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Anaphylaxis after vaccination reported to the Vaccine Adverse Event Reporting System, 1990–2016

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Abstract

Background: Anaphylaxis, a rare and potentially life-threatening hypersensitivity reaction, can occur after vaccination.

Objective: We sought to describe reports of anaphylaxis after vaccination made to the Vaccine Adverse Event Reporting System (VAERS) during 1990–2016.

Methods: We identified domestic reports of anaphylaxis within VAERS using a combination of Medical Dictionary for Regulatory Activity queries and Preferred Terms. We performed a descriptive analysis, including history of hypersensitivity (anaphylaxis, respiratory allergies, and drug allergies) and vaccines given. We reviewed all serious reports and all nonserious reports with available medical records to determine if they met the Brighton Collaboration case definition for anaphylaxis or received a physician's diagnosis.

Results: During the analytic period, VAERS received 467,960 total reports; 828 met the Brighton Collaboration case definition or received a physician's diagnosis of anaphylaxis: 654 (79%) were classified as serious, and 669 (81%) had medical records available. Of 478 reports in children aged less than 19 years, 65% were male; childhood vaccines were most commonly reported. Of 350 reports in persons aged 19 years or greater, 80% were female, and influenza vaccines were most frequently reported. Overall, 41% of reports described persons with no history of hypersensitivity. We identified 8 deaths, 4 among persons with no history of hypersensitivity.

Conclusion: Anaphylaxis after vaccination is rare in the United States and can occur among persons with no history of hypersensitivity. Most persons recover fully with treatment, but serious complications, including death, can occur. (J Allergy Clin Immunol 2019;143:1465–73.)

Keywords

Vaccine Adverse Event Reporting System; vaccine; adverse event; anaphylaxis; hypersensitivity; epidemiology; Brighton

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Anaphylaxis is an acute hypersensitivity reaction that involves multiple organ systems and can present with variable severity, ranging from mild to life-threatening.[1] Anaphylaxis occurs because of the sudden release of histamine, tryptase, and other mediators into the systemic circulation from mast cell and basophil granules.[2] This release (also known as degranulation) most often occurs in persons with prior exposure to an antigen, where that exposure leads to production of IgE antibodies that bind mast cells and basophils, leading to degranulation on subsequent exposure to the same antigen (now allergen); direct degranulation through nonimmunologic mechanisms can also occur. The symptoms of anaphylaxis are many and can include generalized urticarial rash, airway swelling and difficulty breathing, hypotension, nausea, or vomiting. Anaphylaxis occurs in the United States with a rate as high as 100 cases per 100,000 population,[3] leading to as many as 1000 deaths annually.[4]

Anaphylaxis after vaccination is rare,[5–7] and estimated occurrence varies with the surveillance systems used to obtain data. National active surveillance in the United Kingdom found a rate of 12 cases per 100,000 doses distributed after single-component measles vaccine among children aged less than 16 years.[8] Reporting from selected health care organizations in the United States found an overall rate of anaphylaxis after vaccination of 1.3 cases per million doses administered to both children and adults.[9] Available data seem to suggest a particular patient profile for persons who experience anaphylaxis after vaccination: the vast majority have a history of atopy (ie, a history of atopic disease, such as asthma, allergic rhinitis, atopic dermatitis, or food or drug allergy).[9] Despite the sometimes dramatic presentation of symptoms, almost all fully recover.[8,9]

The possibility remains that patients without a history of atopy or who do not fully recover exist but go undetected. Such knowledge might improve the awareness and management of anaphylaxis after vaccination. One strength of a national passive surveillance system is the ability to detect rare events occurring after vaccination post-licensure.[10] To describe experiences and outcomes of anaphylaxis reported after vaccination, including affected populations that might have thus far been unrecognized, we reviewed data from a passive surveillance system in the United States.

METHODS

Data source

Health care providers, vaccine manufacturers, vaccine recipients, and other persons can report adverse events (AEs) after US-licensed vaccines to the Vaccine Adverse Event Reporting System (VAERS), a national spontaneous reporting system for monitoring AEs.[10,11] Reported signs and symptoms are coded by using Medical Dictionary for Regulatory Activities (MedDRA) Preferred Terms (PTs).[12] MedDRA PTs need not be medically confirmed diagnoses, and a VAERS report can be assigned multiple MedDRA PTs. Based on the Code of Federal Regulations, a report is classified as serious if 1 or more of the following conditions is reported: death, life-threatening illness, hospitalization or prolongation of existing hospitalization, permanent disability, or a congenital anomaly or birth defect.[13] Because of these criteria, reported anaphylaxis might be of clinically severe

presentation but not necessarily classified as a serious report. Serious reports from vaccine manufacturers typically do not contain medical records that VAERS personnel can review: these reports of AEs are usually received by vaccine manufacturers directly, who subsequently request and review medical records per regulatory processes[10] and then report the AEs to the VAERS as serious reports. For serious reports from nonmanufacturers, medical records are routinely requested and made available to VAERS personnel.

