] and MMRvaccines.[63,64]

Although precise biological mechanisms underlying sex–specific responses are unknown, genetic and hormonal factors are considered important.[58] Sex hormones have been shown to modulate immune responses,[65,66] and Hox et al[67] recently found that sex-specific differences in a mouse model of anaphylaxis were due to the female steroid estradiol. The recent VSD study also found that 85% of cases had pre-existing atopic disease, which was

consistent with earlier reports emphasizing coexisting atopic disease, particularly asthma, as being clinical risk factors for anaphylaxis.[44]

FUTURE RESEARCH DIRECTIONS

New influenza vaccines

Until recently, annual seasonal influenza vaccines were consistently designed to protect against 3 different viruses (trivalent vaccines); these included an influenza A H1N1 virus, an influenza A H3N2 virus, and 1 type B virus. Because there are 2 different lineages of B viruses, some current vaccines now contain 2 B strains in addition to the 2 A strains (quadrivalent vaccine) to provide broader protection against circulating influenza viruses. Since 2014, a quadrivalent formulation of Fluzone Intradermal (Sanofi Pasteur, Swiftwater, Pa) has been approved for use in persons aged 18 through 64 years. Fluzone Intradermal provides an immune response similar to that of the regular intramuscular vaccine but requires less antigen.[29] Currently, the following quadrivalent influenza vaccines are licensed and approved for use in adults aged more than 65 years in the United States: Afluria Quadrivalent (Seqirus), Fluarix Quadrivalent (GlaxoSmithKline), Flulaval Quadrivalent (GlaxoSmithKline), and Fluzone Quadrivalent (Sanofi Pasteur).[18] In prelicensure clinical trials of all 4 IIV4 vaccines and Fluad (Seqirus) vaccine, allergic reactions were not listed among the most common adverse events, and no major concerns were identified.[29–33]

The elderly are a high-risk group to receive the influenza vaccine. Aging is associated with a decrease in normal function of the immune systems, both cellular and humoral, a state of immunosenescence.[68] This involves both the host's capacity to respond to infections and the development of long-term immune memory, especially by means of vaccination. Two recent approaches designed to improve influenza vaccine effectiveness by enhancing the immune response include (1) increasing the hemagglutinin (HA) content of the vaccine and (2) adding a suitable adjuvant to the vaccine. Fluzone High-Dose vaccine contains 4 times the amount of antigen contained in regular TIV.[18] Since licensure, Fluzone High-Dose continues to be a trivalent inactivated vaccine.

On November 24, 2015, the FDA licensed Fluad, the first seasonal influenza vaccine in the United States containing an adjuvant. Fluad was approved and recommended for use in adults aged 65 years and older starting in the 2016–2017 influenza season.[18] Fluad is manufactured by using an egg-based process and is formulated with the adjuvant MF59.[30] There was no increased risk of allergic reactions noted in a pooled analysis of safety of the MF59 adjuvanted seasonal and pandemic influenza vaccines from 64 clinical trials conducted in European countries, United States, Australia, and South American countries in the general population and subjects aged more than 65 years.[31]

Two pediatric clinical trials of the vaccine comparing it with nonadjuvanted trivalent vaccines did not identify any increased risk of allergic reactions or severe adverse events; however, the vaccine was noted to be more reactogenic.[69,70] Based on data from the Nolan et al study,[70] in January 2015, Health Canada approved the use of Fluad Pediatric (Seqirus) for use in children 6 months to less than 2 years of age.[71]

Another recent innovation has been the introduction of a cell-based influenza vaccine made by growing viruses in animal cells (Madin–Darby Canine Kidney) in liquid culture rather than the traditional egg-based vaccine manufacturing process. Among its many advantages, cell-based technology is more flexible than the traditional egg culture method and is not reliant on an adequate egg supply; also, the cell-based vaccine viruses offer potentially better protection because they are more similar to circulating influenza viruses because virus grown in eggs can acquire egg-adapted changes that attenuate the vaccine's protective efficacy. Flucelvax quadrivalent (ccIIV4; Seqirus) is manufactured by using this process and approved for persons aged 4 years of age or greater.[18]

Another recently approved production technology for influenza vaccines involves use of recombinant technology. This production process does not require chicken egg–grown vaccine virus. Flublok (Protein Sciences, Meriden, Conn) is the first recombinant HA influenza vaccine; first licensed by the FDA in January 2013 as the trivalent product, it was recommended the same year by ACIP as a vaccine alternative for patients with egg allergy.[72] For the 2017–2018 season, the vaccine is available as both trivalent and quadrivalent formulations for use in adults aged 18 years or greater.[18] The manufacturing process involves replication of influenza HA protein by using insect cells and produces a purified HA that contains no egg protein, preservatives, or antibiotics.[72] Prelicensure data indicated that Flublok is well tolerated and raises higher antibody titers than IIV for influenza A viruses, likely because of the 3-fold higher rHA antigen content in Flublok. Although free of egg protein, allergic reactions after Flublok have been reported to the US VAERS among patients with a self-reported egg allergy or prior allergic reaction to IIV.[73] Importantly, VAERS is a passive surveillance system and thus has several limitations (eg, including underreporting and lack of a comparison group), so that it is usually not possible to verify a causal association between a vaccine and an adverse event.[74]

