

A systematic review of validated methods for identifying anaphylaxis, including anaphylactic shock and angioneurotic edema, using administrative and claims data

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ABSTRACT

Purpose The Food and Drug Administration's Mini-Sentinel pilot program initially aims to conduct active surveillance to refine safety signals that emerge for marketed medical products. A key facet of this surveillance is to develop and understand the validity of algorithms for identifying health outcomes of interest from administrative and claims data. This article summarizes the process and findings of the algorithm review of anaphylaxis.

Methods PubMed and Iowa Drug Information Service searches were conducted to identify citations applicable to the anaphylaxis health outcome of interest. Level 1 abstract reviews and Level 2 full-text reviews were conducted to find articles using administrative and claims data to identify anaphylaxis and including validation estimates of the coding algorithms.

Results Our search revealed limited literature focusing on anaphylaxis that provided administrative and claims data-based algorithms and validation estimates. Only four studies identified via literature searches provided validated algorithms; however, two additional studies were identified by Mini-Sentinel collaborators and were incorporated. The *International Classification of Diseases, Ninth Revision*, codes varied, as did the positive predictive value, depending on the cohort characteristics and the specific codes used to identify anaphylaxis.

Conclusions Research needs to be conducted on designing validation studies to test anaphylaxis algorithms and estimating their predictive power, sensitivity, and specificity. Copyright © 2012 John Wiley & Sons, Ltd.

KEY WORDS—anaphylaxis; administrative and claims data; Mini-Sentinel; coding algorithm

INTRODUCTION

Mini-Sentinel is the Food and Drug Administration's (FDA) pilot program that aims to conduct active surveillance of automated healthcare data. The initial goal is to refine safety signals that emerge for marketed medical products. The essential components of this exercise are (i) to identify administrative and claims data-friendly algorithms used to detect various health outcomes of interest (HOIs) and (ii) to identify the performance characteristics of these algorithms as measured within the studies in which they were used. The full report can be found at http://mini-sentinel.org/foundational_activities/related_projects/default.aspx.

In this article, we describe the algorithm review process and findings for 1 of the 20 HOIs selected for review by the FDA: anaphylaxis, including anaphylactic shock and angioneurotic edema.

Anaphylaxis is defined by the World Allergy Organization as 'a severe, life-threatening generalized or systemic hypersensitivity reaction'.¹ The diagnosis is considered to be highly likely when one of three clinical criteria is met: (i) acute onset of an illness with involvement of the skin, mucosal tissue, or both AND respiratory compromise and/or hypotension; (ii) exposure to a likely allergen AND rapid development of two or more skin-mucosal involvement, respiratory compromise, hypotension, or persistent GI symptoms; or (iii) exposure to a known allergen and rapid development of hypotension.² Cutaneous involvement—mainly angioneurotic edema (angioedema) or urticaria (hives)—is the most frequent manifestation of anaphylaxis, reported in 80% to 90% of episodes.³ Other manifestations can include respiratory tract involvement (up to 70% of cases), gastrointestinal tract involvement (45%), cardiovascular system involvement (45%), and central nervous system involvement (15%).^{3,4} Differential diagnosis includes acute generalized hives, acute asthma, syncope, panic attack, aspiration of a foreign body, cardiovascular

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events, neurologic events, vasodepressor reactions, flushing episodes, postprandial syndromes (e.g. monosodium glutamate (MSG) reaction, scombroidosis), endogenous histamine syndromes, vocal cord dysfunction, and other forms of shock.^{3,4} Laboratory tests for serum tryptase, plasma, or urine histamine can help establish the diagnosis of anaphylaxis.³ The lifetime prevalence of anaphylaxis from all triggers is estimated to range from 0.05% to 2.0%, with the largest number of incident cases occurring in children and adolescents.⁵

