Published in final edited form as:

Curr Treat Options Allergy. 2019 September ; 6(3): 297–308. doi:10.1007/s40521-019-00215-0.

Vaccine-Associated Anaphylaxis

Michael M. McNeil, MD, MPH

Immunization Safety Office, Division of Healthcare Quality Promotion, National Center for Zoonotic and Emerging Infectious Diseases, Centers for Disease Control and Prevention, Mailstop V18-4, CDC, 1600 Clifton Rd, Atlanta, GA, 30333, USA

Abstract

Purpose of Review—Anaphylaxis is a rare, serious hypersensitivity reaction following vaccination, which is rapid in onset and characterized by multisystem involvement. Although anaphylaxis may occur after any vaccine, understanding the risk for this outcome, particularly following influenza vaccines, is important because of the large number of persons vaccinated annually. *Recent Findings* Two recent CDC safety studies confirmed the rarity of post-vaccination anaphylaxis. In a 25-year review of data from the Vaccine Adverse Event Reporting System (VAERS), reports in children were most common following childhood vaccinations and among adults more often followed influenza vaccine. In a Vaccine Safety Datalink (VSD) study, the estimated incidence of anaphylaxis was 1.3 per million vaccine doses administered for all vaccines and 1.6 per million doses for IIV3 (trivalent) influenza vaccine.

Summary—Despite its rarity, its rapid onset (usually within minutes) and potentially lethal nature require that all personnel and facilities providing vaccinations have procedures in place for anaphylaxis management.

Keywords

Anaphylaxis; Influenza vaccination; Surveillance; Vaccine safety

Anaphylaxis

Anaphylaxis is an acute, systemic, and potentially life-threatening hypersensitivity reaction with multiple organ system involvement [1]. In the USA, the rate of anaphylaxis from all causes is as high as 100 cases per 100,000 population and is associated with as many as 1,000 deaths per year [2]. The major systems involved include the skin, cardiovascular,

mmm2@cdc.gov.

Conflict of Interest

Michael M. McNeil declares that he has no conflict of interest.

Human and Animal rights and Informed Consent

This article does not contain any studies with human or animal subjects performed by any of the authors.

Disclaimer

The findings and conclusions in this report are those of the author and do not necessarily represent the official position of the Centers for Disease Control and Prevention (CDC). Use of trade names and commercial sources is for identification only and does not imply endorsement by the Centers for Disease Control and Prevention or the US Department of Health and Human Services.

Publisher's Note

Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.

respiratory, and gastrointestinal systems with common symptoms being a generalized urticarial rash, airway swelling and difficulty breathing, hypotension and nausea and vomiting [2–5]. In a specific individual, the severity and type of symptoms experienced may vary depending upon the predominant system(s) affected. The underlying pathophysiologic mechanism is the sudden release of pre-formed mediators (histamine and others) contained in mast cell and basophil granules into the systemic circulation. This rapid "degranulation" occurs most often in individuals sensitized by a prior exposure to an antigen, where that exposure leads to the production of IgE antibodies, which bind to the surface of the mast cells and basophils [3–5]. A subsequent exposure to the same antigen (now allergen) precipitates the degranulation process. Less commonly, degranulation due to non-immunologic mechanisms can also occur (e.g., certain drugs acting directly on mast cells). Many different potential allergenic exposures have been associated with the development of IgE-mediated anaphylaxis including food (e.g., milk, eggs, peanuts, shellfish, gelatin), food additives (e.g., yeast), venoms (e.g., insect stings), environmental exposures (e.g., grass pollen), latex (e.g., surgical gloves), diagnostic reagents (e.g., radiographic contrast media), drugs (e.g., antibiotics, nonsteroidal anti-inflammatory drugs), and immunizations [1–6].

Hypersensitivity reactions following vaccination are not uncommon; however fortunately, these are often non-serious, and in many instances, they may not be immunologically mediated and not reproducible on re-exposure [6, 7, 8•, 9•]. Serious post-vaccination immunologically mediated reactions, including anaphylaxis, are exceedingly rare. However, virtually all vaccines have the potential to trigger these outcomes [10]. In a patient with vaccine-associated, potentially immunologically mediated, hypersensitivity, it is important to identify the mechanism of the reaction. If there is confirmation of acute hypersensitivity, and the patient is required to receive a further vaccine dose(s), desensitization to the vaccine may be undertaken or, in a low-risk individual, the vaccine may be administered in split doses (one-tenth of the dose and then nine-tenths of the dose) [6].