Hypersensitivity reactions after repeat influenza vaccine doses

In 2011, Glanz et al[75] reported results of a post marketing safety study after TIV in inpatient and emergency department settings. In a secondary analysis, among children who received multiple annual TIV doses, there was a dose response for vaccine-induced allergic reactions shortly after vaccination.

There is precedent for the biological plausibility that certain subpopulations become susceptible to vaccine-induced reactions after multiple exposures. For example, the fifth booster dose of DTaP vaccine administered between the ages of 4 to 6 years is associated with whole-limb redness or swelling in approximately 1% to 2% of vaccine recipients. Glanz et al[75] commented that with the influenza vaccination being universally recommended for all age groups, these associations warrant further study in a larger population across a wider age range. Furthermore, future research should also focus on developing analytic methods to measure cumulative risk when there are multiple annual exposures and events across a lifetime.

Possible long-term effects

Allergy represents one of the major health problems of most modern societies. For reasons unknown, the atopic diseases of asthma, rhinitis, and atopic dermatitis, in which IgE antibodies play a role in most cases, have increased dramatically in recent decades.[76] This increase coincided with improved hygiene and socioeconomic conditions and with a decrease in the incidence of many infectious diseases. Strachan's hygiene hypothesis holds that improved hygiene reduces microbial exposures, which are important in priming the immune response and protective against atopic disorders.[77] This hypothesis was expanded to cover asthma and autoimmune diseases.[78] Thus in Western populations lack of exposure to infectious agents and environmental microbes during childhood might predispose to allergy and asthma. At the immunologic level, this hypothesis was initially interpreted as an absence of immune deviation of allergen-specific responses from a T_H2 (allergic) to a T_H1 (nonallergic) phenotype; more recently, however, the importance of reduced activity of protective regulatory T cells to allergens has been emphasized.[79] The process of polarization of the immune system from a T_H2 to a T_H1 response has been called immune deviation and is considered to act principally in early childhood.

Early-life factors, particularly altered environmental experiences, including various infections, can exacerbate allergic disease and promote tolerance.[78–83] The hygiene hypothesis has been invoked to suggest that vaccines, by preventing certain childhood infections, could potentially increase the risk of allergies or asthma. Alternatively, by containing vaccine antigens designed to stimulate the immune system similar to pathogens, vaccines protect against and might modulate the immune response to decrease the risk of atopy, or vaccines might stimulate the immune system in a way that promotes atopic disease independent of the effect on infections.[84] To date, there is no evidence to support the hypothesis that routine infant immunizations increase the risk of atopic disease, and one recent cross-sectional study found weak support of the hypothesis that immunizations can slightly decrease the risk of atopy in later life.[84] These latter investigators also suggested that areas for additional research include the potential effects of timing of vaccination and of the number of antigens administered by means of vaccination on the risk of atopic diseases.

There is evidence that immunizations given early in life have the potential to deviate the immune system toward a more or less allergenic phenotype.[85] Timing of routine immunizations in infancy can affect susceptibility to allergic disease as a consequence of nontargeted vaccine effects on the susceptibility to infections and allergic diseases. However, as commented on by Kiraly et al,[85] observational studies that have investigated the age of pertussis vaccination in infants and allergic disease have found conflicting results, possibly as a result of methodological issues (eg, confounding because of factors associated with receipt or refusal of vaccination and possible variability in studied schedules) and predominantly studied diphtheria, tetanus whole-cell pertussis vaccine, a vaccine no longer used in most industrial countries. Furthermore, Kiraly et al's recent population-based cohort study found no overall association between delayed DTaP administration and food allergy, although children with delayed DTaP administration did have less eczema and less use of eczema medication.[85]

CONCLUSIONS

Recent advances in vaccine technology allow for improved targeting of the immunologic effects of vaccines, particularly when adjuvants are used. When human clinical trials of new vaccines or vaccine components are planned, careful monitoring for adverse events, particularly those that might have an underlying allergic cause, is needed. Because trials are limited in their sample size, postmarketing safety surveillance is required to detect rare serious adverse events, which can be facilitated by use of electronic health records. There is also a need for more research to elucidate the pathophysiology of various IgE and non-IgE vaccine-related allergic disorders and potential risk factors for allergic diseases, including the role of repeated annual inactivated influenza vaccine doses, the number of vaccine antigens, and the timing of routine infant vaccinations.