Descriptive analysis

We searched the VAERS database for reports of anaphylaxis after vaccination in the United States with a vaccination date of January 1, 1990, through December 31, 2016 (among reports received by the Centers for Disease Control and Prevention through February 28, 2017). We conducted this search using 3 approaches of increasing specificity; each approach searched through all reports to VAERS during the specified period: (1) using the MedDRA System Organ Class (SOC; the highest level of the MedDRA hierarchy that provides the broadest classification for AEs) to identify reports involving the SOCs “skin and subcutaneous tissue disorders,” “immune system disorders,” and “respiratory, thoracic, and mediastinal disorders”;(2) using the Standardized MedDRA Query (SMQ) query (which identifies reports with any of a predetermined set of PTs) for “anaphylactic reaction” or “anaphylactic/anaphylactoid shock conditions”; and (3) identifying reports with the PTs “anaphylactic reaction,” “anaphylactic shock,” “anaphylactoid reaction,” and/or “anaphylactoid shock.” We also identified reports containing the following PTs in combinations that might meet the Brighton Criteria case definition for anaphylaxis: “angioedema,” “generalized erythema,” “urticaria,” “urticarial rash,” “cyanosis,” “grunting,” “stridor,” “tachypnea,” “wheezing,” “loss of consciousness,” “tachycardia,” “abdominal pain,” “diarrhea,” “nausea,” “vomiting,” and “tryptase increased.”

We reviewed all serious reports (including serious reports from vaccine manufacturers) and all nonserious reports (including from vaccine manufacturers) for which medical records were available that described cases of anaphylaxis meeting the Brighton Criteria case definition for anaphylaxis (Appendices A and B).[14] We also reviewed cases that did not meet the Brighton Criteria case definition but received a physician’s diagnosis of anaphylaxis. We then limited analysis to reports describing symptoms within 1 day of receiving vaccine. We stratified the data by age group (<4 years, 4–10 years, 11–18 years, 19–49 years, and ≥50 years), taking into account recommended vaccination schedules[15,16] and previous descriptions of anaphylaxis after vaccination related to age.[5,9] For each age group, we analyzed reports by the seriousness of the report (serious or nonserious), sex, and time from vaccination to symptom onset. Reports were further analyzed by history of hypersensitivity (respiratory allergies, including allergic rhinitis, sinusitis, and bronchitis; asthma; anaphylaxis; and allergies to foods or medications) that have previously been described as risks for future anaphylaxis,[17] including atopic dermatitis (which has been associated with food allergies and anaphylaxis[18]), treatment received, and whether vaccines were given alone or concomitantly with other vaccines.

Nonserious reports that were not reviewed (because they lacked medical records for review) still contained data for age, sex, days from vaccination to onset of symptoms, symptoms, and

vaccines received. For reports describing symptoms within 1 day of vaccination, we described distributions by age group, sex, reports potentially meeting the Brighton case definition, and vaccines administered.

Estimated rates of anaphylaxis for combined measles, mumps, and rubella vaccine (MMR); pneumococcal polysaccharide vaccine; and varicella vaccine were calculated by using reports received during the specified time period (eg, 2006–2016) as the numerator divided by doses distributed by their manufacturer[19] during the same time period (Merck and Company, Whitehouse Station, NJ, personal communication) as the denominator. These rates were reported as reports per 1 million doses distributed. For influenza vaccine (all types), annual estimated rates of anaphylaxis were calculated by using reports received during the specified time period as the numerator and population estimates and vaccine coverage per year as the denominator,[20,21] from which a median rate of cases per doses administered was estimated.

RESULTS

Of 467,960 reports to VAERS during the analytic period,[22] we identified 282,249 reports to the VAERS database containing 1 or more of the MedDRA SOCs listed in the Methods section. SMQs reduced this number to 15,404 reports. To further increase the specificity of our query, we then limited our search to the PTs of “anaphylactic reaction,” “anaphylactic shock,” “anaphylactoid reaction,” “anaphylactoid shock,” and selected PTs in combinations that might meet the Brighton definition: this approach yielded 2,317 reports (including reports from vaccine manufacturers). Of these 2,317 reports, 1,090 were serious, and 1,227 were nonserious. We reviewed all 1,090 serious reports and the 239 nonserious reports for which medical records were available: 863 either met the Brighton Collaboration case definition or included a diagnosis of anaphylaxis by a physician; 828 reports described symptoms within 1 day of receiving vaccine. Our analysis focused on these 828 reports.