Vaccine Components Known to Cause Hypersensitivity

In addition to the active component (the antigen) which induces the immune response, other potentially allergenic vaccine constituents include residual animal protein, antimicrobial agents, preservatives, stabilizers, adjuvants, and other components [6, 7, 8•, 9•]. Individual vaccine ingredients implicated in causing acute vaccine reactions include egg protein, gelatin, milk proteins, and other additives and trace compounds remaining from the manufacturing process. Natural rubber latex, which may be in the syringe plunger, the tips of pre-filled syringes and vaccine vial stoppers, is another potential trigger for anaphylaxis [6, 7, 8•, 9•]. The manufacturer's package insert for each of the currently available US licensed vaccines may be found on the FDA website at https://www.fda.gov/BiologicsBloodVaccines/Vaccines/ApprovedProducts/ucm093833.htm and lists the amount and the purpose of each excipient and media substance contained in the vaccine. This information is consolidated in the CDC Pink Book Vaccine Excipient and Media Summary (excipients included in US vaccines, by vaccine summary table available at https://www.cdc.gov/vaccines/pubs/pinkbook/downloads/appendices/b/excipient-table-2.pdf

There are several recent published reviews detailing the role of different excipients and media in vaccines, which have the potential to cause hypersensitivity reactions including anaphylaxis [6, 7, 8•, 9•]. This review will not discuss these further with the exception of egg protein, which has been of concern recently with influenza vaccines and stimulated revised recommendations from the CDC's Advisory Committee on Immunization Practices (ACIP)

Egg allergy is the most frequent type of food allergy among children with sensitizations occurring particularly in children before 5 years of age. Exposure to commonly used vaccines that contain small amounts of residual egg protein (ovalbumin) from the vaccine manufacturing process has been of concern as a possible cause of acute onset hypersensitivity reactions, including anaphylaxis. Ovalbumin concentration in vaccines is not always reported and can vary among vaccine brands and batches. Concentrations are usually higher in vaccines cultured on embryonic chicken eggs (influenza, yellow fever, and rabies) and lower in vaccines cultured on fibroblasts of chicken embryos (measles, mumps, and rubella vaccine [MMR; Merck, Whitehouse Station, NJ]) [6, 7, 8•, 9•]. Most of the studies that have assessed the safety of vaccines containing egg proteins in patients with egg allergy have evaluated the influenza vaccines.

Influenza Vaccine and Egg Allergy

Following the 2010 recommendations by the ACIP for universal annual influenza vaccination of all persons older than 6 months of age [10], the total number of influenza doses distributed in the USA has steadily increased up to approximately 155 million in the 2017–2018 season (the last season with complete data) (https://www.cdc.gov/flu/professionals/vaccination/vaccinesupply.htm). This dramatic increase in vaccination coverage recently prompted increased concern for rare vaccine adverse events including acute hypersensitivity and anaphylaxis resulting from egg protein contained in certain influenza vaccines. A review of recently available evidence from several studies in the medical literature has shown that severe allergic reactions to the currently available egg-based vaccines in persons with egg allergy are rare, and therefore, the ACIP has modified its recommendations for these individuals. The current 2018–2019 recommendations for influenza vaccination of persons with allergies state that persons with a history of egg allergy of any severity may receive any licensed, recommended, and age-appropriate influenza vaccine including inactivated influenza vaccine (IIV), quadrivalent recombinant influenza vaccine (RIV4), or quadrivalent live attenuated influenza vaccine (LAIV4) [11••]. However, persons with a history of severe allergic reaction to egg should be vaccinated in a medical setting and the vaccine administration supervised by a health care provider able to recognize and manage severe allergic conditions. Despite there being no specific post-vaccination observation period recommended for egg-allergic persons, the ACIP's General Best Practice Guidance (https://www.cdc.gov/vaccines/hcp/acip-recs/general-recs/index.html) advises providers to consider observing vaccinees for 15 minutes following any vaccine administration to lessen the risk of injury should syncope occur. While the ACIP recommendation reflects official CDC policy, the guidance provided by the American Academy of Pediatrics (AAP) for the 2018–2019 season is a more general policy, which

states that children with egg allergy can receive influenza vaccine with no additional precautions than those considered for any vaccine [12].