Abbreviations used

ACIP	Advisory Committee on Immunization Practices Alpha-gal: Galactose-a-1,3-galactose
DTaP	Diphtheria, tetanus, and acellular pertussis vaccine
FDA	US Food and Drug Administration
HA	Hemagglutinin
MF59	Oil-in-water emulsion of squalene adjuvant
MMR	Measles, mumps, and rubella vaccine
Tdap	Tetanus, reduced diphtheria, and acellular pertussis vaccine
TIV	Trivalent inactivated influenza vaccine
VAERS	Vaccine Adverse Event Reporting System
VSD	Vaccine Safety Datalink

REFERENCES

1. National Vaccine Advisory Committee. Protecting the public's health: critical functions of the Section 317 Immunization Program—a report of the National Vaccine Advisory Committee. Public Health Rep 2013;128:78–95. [PubMed: 23450872]
2. Robinson CL, Romero JR, Kempe A, Pellegrini C. Advisory Committee on Immunization Practices (ACIP) Child/Adolescent Immunization Work Group. Advisory Committee on Immunization Practices Recommended immunization schedule for children and adolescents aged 18 years or younger—United States, 2017. MMWR Morb Mortal Wkly Rep 2017;66:134–5. [PubMed: 28182607]
3. Scarbrough Lefebvre CD, Terlinden A, Standaert B. Dissecting the indirect effects caused by vaccines into the basic elements. Hum Vaccines Immunother 2015;11:2142–57.
4. Caubet JC, Ponvert C. Vaccine allergy. Immunol Allergy Clin North Am 2014;34: 597–613. [PubMed: 25017679]
5. Dreskin SC, Halsey NA, Kelso JM, Wood RA, Hummell DS, Edwards KM, et al. International consensus (ICON): allergic reactions to vaccines. World Allergy J 2016;9:32.

6. Simons FER, Ebisawa M, Sanchez-Borges M, Thong BY, Worm M, Kase Tanno L, et al. 2015 update of the evidence base: World Allergy Organization anaphylaxis guidelines. World Allergy Organ J 2015;8:32. [PubMed: 26525001]
7. Simons FER, Sampson HA. Anaphylaxis: unique aspects of clinical diagnosis and management in infants (birth to age 2 years). J Allergy Clin Immunol 2015;135:1125–31. [PubMed: 25441636]
8. Lieberman P, Nicklas RA, Randolph C, Oppenheimer J, Berstein D, Bernstein J, et al. Anaphylaxis–a practice parameter update 2015. Ann Allergy Asthma Immunol 2015;115:341–84. [PubMed: 26505932]
9. Nilsson L, Brockow K, Alm J, Cardona V, Caubert JC, Gomes E, et al. Vaccination and allergy: EAACI position paper, practical aspects. Pediatr Allergy Immunol 2017;28:628–40. [PubMed: 28779496]
10. Zafack JG, De Serres G, Rouleau I, Gari epy MC, Gagnon R, Drolet JP, et al. Clinical approach used in medical consultations for allergic-like events following immunization: case series report in relation to practice guidelines. J Allergy Clin Immunol 2017;5:718–27.
11. Radonjic-Hoesli S, Hofmeier KS, Micaletto S, Schmid-Grendelmeier P, Bircher A, Simon D. Urticaria and angioedema: an update on classification and pathogenesis. Clin Rev Allergy Immunol 2017 [Epub ahead of print].
12. Jaiganesh T, Weise M, Hollingsworth J, Hughan C, Kamara M, Wood P, et al. Acute angioedema: recognition and management in the emergency department. Eur J Emerg Med 2013;20:10–7. [PubMed: 22976464]
13. Miliauskas JR, Mukherjee T, Dixon B. Postimmunization (vaccination) injection-site reactions. A report of four cases and review of the literature. Am J Surg Pathol 1993;17:516–24. [PubMed: 8470766]
14. Lauren CT, Belsito DV, Morel KD, LaRussa P. Case report of subcutaneous nodules and sterile abscesses due to delayed hypersensitivity to aluminum containing vaccines. Pediatrics 2016;138:e20141690. [PubMed: 27677573]
15. Stratton K, Ford A, Rusch E, Clayton EW, editors. Adverse effects of vaccines; evidence and causality. Washington (DC): Institute of Medicine, National Academies Press; 2001.
16. Echeverria-Zudaire LA, Ortigosa-del Castillo L, Alonso−Lebrero E, Alvarez-Garc ıa FJ, Cort es-Alvarez N, Garc ıa-S anchez N, et al. Consensus document on the approach to children with allergic reactions after vaccination or allergy to vaccine components. Allergol Immunopathol (Madr) 2015;43:304–25. [PubMed: 25891956]
17. Kelso JM. Influenza vaccine and egg allergy: nearing the end of an evidence-based journey. J Allergy Clin Immunol 2015;3:140–1.
18. Grohskopf LA, Sokolow LZ, Broder KR, Walter EB, Bresee JS, Fry AM, 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(RR-2):1–24.
19. Committee on Infectious Diseases. Recommendations for prevention and control of influenza in children, 2017–2018. Pediatrics 2017;140:e20172550. [PubMed: 28870977]
20. Kelso JM, Jones RT, Yunginger JW. Anaphylaxis to measles, mumps, and rubella vaccine mediated by IgE to gelatin. J Allergy Clin Immunol 1993;91:867–72. [PubMed: 8473675]
21. Pool V, Braun MM, Kelso JM, Mootrey G, Chen RT, Yunginger JW, et al. Prevalence of anti-gelatin IgE antibodies in people with anaphylaxis after measles-mumps rubella vaccine in the United States. Pediatrics 2002;110:e71. [PubMed: 12456938]
22. Commins SP, Satinover SM, Hosen J, Mozena J, Borish L, Lewis BD, et al. Delayed anaphylaxis, angioedema, or urticaria after consumption of red meat in patients with IgE antibodies specific for galactose-alpha-1,3-galactose. J Allergy Clin Immunol 2009;123:426–33. [PubMed: 19070355]
23. Stone CA, Hemler JA, Commins SP, Schuyler AJ, Phillips EJ, Peebles RS, et al. Anaphylaxis after zoster vaccine: Implicating alpha-gal allergy as a possible mechanism. J Allergy Clin Immunol 2017;139:1710–3.e2. [PubMed: 27986511]
24. DiMiceli L, Pool V, Kelso JM, Shadomy SV, Iskander J. VAERS Team. Vaccination of yeast sensitive individuals: review of safety data in the US Vaccine Adverse Event Reporting System (VAERS). Vaccine 2006;24:703–7. [PubMed: 16154669]