Of the 828 reports that either met the Brighton case definition or included a diagnosis of anaphylaxis by a physician, and also described symptoms within 24 hours of receiving the vaccine, 654 (79%) were classified as serious (Table I), and 669 (81%) had medical records available for review. Median age for persons in these reports was 12 years (range, <1–86 years); the 2 age groups with the most reports were aged 4 to 10 years and 19 to 49 years, respectively. Most persons aged less than 19 years were male (65%), whereas most persons aged 19 years or older were female (80%). Of reports with time to onset of symptoms available, 77% described symptoms less than 2 hours after vaccination: considering all age groups, median time to onset after vaccination was 20 minutes (range, <1 minute to 24 hours). Most reports (85%) met either Brighton level 1 or 2 criteria (Appendices A and B).

Overall, 487 (59%) reports described persons with a history of hypersensitivity (Table II). The proportion of persons with a history of hypersensitivity increased with age group, from 38% (persons aged <4 years) to 64% (persons aged 19–49 years). Persons aged less than 19 years who had a history of hypersensitivity were mostly male (67%) and most commonly had respiratory allergies (62%); persons aged 19 years or greater were mostly female (71%), and they most commonly had drug allergies (64%), most frequently to penicillin (66 [46%]

reports). Most of these 487 persons with a history of hypersensitivity received treatment with antihistamines, epinephrine, and/or steroids: few reports (6%) did not document treatment. Time to onset of symptoms after vaccination was less than 2 hours for most persons with a history of hypersensitivity (70%).

Of 341 (41%) reports describing persons without a history of hypersensitivity, most (81%) were serious (Table III). These reports described persons aged less than 19 years who were mostly male (61%), and persons aged 19 years or older who were mostly female (72%). Most persons received treatment with antihistamines, epinephrine, and/or steroids; few reports (11%) did not document treatment. Time to onset of symptoms after vaccination was less than 2 hours for most persons without a history of hypersensitivity (68%).

Overall, the most commonly reported vaccines associated with reports of anaphylaxis were influenza vaccines (all types; 330 [40%] reports; Table IV). For persons aged less than 19 years, MMR (196 reports), varicella vaccines (178 reports), and vaccines containing diphtheria toxoids, tetanus toxoids, and/or acellular pertussis (eg, combined diphtheria, tetanus, and acellular pertussis vaccine and combined tetanus, diphtheria, and acellular pertussis vaccine; 165 reports) were most commonly reported. For persons aged 19 years or greater, influenza vaccine (all types) was most commonly reported (224 reports). Among 467 persons who received only a single vaccine, the most commonly reported vaccine was influenza vaccine (all types; 254 [54%] reports); among persons aged 4 to 10 years, varicella vaccine was reported nearly as frequently (29 reports, Table V). Among 171 persons who received only a single vaccine and had no history of hypersensitivity, the most commonly reported vaccines were influenza vaccines (all types; 83 [49%] reports), except among persons aged 4 to 10 years (for whom varicella vaccine was most common (11 [33%] reports) and among persons aged 11 to 18 years (for whom MMR was most common (3 [23%] reports).

We identified 8 reports of death (Table VI). Of 7 reports with time to onset of symptoms available, 5 reported a time to onset of 20 minutes or less after vaccination. Described persons had a median age of 48 years (range, 42–84 years), 6 of whom received trivalent inactivated influenza vaccine. Half (50%) of reports described persons with no history of hypersensitivity, including the only death reported among persons aged less than 19 years (a 2-year-old boy).

Of 988 nonserious reports that were not reviewed, 857 reported onset of symptoms within 1 day of vaccination; 855 reported age data. Almost half of reports (411 [48%] reports) described combinations of symptoms that could potentially meet the Brighton Criteria case definition. Of 484 reports describing persons aged less than 19 years, most (57%) were male; of 391 reports describing persons aged 19 years or greater, most (79%) were female. Whether given with other vaccines (274 reports) or alone (229 reports), influenza vaccines (all types) were the most commonly reported vaccines.