Anaphylaxis can be classified in four ways, according to the trigger mechanism: IgE-mediated allergic (the most common, including food, medications, and insect stings), IgE-independent allergic (formerly classified as anaphylactoid), nonallergic (uncommon, including physical factors and ethanol), or idiopathic.^{1,4} Food is the most common trigger of anaphylaxis, representing 33% to 56% of all anaphylaxis cases⁶ and 30% of fatal cases.³ Medications, primarily antibiotics and nonsteroidal anti-inflammatories, are the second-most common cause of anaphylaxis overall and the primary cause in adults.³ Insect stings are the next-most common trigger, accounting for 18.5% of anaphylaxis cases in the USA⁶ and affecting 3% of adults and 1% of children who have been exposed to stings.³ Other specific triggers include natural rubber latex (a notable risk for healthcare workers, children with spina bifida, or workers with occupational exposure to latex), vaccines (rare, but sometimes fatal), seminal fluid anaphylaxis, and exercise-induced anaphylaxis (both very rare).³

Epinephrine is universally recommended as the primary treatment for acute anaphylaxis, and it can be administered subcutaneously, intramuscularly, or intravenously; however, intravenous administration is only indicated in cases of severe hypotension, cardiovascular arrest, or failure to respond to epinephrine via other routes of administration.^{3,4} H1 and H2 antihistamines and corticosteroids are often used in conjunction with epinephrine and may provide enhanced symptomatic relief for urticaria-angioedema and pruritus.² In cases of persistent hypotension, fluid resuscitation or other medications such as vasopressors or glucagon (for patients taking β -blockers) are used.^{2,3} In addition, it is recommended that patients in anaphylactic shock (anaphylaxis with signs of critical organ hypoperfusion) be placed in a recumbent position, with the legs elevated, to increase stroke volume and cardiac output.²

METHODS

The general search strategy originated from prior work by the OMOP and its contractors and was modified slightly for the 20 HOIs selected for review.

Details of the methods for these systematic reviews can be found in the accompanying manuscript by Carnahan and Moores.⁷ In brief, the base PubMed search was combined with the following terms to represent the HOI: 'anaphylaxis', 'anaphylactic' and 'shock', 'anaphylactic shock', 'angioneurotic oedema', 'angioedema', 'angioneurotic' and 'edema', 'angioneurotic edema' and 'angioneurotic' and 'edema'. To identify other relevant articles that were not found in the PubMed search, the Iowa Drug Information Service (IDIS) database was also searched using a similar search strategy. The details of these searches can be found in the full report on the Mini-Sentinel Web site. Both the PubMed and the IDIS searches were conducted on 10 May 2010. All searches were restricted to articles published in 1990 or later.

The search results from different databases were compiled and duplicate results eliminated by University of Iowa investigators, who used a citation manager program. The results were then output and provided to organizations contracted to conduct the literature reviews. Mini-Sentinel collaborators were also asked to help identify relevant validation studies.

The abstract of each citation identified was reviewed by two investigators. When either investigator selected an article for full-text review, the full text was reviewed by both investigators. Agreement on whether to review the full text or include the article in the evidence table was calculated using the Cohen's kappa statistic. If fewer than five studies were identified that performed validation of the algorithm, up to 10 studies with algorithms but without algorithm validation were reported.

A single investigator abstracted each study for the final evidence table. The data included in the table were confirmed by a second investigator for accuracy. A clinician or topic expert was consulted to review the results of the evidence table and to discuss how they compared with diagnostic methods currently used in clinical practice. This included whether certain diagnostic codes used in clinical practice were missing from the algorithms and the appropriateness of the validation definitions compared with diagnostic criteria currently used in clinical practice.

RESULTS

The PubMed and IDIS searches identified 124 and 14 citations, respectively. A subsequent PubMed search was conducted to amend the original search strategy with relevant databases that were not originally included; this search identified one citation. The total number of unique citations from the combined searches was 134.

Of the 134 abstracts reviewed, we ultimately accepted 23 for full-text review. Because of the straightforward inclusion criteria, which consisted of (i) examination of the HOI, (ii) use of an administrative and claims database, and (iii) study conducted in the USA or Canada, the two reviewers generally agreed on the acceptance/rejection status of an abstract for full-text review (i.e. Cohen's kappa = 0.97). There was, however, limited agreement on the reason of rejection. Among the 111 abstracts rejected, interrater agreement (via kappa coefficient) was 0.00, 0.24, and 0.70 for the three inclusion criteria, respectively. This seemingly low agreement results from only a single rejection reason being captured in our abstract review database. These low kappa coefficients should therefore be considered as resulting from the different reviewers focusing on different criteria than a true lack of agreement; they also illustrate that many rejected articles fulfilled multiple exclusion criteria.