Recent CDC Anaphylaxis Surveillance and Research Studies

Before discussing specific studies on anaphylaxis, a brief overview of the CDC vaccine safety infrastructure and the standard Brighton Collaboration case definition used in these studies is in order.

The CDC Vaccine Safety Infrastructure

Vaccines, like other pharmaceutical products, undergo extensive safety and efficacy evaluations in the laboratory, in animals, and in sequentially phased human clinical trials (Fig. 1). Initial human studies, referred to as phase 1, are safety and immunogenicity studies performed in a small number of closely monitored subjects. Phase 2 studies are dose-ranging studies, which may enroll up to a few hundred subjects. Finally, phase 3 trials typically involve many thousands of individuals and may require several years to complete; however, these provide critical documentation of the vaccine's effectiveness and important additional safety data required for licensing. Following successful completion of all three phases of clinical development, the vaccine manufacturer submits a biologic license application (BLA) to the FDA. Consideration of the BLA by the FDA involves review by a multidisciplinary expert panel of the efficacy and safety information from the clinical trials, to inform a risk/benefit assessment and to make a recommendation (or not) for approval of the vaccine. As part of the overall evaluation, the FDA also reviews the product labeling, the manufacturing facility, and the manufacturing protocols. However, following successful approval by the FDA, the agency continues to oversee the production of the vaccine to ensure continuing safety. In addition, many vaccines undergo phase 4 studies sponsored by the manufacturer, which are formal studies conducted once the vaccine is on the market.

Following licensing, the ACIP makes specific recommendations for the incorporation of the vaccine into the age-appropriate routine immunization schedule following an in-depth review of vaccine-related data, including data on disease epidemiology, vaccine efficacy and effectiveness, vaccine safety, feasibility of program implementation, and economic aspects of immunization policy [13]. However, even the largest pre-licensure trials are inadequate to assess the vaccine's potential to induce rare adverse events. Therefore, post-licensure safety monitoring is critical because extremely rare serious adverse events (e.g., anaphylaxis), adverse events with delayed onset (e.g., Guillain Barré syndrome), or adverse events in specific subpopulations (e.g., pregnant women) are unlikely to be detected and assessed until the vaccine is more widely used in the population. Following licensure by FDA, and often along with recommendations by ACIP, vaccines are continuously monitored for safety by CDC and FDA (Fig. 1). FDA and CDC rely upon various post-licensure surveillance systems to detect and study adverse events that occur after immunizations, and further discussion will describe the approach and three of these systems in use by the CDC.

The CDC surveillance and research activities prioritize the safety evaluation of new vaccines and established vaccines where there has been a change in the recommendations (e.g., Tdap vaccine in pregnant women). A long-standing focus of the CDC research agenda is the

pharmacovigilance safety assessment of the annual seasonal influenza vaccines, which have traditionally been IIV3 (trivalent) vaccines, and these in some years have included strain changes to match the circulating viruses. In 2009, there was the novel pandemic H1N1 monovalent vaccine. However, new influenza vaccines continue to be introduced (quadrivalent, high dose, adjuvanted, cell culture-based, and recombinant) and require rapid safety assessment through pharmacovigilance reports as well as epidemiologic studies to investigate any potential safety signals.

CDC uses three complementary systems to monitor and study the safety of US licensed vaccines (Table 1). These include the Vaccine Adverse Event Reporting System (VAERS), the Vaccine Safety Datalink (VSD), and the Clinical Immunization Safety Assessment (CISA) project. The VAERS is a national, spontaneous surveillance system co-managed with FDA, which receives more than 40,000 AE reports annually following all US licensed vaccines [14]. Healthcare providers, vaccine manufacturers, vaccine recipients, and the public can report to the VAERS, which serves as an “early warning” system and is useful for detecting rare, serious longer-term adverse events following immunization (AEFI), which may have gone undetected in pre-licensure human clinical trials. However, VAERS is subject to several limitations including under-reporting, reporting biases, inconsistent data quality and completeness, changes in reporting over time, and the lack of an unvaccinated comparison group. Consequently, VAERS data generally cannot establish if a vaccine caused a particular AEFI, including anaphylaxis. Thus, VAERS serves primarily for hypothesis generation, and once an AEFI signal is identified, this can be further studied in a more robust system such as the VSD.