The estimated rate of anaphylaxis reported to VAERS during 1990 to 2016 after MMR was 0.6 per 1 million doses distributed, and after pneumococcal polysaccharide vaccine was 0.2 per 1 million doses distributed; during 2006 to 2016, the estimated rate after varicella

vaccine was 1.2 per 1 million doses distributed. During 2010 to 2016, after influenza vaccine (all types) among persons aged 1 to 84 years, the median estimated annual rate was0.2 (range, 0.1–0.4) per 1 million doses administered. When considering only reports meeting Brighton Collaboration case certainty levels 1 and 2 (ie, cases with high diagnostic certainty of anaphylaxis), the median estimated annual rate after influenza vaccine (all types) decreased to 0.1 (range, 0.1–0.4) per 1 million doses administered; all other estimated rates remained unchanged. Notably, the 411 unreviewed nonserious reports that could meet the Brighton Criteria case definition could increase included reports by 50%; however, 173 (72%) of 239 nonserious reports that were reviewed met the Brighton case definition. Assuming a 72% increase in estimated rates to account for potentially missed nonserious reports that might have met the Brighton case definition, the estimated rate of anaphylaxis after MMR would be 1.1, after pneumococcal polysaccharide vaccine would be 0.3, and after varicella vaccine would be 2.1 per 1 million doses distributed; after influenza vaccine (all types), the median estimated annual rate would increase to 0.3 (range, 0.2–0.8) per 1 million doses administered.

DISCUSSION

Anaphylaxis after vaccination is a rarely reported event in the United States, with a reported rate of 1.3 cases per 1 million doses administered.[9] The data in this report reflect this rarity and are consistent with analyses of other passive reporting systems describing the frequency of anaphylaxis after vaccination.[8,23] Given this rarity, anaphylaxis after vaccination severe enough to cause death is an exceptionally rare outcome.

Some findings in this analysis are consistent with previous observations. The predominance of male sex in younger age groups (eg, aged <19 years) and female sex in older age groups (eg, aged ≥19 years) has been observed in previous analyses.[9,24,25] Most reports in this analysis (67%) noted symptoms less than 2 hours after vaccination (Table I), which is consistent with the rapid development of symptoms described by other investigators.[9,26] Reported histories of hypersensitivity were also similar to histories described by other investigators, including respiratory allergies, such as asthma and drug allergies.[27–29] Although histories of sensitivity to penicillin or cephalosporins were commonly reported, vaccines do not contain these antibiotics; therefore patients with such sensitivities might be predisposed to allergic reactions in general. Notably, a history of asthma can increase the likelihood of a severe or even fatal episode of anaphylaxis.[30]

Contrasting previous reports,[5,9] many persons with reported anaphylaxis after vaccination (41%) described no history of hypersensitivity (Table III). Such persons did not appreciably differ from persons with a reported history of hypersensitivity (eg, similar proportions by sex and age group; Table II), including time to onset of symptoms. Regardless of history of hypersensitivity, similar proportions of patients received drug treatment (≥89%). We observed a somewhat greater proportion of persons indicating treatment with epinephrine relative to other reports.[9,31] This difference might reflect the passive reporting nature of VAERS but might also reflect a diverse range of symptom severity, with some persons experiencing symptoms mild enough to be managed with other medications (eg, steroids and antihistamines) despite epinephrine’s status as a first-line treatment for anaphylaxis.[9,32]

These observations underscore current recommendations that any provider administering vaccines should have emergency protocols and supplies on hand, including epinephrine, should a patient develop anaphylaxis.[33]

Vaccines for which anaphylaxis was reported reflected the recommended vaccine schedule for persons of the patient's age (Tables IV and V). Multiple vaccines are routinely recommended for persons aged less than 19 years and are often given at the same provider visit[33]; the vaccines that were commonly reported for this age group in our analysis reflect the age-appropriate recommended vaccines (eg, MMR and combined diphtheria, tetanus, and acellular pertussis vaccine). Persons aged 19 years or greater tend to receive relatively fewer vaccines (except for influenza vaccine, which is recommended annually[15]) and might have greater opportunity to receive such vaccines singly. The predominance of reports of influenza vaccine in persons aged 19 years or greater might reflect the relatively greater frequency of administering this vaccine compared with other vaccines. Notably, anaphylaxis after hepatitis A vaccine had not been reported previously.[34] Reports of anaphylaxis after hepatitis A vaccine within VAERS but not in other surveillance mechanisms[9] reflect the increased sensitivity of a nationwide passive surveillance system like VAERS.

Of the 8 reports describing anaphylaxis and death after vaccination, 6 were documented previously[35]; the other 2 reports (describing the boy aged 2 years and the woman aged 43 years) had not been described before this analysis. The rapid onset of symptoms after vaccination (within 20 minutes) in many cases suggests vaccine played a role in these episodes of anaphylaxis,[36] but other factors might have played a role (eg, the patient with allergies to penicillin who received ceftriaxone before vaccination). Half of these deaths occurred in persons with no history of hypersensitivity, underscoring the need for vigilance of all vaccinated persons and to be prepared for immediate intervention, if needed.[33]