Of the 23 full-text articles reviewed, 14 articles were excluded: 3 articles for not being administrative and claims database studies, 4 articles for not including validation of the outcome of interest or not reporting validity statistics, 6 articles for not including *International Classification of Diseases, Ninth Revision* (ICD-9) codes, and 1 article for not focusing on the HOI. Of the remaining nine studies, one did not provide validation estimates⁸ but used the same cohort as an earlier study by the same lead author,⁹ one did not provide validation estimates¹⁰ but described the algorithm used in another article by the same lead author that did provide validation estimates,¹¹ one did not have validation estimates and used death certificates,¹² one validated several anaphylaxis-specific and nonspecific codes in the context of developing a broader hypersensitivity reaction algorithm,¹³ and one provided validation but did not define the specific algorithm used.¹⁴ Reviewers identified no additional citations for review from full-text article references. This left four articles with reported validation of the anaphylaxis coding algorithm directly in the article or within a reference cited in the article.^{9,11,15,16} Cohen's kappa for agreement between reviewers on inclusion versus exclusion of full-text articles reviewed was 0.75.

In addition to these four articles with reported validation statistics, Mini-Sentinel collaborators provided two additional validation studies that were not identified by the PubMed and IDIS searches. Of these, one had not been indexed at the time the search was conducted¹⁷; the other was an excluded study type in PubMed, although it was picked up in the hypersensitivity search (presumably via IDIS).¹⁸ These two reports are therefore incorporated into this review.

SUMMARY OF ALGORITHMS

The codes included in the algorithms as well as the positive predictive values (PPVs) of the six identified citations with validation estimates (four via literature search and two via Mini-Sentinel collaborators) are presented in Table 1. As can be seen, coding algorithms for anaphylaxis, including anaphylactic shock and angioneurotic edema, varied depending on the outcome of interest.

Bohlke *et al.*¹¹ used 10 ICD-9 diagnostic codes because their study interest was all-cause anaphylaxis. Note that this study focused on children and adolescents younger than 18 years who were enrolled at a Washington State health maintenance organization (Group Health Cooperative) for any duration between 1991 and 1997. The authors reported that the code with the highest PPV for anaphylaxis was ICD-9 code 995.0 (anaphylactic shock); approximately 55% of the visits with this code were confirmed by chart review as being 'probable' or 'possible' anaphylaxis. The code with the second-highest PPV (10%) in this study was ICD-9 code 995.6 (anaphylactic shock caused by adverse food reaction). Among the nonspecific codes, the highest PPV (7.4%) derived from ICD-9 code 995.1 (angioneurotic edema).

The articles of Brown *et al.*⁹ and Miller *et al.*¹⁶ are similar in that they both examined angiotensin-converting enzyme (ACE) inhibitor-associated angioedema. They both used the same ICD-9 code, 995.1 (angioneurotic edema), specific to the angioedema outcome. Via chart reviews, these studies validated 90% and 95.3% of the administrative and claims-identified angioedema cases, respectively.

Johannes *et al.*¹⁵ studied serious allergic reactions to fluoroquinolone antibacterials using three ICD-9 diagnostic codes and two procedure codes to identify possible anaphylaxis. Clinical review confirmed anaphylaxis in 16 of 28 (57.1%) patients with ICD-9 code 995.0 (anaphylactic shock) and in 1 of 35 (2.9%) patients on the basis of a procedure code consistent with resuscitation.

Iribarren *et al.*¹⁷ studied anaphylactic shock and other allergy diagnoses using data from Kaiser Permanente of Northern California. The authors cited Bohlke *et al.*¹¹ as the basis for their algorithms, and they undertook their own validation of the 'other anaphylactic shock' ICD-9 code (995.0). On review of the medical records, 52% of events were confirmed as probable anaphylactic shock, 72% were considered probable or possible anaphylactic shock, and 93% of cases had probable, possible, or a history of anaphylactic shock.