25. Kattan JD, Konstantinou GN, Cox AL, Nowak-Węgrzyn A, Gimenez G, Sampson HA, et al. Anaphylaxis to diphtheria, tetanus, and pertussis vaccines among children with cow's milk allergy. J Allergy Clin Immunol 2011;128:215–8. [PubMed: 21624648]
26. Bergfors E, Trollfors B. Sixty-four children with persistent itching nodules and contact allergy to aluminium after vaccination with aluminium-adsorbed vaccinesprognosis and outcome after booster vaccination. Eur J Pediatr 2013;172:171–7. [PubMed: 23052615]
27. Rouleaux I, De Serres G, Drolet JP, Skowronski DM, Ouakki M, Toth E, et al. Increased risk of anaphylaxis following administration of 2009 AS03-adjuvanted monovalent pandemic A/H1N1 (H1N1pdm09) vaccine. Vaccine 2013;31:5989à396. [PubMed: 24144473]
28. Rouleaux I, De Serres G, Skowronski DM, Drolet JP, Lemire C, Toth E, et al. Risk factors associated with anaphylaxis and other allergic-like events following receipt of 2009 monovalent AS03-adjuvanted pandemic influenza vaccine in Quebec, Canada. Vaccine 2014;32:3480–7. [PubMed: 24793951]
29. Grohskopf LA, Sokolow LZ, Broder KR, Olsen SJ, Karron RA, Jernigan DB, et al. Prevention and control of seasonal influenza with vaccines: recommendations of the Advisory Committee on Immunization Practices (ACIP)-United States, 2016–17 influenza season. MMWR Morb Mortal Wkly Recomm Rep 2016;65:691–7.
30. Tsai TF. FluadÒ-MF59Ò-Adjuvanted influenza vaccine in older adults. Infect Chemother 2013;45:159–74. [PubMed: 24265964]
31. Pellegrini M, Nicolay U, Lindert K, Groth N, Della Cioppa G. MF59-adjuvanted versus non-adjuvanted influenza vaccines: integrated analysis from a large safety database. Vaccine 2009;27:6959–65. [PubMed: 19751689]
32. Cuhna JP. RxList FLUAD. Available at: http://www.rxlist.com/fluad-side-effectsdrug-center.htm (date of last RxList review 7/3/2017). Accessed October 20, 2017.
33. 11 23, 2015 Summary basis for regulatory action–FLUAD. Available at: https://www.fda.gov/BiologicsBloodVaccines/Vaccines/ApprovedProducts/ucm473989.htm. Accessed December 12, 2017.
34. Centers for Disease Control and Prevention. In: Hamborsky J, Kroger A, Wolfe S, editors. Epidemiology and prevention of vaccine-preventable diseases. 13th ed Washington (DC): Public Health Foundation; 2015.
35. Leventhal JS, Berger EM, Brauer JA, Cohen DE. Hypersensitivity reactions to vaccine constituents: a case series and review of the literature. Dermatitis 2012;23:102–9. [PubMed: 22653170]
36. Kroger AT, Duchin J, Vázquez M. General best practice guidelines for immunization. Best Practices Guidance of the Advisory Committee on Immunization Practices (ACIP). Available at: www.cdc.gov/vaccines/hcp/acip-recs/generalrecs/downloads/general-recs.pdf. Accessed December 12, 2017.
37. Vogt T, Landthaler M, Stolz W. Generalized eczema in an 18-month-old boy due to phenoxyethanol in DPT vaccine. Contact Dermatitis 1998;38:50–1.
38. Nagao M, Fujisawa T, Ihara T, Kino Y. Highly increased levels of IgE antibodies to vaccine components in children with influenza vaccine–associated anaphylaxis. J Allergy Clin Immunol 2016;137:861–7. [PubMed: 26365388]
39. Russell M, Pool V, Kelso JM, Tomazic-Jezic VJ. Vaccination of persons allergic to latex: a review of safety data in the Vaccine Adverse Event Reporting System (VAERS). Vaccine 2004;23:664–7. [PubMed: 15542187]
40. Arroabarren E, Anda M, Sanz ML. Anaphylaxis to pneumococcal vaccine; CRM(197): novel cause of vaccine allergy. Pediatr Allergy Immunol 2016;27:425–37.
41. Ruggeberg JU, Gold MS, Bayas JM, Blum MD, Bonhoeffer J, Friedlander S, et al. Anaphylaxis: case definition and guidelines for data collection, analysis, and presentation of immunization safety data. Vaccine 2007;25:5675–84. [PubMed: 17448577]
42. Sampson HA, Mûnoz-Furlong A, Bock SA, Schmitt C, Bass R, Chowdary BA, 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;117:391–7. [PubMed: 16461139]