McNeil et al[9] reviewed diagnoses of anaphylaxis among persons of all ages enrolled in health plans during January 2009 to December 2011. Diagnoses of anaphylaxis were identified by using International Classification of Diseases, Ninth Revision, codes and review of medical records: 33 persons were identified with anaphylaxis (Brighton level 1 or 2) associated with vaccination, with an estimated overall incidence of 1.31 cases of anaphylaxis per million doses of vaccine administered (including rates of 5.1 and 5.8 cases per million doses administered for MMR and varicella vaccines, respectively).[9] Because VAERS does not collect data on doses administered, our estimated rates used either doses distributed or vaccination coverage as a denominator. Our comparatively lower rates reflect this larger denominator, as well as incomplete reporting to VAERS (including possible episodes of anaphylaxis that were aborted before development of symptoms that would fulfill Brighton case certainty criteria). These 2 analyses provide complementary information on anaphylaxis after vaccination: although both analyses applied Brighton Criteria and reviewed medical records (when possible), the greater volume of reports within VAERS allowed a greater ability to detect events, whereas data from McNeil et al[9] allowed a more robust estimation of risk.

Our analysis has limitations. VAERS is a passive reporting system and is subject to limitations like underreporting, reporting biases, inconsistent data quality and completeness,

changes in reporting over time, and lack of an unvaccinated comparison group.[11,37] For these reasons, VAERS data generally cannot establish whether a vaccine caused a particular AE, including anaphylaxis.[10] A broader search including more PTs could potentially capture more reports of anaphylaxis within VAERS. Our results suggest reviewing nonserious reports without available medical records could increase included reports by 411 reports. Assuming all 411 reports included a history of hypersensitivity, a minimum of 341 (28%) of 1239 reports would describe persons without a history of hypersensitivity, still a substantial proportion of reports. Furthermore, even assuming estimated rates increased by 72% to account for potentially missed reports, estimated rates of anaphylaxis after selected vaccines remained well below previously reported estimates.[5,9] As mentioned, VAERS does not collect data on doses administered and estimated rates based on doses distributed are likely underestimates. Despite these limitations, VAERS remains a valuable tool for detecting unusual or unexpected patterns of reported AEs that might indicate vaccine safety concerns that warrant further investigation.[38,39]

Although rare after vaccination (1.3 cases per 1 million doses administered), anaphylaxis can be a life-threatening event. For this reason, vaccine safety surveillance systems specifically monitor for this outcome.[5,9] Awareness of anaphylaxis after vaccination (and its potentially severe outcomes) can improve both detection and reported data quality of anaphylaxis after vaccination. Fortunately, the data in this analysis and elsewhere indicate that anaphylaxis after vaccination (and the possibility of death) is a rare event.

APPENDIX A.: Summary of Brighton Collaboration case definition for anaphylaxis14*

For all levels of diagnostic certainty, anaphylaxis is a clinical syndrome characterized by sudden onset, rapid progression of signs and symptoms, AND involving multiple (≥2) organ systems, as follows:

Level 1 of diagnostic certainty

- ≥1 major dermatologic AND
- ≥1 major cardiovascular AND/OR ≥1 major respiratory criterion

Level 2 of diagnostic certainty

- ≥1 major cardiovascular AND ≥1 major respiratory criterion

OR

- ≥1 major cardiovascular OR respiratory criterion AND
  1. ≥1 minor criterion involving ≥1 different system (other than cardiovascular or respiratory systems)

OR

  2. (≥1 major dermatologic) AND (≥1 minor cardiovascular AND/OR minor respiratory criterion)

Level 3 of diagnostic certainty

- ≥1 minor cardiovascular OR respiratory criterion

AND

- ≥1 minor criterion from each of ≥2 different systems/categories

This appendix describes the criteria for each level of diagnostic certainty specified in the Brighton Collaboration case definition for anaphylaxis.

*The case definition should be applied when there is no clear alternative diagnosis for the reported event to account for the combination of symptoms.

APPENDIX B.: Major and minor criteria used in Brighton Collaboration case definition for anaphylaxsis14*

	Major criteria	Minor criteria
Dermatologie or mucosal	• Generalized urticaria (hives) or generalized erythema • Angioedema,* localized or generalized • Generalized pruritus with skin rash	• Generalized pruritus without skin rash • Generalized prickle sensation • Localized injection-site urticaria • Red and itchy eyes
Cardiovascular	• Measured hypotension • Clinical diagnosis of uncompensated shock indicated by the combination of ≥3 of the following: – tachycardia – capillary refill time >3 s – reduced central pulse volume – decreased level or loss of consciousness	• Reduced peripheral circulation, as indicated by the combination of ≥2 of the following: – tachycardia, and – capillary refill time >3 s without hypotension – decreased level of consciousness
Respiratory	• Bilateral wheeze (bronchospasm) • Stridor • Upper airway swelling (lip, tongue, throat, uvula, or larynx) • Respiratory distress, ≥2 of the following: – tachypnea – increased use of accessory muscles (eg, sternocleidomastoid and intercostals) – recession – cyanosis – grunting	• Persistent dry cough • Hoarse voice • Difficulty breathing without wheeze or stridor • Sensation of throat closure • Sneezing, rhinorrhea
Gastrointestinal		• Diarrhea • Abdominal pain • Nausea • Vomiting
Laboratory		• Mast cell tryptase level increase > upper normal limit

This appendix describes the signs and symptoms by organ system that are considered major and minor criteria.