Table 1. Anaphylaxis coding algorithms and PPV of citations with validation

Citation	Study population and time period	Description of outcome studied	Algorithm	Validation/adjudication procedure and operational definition	Validation statistics
Brown <i>et al.</i> ⁹	Tennessee Medicaid Program. The study cohort consisted of enrollees who were 15 years of age and older with at least 1 year of Medicaid enrollment to ensure a full year of previous drug exposure information before cohort entry ($n = 91$), 1986–1992	Risk of ACE inhibitor-associated angioedema	Angioneurotic edema (<i>ICD-9-CM</i> code of 995.1): based on first paid claim with a coded diagnosis of angioneurotic edema while receiving an ACE inhibitor	Medical record review. Angioedema was defined as swelling of the face, lips, mouth, or airway	PPV = 90% (82 of 91); PPV was 98% in black subjects and 78% in white subjects
Bohlke <i>et al.</i> ¹¹	Group Health Cooperative data, 1991–1997. The study population consisted of the 229,422 children and adolescents under the age of 18 years	Incidence of anaphylaxis from all causes	Codes specific to anaphylaxis: 995.0 (anaphylactic shock), 995.6 (anaphylactic shock caused by adverse food reaction), 999.4 (anaphylactic shock caused by serum), 995.4 (shock caused by anesthesia); codes not specific to anaphylaxis: 989.5 (toxic effect of venom), 708.0 (allergic urticaria), 708.9 (urticaria unspecified), 995.1 (angioneurotic edema), 995.3 (allergy, unspecified), 695.1 (erythema multiforme)	Validation was performed via chart review; a child was classified as potentially atopic when he or she had a medically recorded history of asthma, hay fever, eczema, allergic bronchitis, reactive airway disease or bronchitis, other allergies, or use of albuterol or another inhaler; episodes were classified as 'probable' or 'possible' anaphylaxis; operational definition: provided in the article as a figure	PPVs for codes specific to anaphylaxis: 995.0 (anaphylactic shock) = 55.3% (57 of 103), 995.6 (anaphylactic shock caused by adverse food reaction) = 9.8% (10 of 102), 999.4 (anaphylactic shock caused by serum) = 0, 995.4 (shock caused by anesthesia) = 0%; PPVs for codes not specific to anaphylaxis: 989.5 (toxic effect of venom) = 4.6% (10 of 216), 708.0 (allergic urticaria) = 5.6% (3 of 54), 708.9 (urticaria unspecified) = 0%, 995.1 (angioneurotic edema) = 7.4% (4 of 54), 995.3 (allergy, unspecified) = 1.3%, 695.1 (erythema multiforme) = 0% PPV for 995.0 (anaphylactic shock) = 57.1% (16 of 28); PPVs for 995.3 (allergy, unspecified) and 995.2 (unspecified adverse effect of drug) were not reported; PPV for CPT 92950 (cardiopulmonary resuscitation) and HCPCS J7640 (adrenaline injection) combined = 2.9% (1 of 35)
Johannes <i>et al.</i> ¹⁵	Ingenix Research Data Mart. The study population comprised patients receiving at least one dispensing of moxifloxacin, ciprofloxacin, levofloxacin, gatifloxacin, phenoxymethyl-penicillin potassium, or a combined group of first-, second-, and third-generation cephalosporins. Patients who were dispensed more than one study drug were placed into each relevant drug group and thus could appear in	Drug-specific incidence of serious allergic reactions after fluoroquinolone, cephalosporin, and phenoxymethyl-penicillin potassium exposure. The authors followed each person for 14 days after each study drug dispensing and counted the first ED or hospitalization (inpatient) visit during this time.	A serious allergic reaction was defined as the presence of at least one claim for services occurring during the index inpatient or ED visit bearing <i>ICD-9</i> diagnosis codes of 995.0 (anaphylactic shock), 995.2 (unspecified adverse effect of drug), 995.3 (allergy, unspecified), a CPT code of 92950 for cardiopulmonary resuscitation, or an HCPCS code for adrenaline injection (J7640).	Medical record review. An abstraction form recorded information in a standardized format from the medical record that might verify the occurrence of an anaphylactoid or anaphylactic reaction. All completed abstraction forms and supporting documentation were reviewed by a clinician (ED physician) for the determination of case status, date of onset, and	