43. Bohlke K, Davis RL, Marcy SM, Braun MM, DeStefano F, Black SB, et al. Risk of anaphylaxis after vaccination of children and adolescents. Pediatrics 2013;112: 815–20.
44. McNeil MM, Weintraub ES, Duffy J, Sukumaran L, Jacobsen SJ, Klein NP, et al. Risk of anaphylaxis after vaccination in children and adults. J Allergy Clin Immunol 2016;137:868–78. [PubMed: 26452420]
45. Brotherton JM, Gold MS, Kemp AS, McIntyre PB, Burgess MA, Campbell-Lloyd S, et al. Anaphylaxis following quadrivalent human papillomavirus vaccination. CMAJ 2008;179:525–33. [PubMed: 18762618]
46. Zhou W, Pool V, Iskander JK, English-Bullard R, Ball R, Wise RP, et al. Surveillance for safety after immunization: Vaccine Adverse Event Reporting Systemn (VAERS)—United States, 1991–2001. MMWR Surveill Summ 2003;52:1–24.
47. Kelso J, Mootrey GT, Tsai TF. Anaphylaxis from yellow fever vaccine. J Allergy Clin Immunol 1999;103:698–701. [PubMed: 10200022]
48. Erlewyn-Lajeunesse M, Hunt LP, Heath PT, Finn A. Anaphylaxis as an adverse event following immunization in the UK and Ireland. Arch Dis Child 2012;97: 487–90. [PubMed: 22275307]
49. Cheng DR, Perret KP, Choo S, Danchin M, Buttery JP, Crawford NW. Pediatric anaphylactic adverse events following immunization in Victoria, Australia from 2007 to 2013. Vaccine 2015;33:1602–7. [PubMed: 25698493]
50. McNeil MM, Gee J, Weintraub ES, Belongia EA, Lee GM, Glanz JM, et al. The Vaccine Safety Datalink: successes and challenges monitoring vaccine safety. Vaccine 2014;32:5390–8. [PubMed: 25108215]
51. Sargant N, Erlewyn-Lajeunesse M, Benger J. Does anaphylaxis masquerade as asthma in children? Emerg Med 2015;32:83–4.
52. Tavares F, Delaigle A, Slavin D, Bauchau V, Fries L, Siefert H. Anaphylaxis following H1N1 pandemic vaccines: safety data in perspective. Vaccine 2011;29:6402–7. [PubMed: 21527305]
53. Erlewyn-Lajeunesse M, Dymond S, Slade I, Mansfield HL, Fish R, Jones O, et al. Diagnositic utility of two case definitions for anaphylaxis: a comparison using a retrospective case notes analysis in the UK. Drug Saf 2010;33:57–64. [PubMed: 20000867]
54. González-Pérez A, Aponte Z, Vidaurre CF, Rodríguez LA. Anaphylaxis epidemiology in patients with and patients without asthma: a United Kingdom database review. J Allergy Clin Immunol 2010;125:1098–104. [PubMed: 20392483]
55. Clark S, Wei W, Rudders SA, Camargo CA Jr. Risk factors for severe anaphylaxis in patients receiving anaphylaxis treatment in US emergency departments and hospitals. J Allergy Clin Immunol 2014;134:1125–30. [PubMed: 24985399]
56. Chen W, Mempel M, Schober W, Behrendt H, Ring J. Gender difference, sex hormones, and immediate type hypersensitivity reactions. Allergy 2008;63:1418–27. [PubMed: 18925878]
57. Decker WW, Campbell RL, Manivannan V, Luke A, St Sauver JL, Weaver A, et al. The etiology and incidence of anaphylaxis in Rochester, Minnesota: a report from the Rochester Epidemiology Project. J Allergy Clin Immunol 2008;122: 1161–5. [PubMed: 18992928]
58. Cook IF. Sexual dimorphism of humoral immunity with human vaccines. Vaccine 2008;26:3551–5. [PubMed: 18524433]
59. Cook IF. Sex differences in injection site reactions with human vaccines. Hum Vaccin 2009;5:441–9. [PubMed: 19377279]
60. Klein SL, Jedlicka A, Pekosz A. The Xs and Y of immune responses to viral vaccines. Lancet Infect Dis 2010;10:338–49. [PubMed: 20417416]
61. Engler RJ, Nelson MR, Klote MM, VanRaden MJ, Huang CY, Cox NJ, et al. Half vs full-dose trivalent inactivated influenza vaccine (2004–2005): age, dose, and sex effects on immune responses. Arch Intern Med 2008;168:2405–14. [PubMed: 19064822]
62. Nichol KL, Margolis KL, Lind A, Murdoch M, McFadden R, Hauge M, et al. Side effects associated with influenza vaccination in healthy working adults. A randomized, placebo–controlled trial. Arch Intern Med 1996;156:1546–50. [PubMed: 8687262]
63. Khalil MK, Al-Mazrou YY, Al-Ghamdi YS, Tumsah S, Al-Jeffri M, Meshkhas A. Effect of gender on reporting of MMR adverse events in Saudi Arabia. East Mediterr Health J 2003;9:152–8. [PubMed: 15562745]