*Not hereditary angioedema.

Abbreviations used

AE	Adverse event
MedDRA	Medical Dictionary for Regulatory Activities
MMR	Combined measles, mumps, and rubella vaccine
PPVS23	Pneumococcal polysaccharide vaccine
PT	Preferred Term
SOC	System Organ Class
VAERS	Vaccine Adverse Event Reporting System

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Clinical implications:

Anaphylaxis of severe or life-threatening severity is very uncommon but can occur, even among persons without a history of hypersensitivity; vaccine providers should be prepared to respond immediately.

TABLE I.

Reported cases of anaphylaxis: General characteristics by age group, 1990–2016

	<4 y (%), n = 118	4–10 y (%), n = 267	11–18 y (%), n = 93	19–49 y (%), n = 233	≥50 y (%), n = 117	Total (%), n = 828
Seriousness of report						
Deaths	1 (1)	0 (0)	0 (0)	3 (1)	4 (3)	8 (1)
Serious, nondeath *	98 (83)	229 (86)	70 (75)	173 (74)	84 (72)	654 (79)
Nonserious	19 (16)	38 (14)	23 (25)	57 (24)	29 (25)	166 (20)
Sex of reported patient						
Male	77 (65)	189 (71)	43 (46)	40 (17)	31 (26)	380 (46)
Female	40 (34)	78 (29)	50 (54)	193 (83)	86 (74)	447 (54)
Not reported	1 (1)	0 (0)	0 (0)	0 (0)	0 (0)	1 (0)
Time to onset of symptoms						
<30 min	59 (50)	176 (66)	36 (39)	96 (41)	35 (30)	402 (49)
30–119 min	27 (23)	46 (17)	18 (19)	58 (25)	18 (15)	167 (20)
2–4 h	11 (9)	7 (3)	16 (17)	27 (12)	18 (15)	79 (10)
4–8 h	8 (7)	6 (2)	2 (2)	13 (6)	15 (13)	44 (5)
8–24 h	7 (6)	2 (1)	7 (8)	12(5)	15 (13)	43 (5)
Not reported	6(5)	30 (11)	14 (15)	27 (12)	16 (14)	93 (11)
Classification						
Brighton level 1	64 (54)	157 (59)	44 (47)	81 (35)	39 (33)	385 (46)
Brighton level 2	42 (36)	81 (30)	24 (26)	114 (49)	54 (46)	315 (38)
Brighton level 3	2 (2)	1 (0)	1 (1)	2 (1)	1 (1)	7 (1)
Physician diagnosed	10 (8)	28 (10)	24 (26)	36 (15)	23 (20)	121 (15)

* Reports in which the patient was hospitalized, had prolongation of hospitalization, had permanent disability, or experienced a life-threatening condition.

TABLE II.

Characteristics of reported cases of anaphylaxis among persons with a history of hypersensitivity by age group, 1990–2016