The VSD is a collaboration between CDC and eight large integrated healthcare organizations, which has large linked databases containing vaccination records and health outcomes data from electronic medical records for a population of more than 12 million people (approximately 3% of US population), which are used for active surveillance and research [15]. A novel approach to expedite the timeliness of post-marketing safety monitoring in VSD is through rapid cycle analysis (RCA), which permits near “real-time” surveillance of pre-specified AEs for priority vaccines (e.g., annual seasonal influenza vaccines, newly licensed vaccines). Anaphylaxis is an outcome routinely included among these pre-specified AEs.

The CISA project is a collaboration of vaccine safety experts from the CDC’s Immunization Safety Office (ISO), seven academic medical research centers, and other partners [16]. The CISA project serves as a vaccine safety resource for US healthcare providers with complex vaccine safety questions about a specific patient to assist with immunization decision-making; it also conducts clinical research to better understand vaccine safety and identify preventive strategies for AEFI and assists CDC and its partners in evaluating emerging vaccine safety issues. Although not discussed further, CISA project collaborators have recently authored several publications on anaphylaxis [6, 7, 17].

Brighton Collaboration Case Definition of Anaphylaxis

Standardized case definitions are crucial in epidemiologic studies as well as human clinical trials. In 2007, the Brighton Collaboration published a standardized surveillance case

definition for post-vaccination anaphylaxis [18]. In general, the Brighton Collaboration case definitions are considered as the gold standard surveillance case definitions for post-vaccination AEs, including anaphylaxis. These criteria designate different levels of diagnostic certainty of the relevant AEFI and are proposed for use in vaccine clinical trials and safety surveillance and research studies. The Brighton Collaboration criteria are distinct from the more specific Second National Institute of Allergy Diseases (NIAID)/Food Allergy and Anaphylaxis (FAAN) criteria published in 2006, which are principally used for the clinical assessment of patients [19].

Anaphylaxis in VAERS

Recently, Su and colleagues reported the findings from their review of US reports of anaphylaxis received by VAERS during 1990–2016 [20•]. These investigators evaluated available data on reports describing symptom onset in the patient within 1 day of receiving vaccine, including a prior history of hypersensitivity, the type of vaccine(s) administered and assessed from the medical records whether the report met the Brighton Collaboration case definition for anaphylaxis or was diagnosed by a physician. During the 26-year study period, a total 828 reported cases were identified which either met the Brighton Collaboration case definition for anaphylaxis or were physician-diagnosed with anaphylaxis. The median age of the cases was 12 years (range, < 1 to 86); however, there were some differences between children and adults. Children aged < 19 years accounted for 478 reports, of which 65% were male. Of the total 828 case reports, 41% described persons with no history of hypersensitivity. There were also 8 death reports; in 7 of these anaphylaxis was identified as the cause of death, and in 6, there was rapid onset of symptoms (within 20 minutes) following vaccination suggesting vaccine exposure as the trigger (one report identified onset of fatal anaphylaxis within 2 minutes following concomitant receipt of trivalent influenza vaccine and intramuscular ceftriaxone in a penicillin allergic adult). The most commonly reported vaccines found associated with anaphylaxis in the VAERS review were influenza vaccines (all types, $n = 330$, 40%); however, among children, routine childhood vaccines (i.e., MMR, varicella, DTaP, Tdap) predominated, and among adults, influenza vaccine (all types) was the commonest vaccine type. Of note, among the 467 individuals who received only a single vaccine, the most commonly reported vaccine was influenza vaccine (all types; $n = 254$, [54%] reports).

These investigators commented that consistent with earlier studies, they found there was a preponderance of males in the younger age group and females in the older age group, symptom onset was rapid within 2 hours after vaccination, and the majority had a prior history of hypersensitivity including asthma and drug allergies [20•]. However, contrary to other studies, 41% of reports described no apparent history of hypersensitivity and more than 89% of reports indicated treatment with epinephrine, the first-line treatment for anaphylaxis. The study also identified rare anaphylaxis death reports, some without a prior history of hypersensitivity supporting the need for vaccine providers to be vigilant when administering all vaccines and prepared for immediate intervention, if needed.