64. Benjamin CM, Chew GC, Silman AJ. Joint and limb symptoms in children after immunisation with measles, mumps, and rubella vaccine. BMJ 1992;304:1075–8. [PubMed: 1586818]
65. Pennell LM, Galligan CL, Fish EN. Sex affects immunity. J Autoimmun 2012;38: 282–91.
66. Verthelyi D Sex hormones as immunomodulators in health and disease. Int Immunopharmacol 2001;1:983–93. [PubMed: 11407317]
67. Hox V, Desai A, Bandara G, Gilfillan AM, Metcalfe DD, Olivera A. Estrogen increases the severity of anaphylaxis in female mice through enhanced endothelial nitric oxide synthase expression and nitric oxide production. J Allergy Clin Immunol 2015;135:729–36. [PubMed: 25553642]
68. Bektas A, Schurman SH, Sen R, Ferrucci L. Human T cell immunosenescence and inflammation in aging. J Leukoc Biol 2017;102:977–88. [PubMed: 28733462]
69. Vesikari T, Pellegrini M, Karvonen A, Groth N, Borkowski A, O'Hagan DT, et al. Enhanced immunogenicity of seasonal influenza vaccines in young children using MF59 adjuvant. Pediatr Infect Dis J 2009;28:563–71. [PubMed: 19561422]
70. Nolan T, Bravo L, Ceballos A, Mitha E, Gray G, Quiambao B, et al. Enhanced and persistent antibody response against homologous and heterologous strains elicited by a MF59Ò-adjuvanted influenza vaccine in infants and young children. Vaccine 2014;32:6146–56. [PubMed: 25223266]
71. An Advisory Committee Statement (ACS) National Advisory Committee on Immunization (NACI), Canadian Immunization Guide Chapter on Influenza and Statement on Seasonal Influenza Vaccine for 2015–2016. Ottawa, Ontario, Canada: Public Health Agency of Canada; 2015.
72. Yang LPH. Recombinant trivalent influenza vaccine (FlublokÒ): a review of its use in the prevention of seasonal influenza in adults. Drugs 2013;73:1357–66. [PubMed: 23928902]
73. Woo EJ, Moro PL, Cano M, Jankoskyi C. Allergic reactions after egg-free recombinant influenza vaccine: reports of the US Vaccine Adverse Event Reporting System. Clin Infect Dis 2015;60:777–80. [PubMed: 25428412]
74. Shimabukuro TT, Nguyen M, Martin D, DeStefano F. Safety monitoring in the Vaccine Adverse Event Reporting System (VAERS). Vaccine 2015;33: 4398–405. [PubMed: 26209838]
75. Glanz JM, Newcomer SR, Hambidge SJ, Daley MF, Narwaney KJ, Xu S, 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;165:749–55. [PubMed: 21810637]
76. Anonymous. Worldwide variation in prevalence of symptoms of asthma, allergic rhinoconjunctivitis, and atopic eczema. The International Study of Asthma and Allergies in Childhood (ISAAC) Steering Committee. Lancet 1998;351:1225–32.
77. Strachan DP. Hay fever, hygiene, and household size. BMJ 1989;299:1259–60. [PubMed: 2513902]
78. Brooks C, Pearce N, Douwes J. The hygiene hypothesis in allergy and asthma: an update. Curr Opinion Allergy Clin Immunol 2013;13:70–7.
79. Romagnani S The increased prevalence of allergy and the hygiene hypothesis: missing immune deviation, reduced immune suppression, or both? Immunology 2004;112:352–63. [PubMed: 15196202]
80. Stiemsma LT, Reynolds LA, Turvey SE, Finlay BB. The hygiene hypothesis: current perspectives and future therapies. Immunotargets Ther 2015;4:143–57. [PubMed: 27471720]
81. Kemp A, Bj€orksten KA. Immune deviation and the hygiene hypothesis: a review of the epidemiological evidence. Pediatr Allergy Immunol 2003;14:74–80. [PubMed: 12675752]
82. Keet CA, Savage JH, Seopaul S, Peng RD, Wood RA, Matsui EC. Temporal trends and racial/ethnic disparity in self-reported pediatric food allergy in the United States. Ann Allergy Asthma Immunol 2014;112:222–9. [PubMed: 24428971]
83. Reynolds LA, Finlay BB. Early life factors that affect allergy development. Nat Rev Immunol 2017;17:518–28. [PubMed: 28504257]
84. Schlaud M, Schmitz R, Poethko-Müller C, Kuhnert R. Vaccinations in the first year of life and risk of atopic disease—results from the KiGGS study. Vaccine 2017;35:5156–62. [PubMed: 28801155]
85. Kiraly N, Koplin JJ, Crawford NW, Bannister S, Flanagan KL, Holt PG, et al. Timing of routine infant vaccinations and risk of food allergy and eczema at one year of age. Allergy 2016;71:541–9. [PubMed: 26707796]