	<4 y (%), n = 44	4–10 y (%), n = 162	11–18 y (%), n = 58	19–49 y (%), n = 149	≥50 y (%), n = 74	Total (%), n = 487
Seriousness of report						
Death	0 (0)	0 (0)	0 (0)	2 (1)	2 (3)	4 (1)
Serious, nondeath *	34 (77)	142 (88)	41 (71)	110 (74)	52 (70)	379 (78)
Nonserious	10 (23)	20 (12)	17 (29)	37 (25)	20 (27)	104 (21)
Sex of reported patient						
Male	33 (75)	117 (72)	28 (48)	20 (13)	16 (22)	214 (44)
Female	11 (25)	45 (28)	30 (52)	129 (87)	58 (78)	273 (56)
Medical history						
Anaphylaxis (any cause)	2 (5)	21 (13)	8 (14)	35 (23)	13 (18)	79 (16)
Atopic dermatitis/eczema	23 (52)	34 (21)	8 (14)	2 (1)	2 (3)	69 (14)
Bee/wasp sting reaction	0 (0)	2 (1)	0 (0)	7 (5)	11 (15)	20 (4)
Drug allergies	6 (14)	34 (21)	13 (22)	89 (60)	53 (72)	195 (40)
Food allergies	22 (50)	64 (40)	27 (47)	43 (29)	11 (15)	167 (34)
Respiratory allergies	15 (34)	110 (68)	38 (66)	75 (50)	28 (38)	266 (55)
Treatment †						
Antihistamines	33 (75)	114 (70)	47 (81)	111 (74)	56 (76)	361 (74)
Epinephrine	30 (68)	108 (67)	43 (74)	96 (64)	32 (43)	309 (63)
Steroids	25 (57)	96 (59)	35 (60)	100 (67)	45 (61)	301 (62)
No treatment specified	2 (5)	7 (4)	2 (3)	7 (5)	9 (12)	27 (6)
Time to onset						
<30 min	19 (43)	111 (69)	21 (36)	65 (44)	23 (31)	239 (49)
30–119 min	12 (27)	25 (15)	12 (21)	38 (26)	13 (18)	100 (21)
2–4 h	4(9)	5 (3)	11 (19)	19 (13)	10 (14)	49 (10)
4–8 h	4 (9)	4 (2)	0 (0)	6 (4)	9 (12)	23 (5)
8–24 h	2 (5)	2 (1)	4 (7)	6 (4)	7 (9)	21 (4)
Not reported	3 (7)	15 (9)	10 (17)	15 (10)	12 (16)	55 (11)

*Reports in which the patient was hospitalized, had prolongation of hospitalization, had permanent disability, or experienced a life-threatening condition.

[†]Some reports described patients who received more than 1 type of treatment.

TABLE III.

Characteristics of reported cases of anaphylaxis among persons without a history of hypersensitivity by age group, 1990–2016

	<4 y (%), n = 74	4–10 y (%), n = 105	11–18 y (%), n = 35	19–49 y (%), n = 84	≥50+ y (%), n = 43	Total (%), n = 341
Seriousness of report						
Death	1 (1)	0 (0)	0 (0)	1 (1)	2 (5)	4 (1)
Serious, nondeath *	64 (86)	87 (83)	29 (83)	63 (75)	32 (74)	275 (81)
Nonserious	9 (12)	18 (17)	6 (17)	20 (24)	9 (21)	62 (18)
Sex of reported patient						
Male	44 (59)	72 (69)	15 (43)	20 (24)	15 (35)	166 (49)
Female	29 (39)	33 (31)	20 (57)	64 (76)	28 (65)	174 (51)
Unreported	1 (1)	0 (0)	0 (0)	0 (0)	0 (0)	1 (0)
Treatment †						
Antihistamines	55 (74)	79 (75)	20 (57)	58 (69)	30 (70)	242 (71)
Epinephrine	42 (57)	79 (75)	25 (71)	45 (54)	25 (58)	216 (63)
Steroids	43 (58)	56 (53)	21 (60)	56 (67)	29 (67)	205 (60)
No treatment specified	10 (14)	7 (7)	3 (9)	12 (14)	4 (9)	36 (11)
Time to onset						
<30 min	40 (54)	65 (62)	15 (43)	31 (37)	12 (28)	163 (48)
30–119 min	15 (20)	21 (20)	6 (17)	20 (24)	5 (12)	67 (20)
2–4 h	7 (9)	2 (2)	5 (14)	8 (10)	8 (19)	30 (9)
4–8 h	5 (7)	2 (2)	2 (6)	7 (8)	6 (14)	22 (6)
8–24 h	4 (5)	0 (0)	3 (9)	6 (7)	8 (19)	21 (6)
Not reported	3 (4)	15 (14)	4 (11)	12 (14)	4 (9)	38 (11)

*Reports in which the patient was hospitalized, had prolongation of hospitalization, had permanent disability, or experienced a life-threatening condition.

†Some reports described patients who received more than 1 type of treatment.

TABLE IV.

Most frequently reported vaccines among reports of anaphylaxis by age group*

Vaccine	<4 y (%), n = 119	4–10 y (%), n = 266	11–18 y (%), n = 93	19–49 y (%), n = 233	≥50 y (%), n = 117	Total (%), n = 828
Influenza, all types	24 (20)	59 (22)	23 (25)	147 (63)	77 (66)	330 (40)
MMR	35 (30)	148 (55)	13 (14)	10 (4)	0 (0)	206 (25)
DTaP/Tdap	41 (35)	96 (36)	28 (30)	23 (10)	6 (5)	194 (23)
Varicella	37 (31)	125 (47)	16 (17)	2 (1)	1 (1)	181 (22)
IPV	18 (15)	91 (34)	2 (2)	2 (1)	1 (1)	114 (14)
Hepatitis A	14 (12)	29 (11)	15 (16)	8 (3)	4 (3)	70 (8)
Hepatitis B	14 (12)	6 (2)	8 (9)	29 (12)	5 (4)	62 (7)
Hib	39 (33)	5 (2)	0 (0)	0 (0)	1 (1)	45 (5)

DTaP/Tdap, Combined diphtheria and tetanus toxoids and acellular pertussis vaccine; *Hib, Haemophilus influenzae type b vaccine; IPV,* inactivated polio vaccine.