Anaphylaxis in VSD

A recent study in the VSD evaluated the risk of anaphylaxis after vaccination in children and adults [21]. The study used data on health plan enrollees who received 25,178,965 vaccine doses during the period January 2009–December 2011. These investigators used diagnostic and procedure codes to identify potential anaphylaxis cases, and then reviewed the medical records of the suspected cases to confirm the diagnosis, apply the Brighton Collaboration case definition for anaphylaxis, and determine the vaccine trigger. The study identified a total of 33 persons with anaphylaxis (Brighton level 1or 2) associated with vaccination for an estimated overall incidence of 1.31 per million vaccine doses administered; the incidence did not differ significantly by age, and there was a non-significant female predominance only among adults. IIIV3 (trivalent) vaccine accounted for 14 of the cases, for which the rate was estimated to be 1.59 per million vaccine doses and no cases occurred following 530,737 LAIV doses. Twenty-eight (85%) cases had a prior history of atopy (anaphylaxis, asthma, or other specific allergies) [21]. This large population study also found no deaths among cases and no cases in children aged less than 4 years.

What the VAERS and VSD Studies Show

The VAERS and VSD studies summarized above provide complementary information from two of the CDC vaccine safety systems on anaphylaxis after vaccination. Both studies applied the Brighton Collaboration case definition for anaphylaxis and reviewed medical records (although the latter was less complete for VAERS). The VAERS review of 26 years of passive reports had a greater ability to identify cases (i.e., total 828 cases) whereas the VSD analysis allowed a more robust estimation of risk. Although these studies confirm its rarity after vaccination (1.3 cases per million vaccine doses administered), anaphylaxis can be a life-threatening event. Anaphylaxis after influenza vaccines is of particular concern because of the large number of persons vaccinated annually. Influenza vaccines are unique in requiring annual review and possibly changes in the vaccine's antigenic composition to match the predicted circulating influenza strains. For this reason, vaccine safety surveillance systems specifically monitor for this outcome.

New Influenza Vaccines

Influenza vaccine manufacturing recently has become more varied (https://www.cdc.gov/flu/prevent/how-fluvaccine-made.htm?). Until recently, the standard manufacturing process for influenza vaccines involved propagation of the vaccine virus strain(s) in embryonated hens' eggs so that small amounts of residual ovalbumin were routinely included in these vaccines.

A recent innovation has been the introduction of cell-culture technology which involves propagating the viruses in mammalian (Madin-Darby canine kidney cells) in liquid culture rather than the traditional egg-based vaccine manufacturing process. Flucelvax® quadrivalent (ccIIV4; Seqirus) is manufactured using this process and approved for use in persons 4 years of age or greater. Through the current 2018–2019 US influenza season, one of the four vaccine viruses provided at the start of this vaccine's manufacturing process has been egg-derived, so that egg proteins might still be present in the finished vaccine; however,

this might change for the 2019–2020 season vaccine to make the entire production process exclusively cell-based (https://www.prnewswire.com/news-releases/seqirus-announces-further-advances-in-cell-based-influenza-vaccine-technology-300831979.html). Cell-based technology is more flexible than the traditional egg culture method and not reliant on an adequate egg supply; in addition, it has the potential advantage of a faster startup time in the event of a pandemic, and also the vaccine viruses are more similar to circulating influenza viruses because the virus grown in eggs can acquire egg-adapted changes that attenuate the vaccine's protective efficacy.

Since 2013, a novel process for manufacturing influenza vaccine using recombinant technology has been approved. This manufacturing process has advantages including the potential for a faster start-up, which might represent an advantage in the event of a pandemic or vaccine supply shortage, mainly because it is not dependent on an egg supply or limited by the selection of vaccine viruses that are adapted for growth in eggs. In 2013, the FDA licensed the first recombinant HA influenza vaccine (Flublok®, Sanofi Pasteur) as a trivalent product, and the vaccine was subsequently recommended by the ACIP as an vaccine alternative for persons with egg allergy. For the 2018–2019 season, the vaccine is available as a quadrivalent formulation licensed for use in persons aged 18 years and above [11••]. The manufacturing process involves replication of influenza HA protein using insect cells and produces purified HA that contains no egg protein, preservatives, or antibiotics. Although free of egg protein, allergic reactions following Flublok® have been reported to VAERS among patients with a self-reported egg allergy or prior allergic reactions to IIV, although it is not known what triggered the reaction in these cases [22].