What do we know?

- Severe allergic reactions to vaccines are rare. Several studies indicate a female predominance and often prior atopy.
- Anaphylaxis is an uncommon and potentially life-threatening allergic reaction that can occur immediately (usually within minutes) after exposure to a vaccine or vaccines.
- Almost any vaccine can cause anaphylaxis, usually because of a vaccine component (eg, egg protein) rather than the vaccine antigen.
- Data from a large epidemiologic study found that anaphylaxis after vaccination (including seasonal influenza vaccines) occurred at a rate of 1.31 for every million vaccine doses given.
- Despite the rarity of postvaccination anaphylaxis, vaccine providers and facilities providing vaccinations should have procedures in place for anaphylaxis management.

What is still unknown?

- Will recent changes in vaccine technology (use of cell-based methods, new adjuvants, and novel influenza vaccines [quadrivalent, high dose, and recombinant]) be factors associated with postvaccination allergic reactions? It will be important to maintain vaccine safety monitoring for anaphylaxis and other allergic reactions.
- What is the immunopathogenesis of postvaccination allergy and in particular anaphylaxis?
- What is the role of sex hormones or other factors in explaining a possible sex difference in the occurrence of postvaccination allergic reactions?
- What is the role of repeated annual inactivated influenza vaccine doses in allergic reactions?
- Is there an association between the number of vaccine antigens and allergic outcomes?
- Is there an association between the timing of routine infant vaccinations and susceptibility to allergic disease?

Table I.

Selected studies with summary rates of anaphylaxis following immunization

Surveillance type, program	Period	Vaccine	Anaphylaxis rate per 100,000	95% CI
Population based				
Bohlke et al, United States[43]	1991–1997	All vaccines	0.07	0.21–0.15
McNeil et al, United States[44]	2009–2011	All vaccines	0.13	0.09–0.18
School based				
Brotherton et al, Australia[45]	April-December 2007	4vHPV vaccine	2.60	1.04–5.35
State/province/national passive surveillance				
Zhou et al, United States[46]	1991–2001	All vaccines	0.02	0.022–0.026
Pool et al, United States[21]	1991–1997	MMR	0.18	0.15–0.21
Kelso et al, United States[47]	1990–1997	Yellow fever vaccine	0.76	0.55–1.04
Erlewyn-Lajeunesse et al, United Kingdom[48]	September 2008-October 2009	Measles vaccine	12.0	—
		2vHPV vaccine	0.14	—
Rouleaux et al, Quebec, Canada[27]	October 2009-December 2009	AS03-adjuvanted A(H1N1)pdm09 vaccine	1.3	1.0–1.7
Cheng et al, New South Wales, Australia[49]	May 2007-May 2013	DTaP	0.36	0.32–0.40
		MMR	1.25	1.18–1.32

AS03, Adjuvant system 03.