*Some reports described patients receiving more than 1 vaccine at the same provider visit.

TABLE V.

Most frequently reported vaccines administered alone among reports of anaphylaxis, by age group

Vaccine	<4 y (%), n = 37	4–10 y (%), n = 90	11–18 y (%), n = 40	19–49 y (%), n = 201	≥50 y (%), n = 99	Total (%), n = 467
Influenza, all types	16 (43)	30 (33)	13 (33)	132 (66)	63 (64)	254 (54)
Varicella	7 (19)	29 (32)	0 (0)	2 (1)	1 (1)	39 (8)
Hepatitis B	2 (5)	1 (1)	2 (5)	24 (12)	4 (4)	33 (7)
MMR	3 (8)	18 (20)	5 (13)	4 (2)	0 (0)	30 (6)
DTaP/Tdap	1 (3)	3 (3)	4 (10)	14 (7)	3 (3)	25 (5)
PPVS23	0 (0)	5 (6)	2 (5)	3 (1)	11 (11)	21 (5)
Herpes zoster, live	0 (0)	0 (0)	0 (0)	0 (0)	12 (12)	12 (3)
4vHPV	0 (0)	0 (0)	6 (15)	3 (1)	0 (0)	9 (2)

DTaP/Tdap, Combined diphtheria and tetanus toxoids and acellular pertussis vaccine; *PPVS23,* pneumococcal polysaccharide vaccine.

TABLE VI.

Reports of death among reports of anaphylaxis

Patient no.	Age (y)	Sex	Past medical history	Vaccine(s) received	Time to onset (min)	Symptoms	Brighton level	Documented cause of death
1	2	Male	Born premature at 33 weeks' gestation; hypoplastic left heart syndrome with subsequent cavopulmonary shunt procedure; periodic cyanosis	Inactivated influenza (not specified), combined measles-mumps-rubella, varicella vaccines	20	Received vaccinations and later experienced cardiopulmonary arrest. Postmortem laboratory tests revealed an increased serum tryptase level.	2	Anaphylactic reaction
2	42	Female	Asthma; hereditary onycho-osteodysplasia; allergies to penicillin, quinolones, and naproxen; hepatitis C infection	Inactivated influenza vaccine, trivalent	2	Received vaccine and intramuscular ceftriaxone concomitantly. The patient then experienced respiratory failure and died. Laboratory tests later revealed an increased serum tryptase level.	2	Anaphylactic reaction
3	43	Female	No hypersensitivities; hypertension; depression	Inactivated influenza vaccine, quadrivalent	<1 d	Received vaccine and was found dead the following morning. On autopsy, the body was noted to have patches of urticaria and airway swelling. Laboratory results included an increased serum tryptase level.	1	Anaphylactic reaction
4	46	Male	Asthma; unspecified allergies; chronic headaches; gout; hypertension	Inactivated influenza vaccine, trivalent	NA	Received vaccine and then had wheezing with subsequent cardiopulmonary arrest.	2	Acute asthmatic bronchitis
5	50	Male	Allergies to angiotensin-converting enzyme inhibitors; past anaphylaxis; hypertension; renal cell carcinoma	Pneumococcal polysaccharide vaccine	0	Received the vaccine and immediately had respiratory difficulty, seizure, and cardiorespiratory arrest.	2	Anaphylactic shock
6	65	Male	None	Inactivated influenza vaccine, trivalent	15	Received vaccine and then experienced airway swelling and cardiopulmonary arrest.	2	Anaphylactic shock
7	70	Male	No hypersensitivities; chronic obstructive pulmonary disease; coronary artery disease	Inactivated influenza vaccine, trivalent	258	Received vaccine and experienced difficulty breathing and then cardiopulmonary arrest.	2	Anaphylactic reaction
8	84	Female	Allergies to penicillin; hypertension	Inactivated influenza vaccine, trivalent	2	Received vaccine, "felt funny," and then collapsed. The patient had ventricular	2	Not documented but medical records indicate

Patient no.	Age (y)	Sex	Past medical history	Vaccine(s) received	Time to onset (min)	Symptoms	Brighton level	Documented cause of death
						fibrillation (later speculated because of hypotension), which progressed to cardiac arrest; on examination, she also had wheezing.		diagnosis of anaphylactic reaction

NA, Not applicable.