IIV3 (trivalent) vaccines which protect against 3 different viruses (influenza A H1N1 virus, influenza H3N2 virus, and 1 type B virus) have been the standard; however since 2013, to provide broader protection against circulating influenza viruses, IIV4 (quadrivalent) influenza vaccines, which contain 2 B strains in addition to 2 A strains, have been licensed and approved. Currently in the USA, there is an IIV4 (quadrivalent) product for all the influenza vaccines, with the exception of two vaccines targeted to protect the elderly (persons aged 65 years and older), (1) IIV3 (trivalent) HD (Fluzone® High-Dose, Sanofi Pasteur) vaccine with 4 times the amount of antigen contained in regular IIV3 (trivalent) vaccine, and (2) aIIV3 (Fluad,® Seqirus) vaccine formulated with the adjuvant MF59, which is recommended for adults aged 65 years and older. https://www.cdc.gov/flu/protect/vaccine/how-fluvaccine-made.htm. Other new adjuvanted vaccines have been introduced for the prevention of herpes zoster and hepatitis B. To date, there has been no evidence from either pre-clinical or post-marketing data that anaphylaxis or other serious AEFIs are associated with any of the new adjuvanted vaccines. Despite some increased reactogenicity, there has been vigorous uptake of both aIIV3 and RZV (Shingrix® GlaxoSmithKline) vaccines; however to date, the use of new hepatitis B vaccine (recombinant) (Heplisav-B®, Dynavax) vaccine has been quite limited. Post-marketing data from the VAERS for the aIIV3 vaccine found only commonly reported symptoms of fever, injection site pain, and injection site erythema, but no unexpected patterns or serious AEFIs were detected, and the overall assessment was consistent with the safety profile observed in pre-licensure clinical trials [23].

In summary, pharmacovigilance and epidemiologic studies conducted in large populations receiving currently used vaccines, confirm the rarity of post-vaccination anaphylaxis. Continuous monitoring of all new vaccines for safety using post-marketing, large-linked, data surveillance systems is routinely conducted by CDC and FDA; and anaphylaxis is included among the pre-specified outcomes monitored. Vaccine manufacturing processes have become more diverse, particularly for influenza vaccines (higher antigen, cell cultured, recombinant, and adjuvanted); of these, recombinant influenza vaccine is free of egg protein, which offers an additional option for persons with egg allergy. Providers should be aware of changing recommendations based on recent published evidence for persons with a history of egg allergy to receive annual influenza vaccination. Although anaphylaxis after immunization is rare, its immediate onset (usually within minutes) and life-threatening nature require that all personnel and facilities providing vaccinations be prepared to treat possible anaphylactic reactions.

Funding

This study was supported solely by the CDC, and no external funding was secured.

References and Recommended Reading

Papers of particular interest, published recently, have been highlighted as:

• Of importance

•• Of major importance

1. Wood RA, Camargo CA, Lieberman P, Sampson HA, Schwartz LB, Zitt M, et al. Anaphylaxis in America: the prevalence and characteristics of anaphylaxis in the United States. J Allergy Clin Immunol. 2014;133:461–7. [PubMed: 24144575]
2. Lee JK, Vadas P. Anaphylaxis mechanisms and management. Clin Exp Allergy. 2011;25:163–75.
3. Castells M and Diagnosis management of anaphylaxis. J Allergy Clin Immunol. 2017;140:321–33. [PubMed: 28780940]
4. Reber L, Hernandez JD, Galli SJ. The pathophysiology of anaphylaxis. J Allergy Clin Immunol. 2017;140:335–48. [PubMed: 28780941]
5. Jimenez-Rodriguez TW, Garcia-Neuer ALA, Castells M. Anaphylaxis in the 21st century: phenotypes, endotypes, and biomarkers. J Asthma Allergy. 2018;11:121–41. [PubMed: 29950872]
6. Dreskin SC, Halsey NA, Kelso JM, Wood RA, Hummell DS, Edwards KM, et al. International Consensus (ICON): allergic reactions to vaccines. World Allergy Organ J. 2016;9:32. [PubMed: 27679682]
7. Wood RA. Allergic reactions to vaccines. Pediatr Allergy Immunol. 2013;24:521–6. [PubMed: 23902374]
8. 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] • Important current review.
9. McNeil MM, DeStefano F. Vaccine-associated hyper-sensitivity. J Allergy Clin Immunol. 2018;141:463–72. [PubMed: 29413255] • Recent review paper.
10. Prevention and control of influenza with vaccines recommendations of the Advisory Committee on Immunization Practices (ACIP). MMWR Recomm Rep. 2010;59:1–62.
11. Grohskopf LA, Sokolow LZ, Broder KR, Walter EB, Fry AM, Jerningan DB. Prevention and control of seasonal influenza with vaccines: recommendations of the Advisory Committee on Immunization Practices-United States, 2018–19 influenza season. MMWR Recomm Rep. 2018;67:1–2.•• Recommendations on influenza vaccines in current season from ACIP.