J Allergy Clin Immunol. Author manuscript; available in PMC 2019 July 01.

Table II.

Incidence of vaccination-triggered anaphylaxis by age, sex, year, and vaccine type[44]

	No. of cases	Doses administered	Rate (/10^6 doses)	Lower 95% CI	Upper 95% CI
Age group (y)					
0–17	18	12,403,201	1.45	0.86	2.29
18–49	9	5,063,802	1.78	0.81	3.37
≥50	6	7,706,962	0.78	0.29	1.69
Sex					
Female	20	13,770,592	1.45	0.89	2.24
Male	13	11,403,373	1.14	0.61	1.95
Year					
2009	11	8,535,631	1.29	0.64	2.31
2010	8	8,207,595	0.98	0.42	1.92
2011	14	8,430,739	1.66	0.91	2.79
Vaccine *					
Any Hep B	0	1,287,074	0	0.00	2.87
RV1	0	57,517	0	0.00	64.13
RV5	0	636,756	0	0.00	5.79
Any DTaP	3	1,449,370	2.07	0.43	6.05
Any HIB	0	1,143,025	0	0.00	3.23
PCV7	0	558,201	0	0.00	6.61
PCV13	0	742,467	0	0.00	4.97
PPSV23	2	698,482	2.86	0.35	10.34
Any IPV	2	1,215,163	1.65	0.20	5.95
TTV	14	8,830,935	1.59	0.87	2.66
LATV	0	530,737	0	0.00	6.95
MIV	3	1,422,921	2.11	0.43	6.16
LAMV	0	298,721	0	0.00	12.35
Other influenza	0	36,338	0	0.00	101.51
Any influenza	17	11,119,652	1.53	0.89	2.45
MMR	3	584,103	5.14	1.06	15.01

	No. of cases	Doses administered	Rate (/10^6 doses)	Lower 95% CI	Upper 95% CI
MMRV	2	100,897	19.8	2.40	71.60
VAR	6	866,129	6.93	2.54	15.08
HAV	4	1,197,047	3.34	0.91	8.56
Tdap	9	3,116,161	2.89	1.32	5.48
Td	0	203,970	0	0.00	18.09
HPV4	1	775,833	1.29	0.03	7.18
MCV4	4	649,199	6.16	1.68	15.78
HZV	2	304,001	6.58	0.80	23.77
Rabies	1	18,041	55.43	1.40	308.79
Typhoid	0	164,483	0	0.00	22.43
YFV	0	34,176	0	0.00	107.93
JEV	0	4,448	0	0.00	828.99
Anthrax	0	81	0	0.00	44520.26
Smallpox	0	31	0	0.00	112188.75
All Vaccines	33	25,173,965	1.31	0.90	1.84

HAV, Hepatitis A vaccine; HIB, Haemophilus influenzae type B vaccine; HPV4, quadrivalent human papillomavirus vaccine; *HZV*, herpes zoster vaccine; *IPV*, inactivated polio vaccine; *JEV*, Japanese encephalitis vaccine; *LAIV*, live attenuated influenza vaccine; *LAMV*, live attenuated monovalent influenza vaccine; *MCV4*, meningococcal conjugate vaccine; *MIV*, influenza A(H1N1)pdm09 monovalent vaccine; MMRV, measles, mumps, rubella, and varicella vaccine; *PCV*, pneumococcal conjugate vaccine; *PPSV*23, pneumococcal polysaccharide vaccine (23-valent); *RV*, rotavirus vaccine; VAR, varicella vaccine; *YFV*, yellow fever vaccine.

* Total count of greater than 33 for vaccines received because some cases received more than 1 vaccine. This includes doses administered alone and coadministered with other vaccines.

J Allergy Clin Immunol. Author manuscript; available in PMC 2019 July 01.

Table III.

Vaccine-specific incidence of anaphylaxis[44]

Vaccine (administered alone)	No. of cases (n = 18)	Doses given alone*	Rate (/10^6 doses)	Lower 95% CI	Upper 95% CI
TTV	10	7,434,628	1.35	0.65	2.47
MIV	2	1,090,279	1.83	0.22	6.63
Tdap	1	1,951,153	0.51	0.01	2.86
PPSV23	1	403,803	2.48	0.06	13.80
HAV	1	296,271	3.38	0.09	18.81
HZV	2	208,407	9.60	1.16	34.67
Rabies	1	11,619	86.1	2.18	479.43

HAV, Hepatitis A vaccine; *HZV*, herpes zoster vaccine; *MIV*, influenza A(H1N1)pdm09 monovalent vaccine; *PPSV*23, pneumococcal polysaccharide vaccine (23-valent).

*Doses of specified vaccine administered without any other concomitant vaccines.

J Allergy Clin Immunol. Author manuscript; available in PMC 2019 July 01.