12. Recommendations for Prevention and Control of Influenza in Children, 2018–2019. Pediatrics. 2018;142:e20182367. [PubMed: 30177511]
13. Smith JC, Snider DE, Pickering LK. Advisory Committee on Immunization Practices. Immunization policy development in the United States: the role of the Advisory Committee on Immunization Practices. Ann Intern Med. 2009;150(1):45–9. [PubMed: 19124820]
14. 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]
15. 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]
16. Williams SE, Klein NP, Halsey N, Dekker CL, Baxter RP, Marchant CD, et al. Overview of the clinical consult case review of adverse events following immunization: Clinical Immunization Safety Assessment (CISA) network 2004–2009. Vaccine. 2011;29:6920–7. [PubMed: 21801776]
17. Wood RA, Berger M, Dreskin SC, Setse R, Engler RJ, Dekker CL, et al. An algorithm for treatment of patients with hypersensitivity reactions after vaccines. Pediatrics. 2008;122:e771–7. [PubMed: 18762513]
18. Rüggeberg 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]
19. Sampson HA, Munoz-Furlong A, Campbell RL, Adkinson NF Jr, Bock SA, Branum A, 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]
20. Su JR, Moro PL, Ng CS, Lewis PW, Said MA, Cano MV. Anaphylaxis after vaccination reported to the Vaccine Adverse Event Reporting System, 1990–2016. J Allergy Clin Immunol. 2019;143:1465–73. [PubMed: 30654049] • Very recent VAERS report.
21. 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]
22. Woo EJ, Moro PL, Cano M, Jankosky C. Postmarketing safety surveillance of trivalent recombinant influenza vaccine: Reports to the Vaccine Adverse Event Reporting System. Vaccine. 2017;35:5618–21. [PubMed: 28886946]
23. Haber P, Moro PL, Ng C, Dores GM, Lewis P, Cano M. Post-licensure surveillance of trivalent adjuvanted influenza vaccine (aIIV3; Fluad), Vaccine Adverse Event Reporting System (VAERS), United States, July 2016–June 2018. Vaccine. 2019;37:1516–20. [PubMed: 30739795]

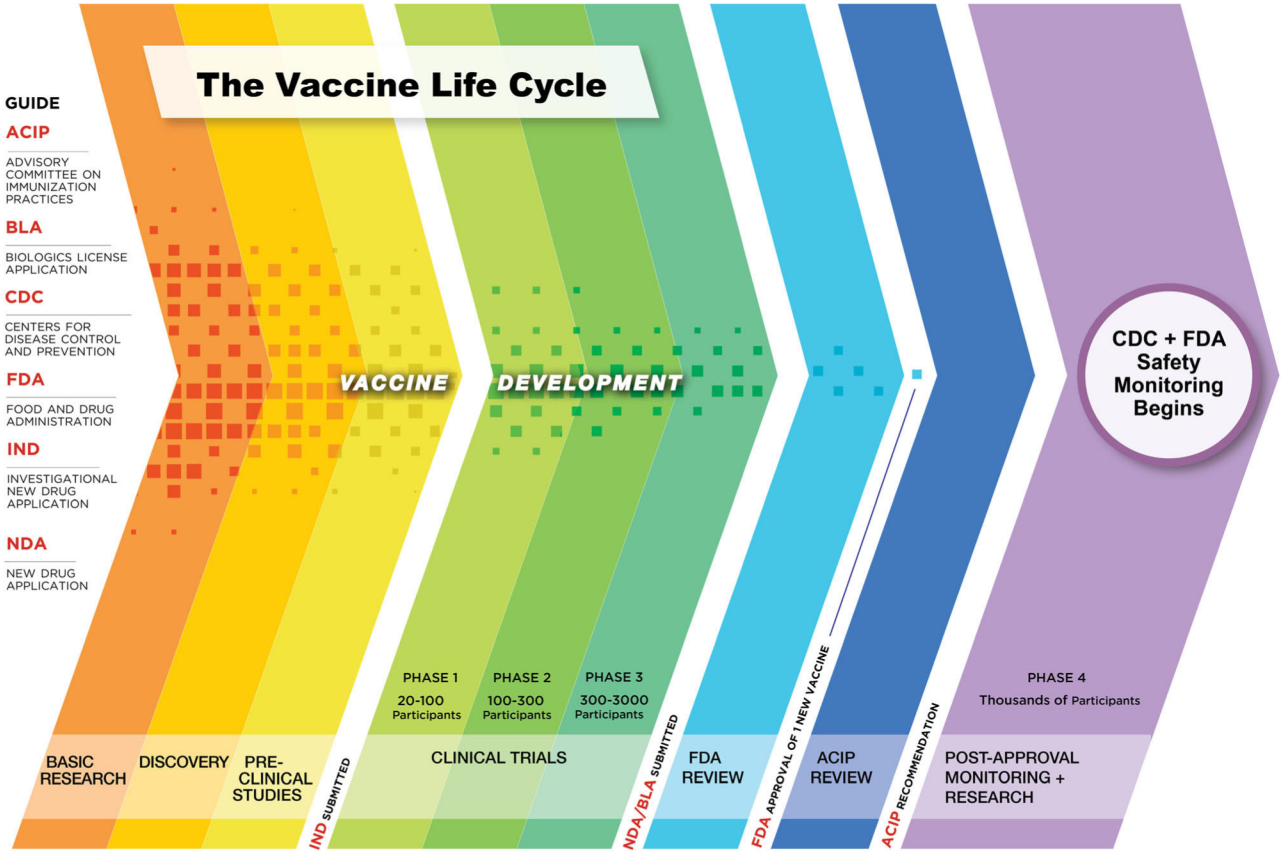

Fig. 1.
The vaccine life cycle

Table 1.

CDC's vaccine safety infrastructure

System/ program	Vaccine Adverse Event Reporting System (VAERS)	Vaccine Safety Datalink (VSD)	Clinical Immunization Safety Assessment (CISA) Project
Collaboration	CDC and FDA	CDC and 8 integrated healthcare organizations	CDC and 7 medical research centers
Description	US frontline spontaneous reporting system that detects potential vaccine safety problems. Serves as the nation's early warning system; can rapidly detect concerns and generate hypotheses for further safety studies. Anyone can report possible vaccine events to VAERS	A collaboration between CDC and eight integrated health care organizations. VSD is a large linked electronic health record-based database system used for active, near real-time monitoring of new vaccines and influenza vaccines, and for epidemiologic research on vaccine safety	A partnership between CDC and seven medical research centers as well as other experts that conducts individual clinical vaccine safety consultations on specific patients to assist with immunization decision-making. CISA also conducts clinical research studies on adverse events following vaccination
Strengths and limitations	Strengths • National data; accepts reports from anyone • Rapid signal detection • Can detect rare adverse events. • Collects information about vaccine, characteristics of vaccinee, and adverse event • Data available to public Limitations • Reporting bias • Inconsistent data quality and completeness • Lack of unvaccinated comparison group • Generally cannot assess if vaccine caused an adverse event • Pregnancy inconsistently reported	Strengths • All medical encounters are available • Vaccine registry data • Can calculate rates • Can assess risk of an adverse event • Can review medical records • Tested algorithm to identify pregnancies • Annual birth cohort approximately 100,000 Limitations • Sample size may be inadequate for very rare adverse events • Vaccines administered outside of medical home may not be captured • Potential for lack of socioeconomic diversity • Data lags	Strengths * • Can implement prospective, multi-site clinical studies (hundreds of subjects) • Expertise in vaccine safety anc many clinical areas • Access to special populations receiving vaccines • Detailed clinical/data on patients • Can collect biological specimens • Ability to recruit controls Limitations * • Sample size limited to study rare adverse events • Potential challenges to recruit and retain subjects • May not have access to vaccine records for vaccines given outside site • Potential for lack of geographic or race/ ethnicity diversity • Clinical studies may be labor and resource-intensive

* Limited to research activities