(Continues)

Table 1. (Continued)

Citation	Study population and time period	Description of outcome studied	Algorithm	Validation/adjudication procedure and operational definition	Validation statistics
Miller ¹⁶ <i>et al.</i>	more than 1 treatment group. Approximately 200 000 initiators were in each treatment group. Sixty-four possible cases of serious allergic reactions were identified from 1 July 2000 to 30 June 2004. VA Health Care System data; cohort consisted of all VA patients who received VA prescriptions for antihypertensive medications ($n = 869$), 1 October 1998 through 31 December 2000.	Incidence of angioedema in new users of ACE inhibitors	ICD-9-CM code 995.1 (angioedema)	any exposure noted as presumed to precipitate the event. Medical chart review. Confirmation of angioedema in the medical chart was based on explicit notation of the diagnosis and description of the relevant symptoms in notes near the time of the code assignment. Additional information from earlier and later notes in the record indicating corrected or alternative diagnoses was applied to reclassify confirmation status.	PPV = 95.3% (82 of 91)
Iribarren <i>et al.</i> ¹⁷	Kaiser Permanente of Northern California (KPNC). The study cohort consisted of 526 406 individuals of all ages with evidence of healthcare utilization for asthma during the study period (1 January 1996 to 31 December 2006) and active KPNC membership on the index date. Patients were excluded for healthcare utilization for COPD within 1 year before the index date. In addition, a reference cohort was formed by individually matching KPNC members without asthma ($n = 526 406$) on age, sex, and race/ethnicity to the asthma cohort.	Incidence of anaphylactic shock and other allergy diagnoses (allergic urticaria, anaphylaxis after stings, angioedema) in an asthma cohort, compared with those without asthma.	Hospitalizations, ambulatory visits, and ED visits with ICD-9 codes: anaphylactic shock 995.6 (anaphylactic shock caused by an adverse food reaction), 999.4 (anaphylactic shock caused by serum), and 995.0 (other anaphylactic shock); other allergy-related diagnoses: 708.0 (allergic urticaria), 989.5 (anaphylaxis after sting(s)), and 995.1 (angioneurotic edema)	ICD-9 code 995.0 was validated via medical record review. A random sample of 120 medical records (access to 109) with that code were abstracted by a trained medical record analyst, and the abstraction was reviewed by a physician asthma specialist investigator using the criteria developed at the Second National Institute of Allergy and Infectious Disease/Food Allergy and Anaphylaxis Network symposium. Each patient was characterized as having likely/probable, possible, a history of, or no anaphylactic shock.	PPVs only available for ICD-9 code 995.0, by patient probability criteria: likely/probable anaphylactic shock, 52% (57 of 109); likely/probable + possible, 72% (79 of 109); likely/probable + possible + history of anaphylactic shock, 93% (102 of 109)
West ¹⁸ <i>et al.</i>	South Carolina EDs for patients <19 years ($n = 63$), 2000–2002	Drug-related anaphylaxis	Probable or possible anaphylaxis: 995.0 (anaphylactic shock) and any drug code* or involvement of at least two systems	Two nurses were responsible for abstracting the medical records, with the primary focus of determining whether the ICD-9-	Probable or possible anaphylaxis: PPV = 38.0% (19 of 50); other drug-related allergic reactions: PPV = 15.0% (2 of 13)

(Continues)

Table 1. (Continued)

Citation	Study population and time period	Description of outcome studied	Algorithm	Validation/adjudication procedure and operational definition	Validation statistics
			(dermatologic, [†] respiratory, [‡] and/or cardiovascular [§]) and any drug code; other drug-related allergic reactions: 995.1 (angioneurotic edema) and a code from the DrugsE category* and at least one of the following: allergic reaction or allergy unspecified, another dermatologic code, or an ICD-9-CM code from DrugsD*	CM codes in the South Carolina Emergency Room Hospital Discharge Data for drug-related anaphylaxis could be substantiated by the clinical notes. A standard abstraction process was used, including abstractor training with extensive data checks to correct inconsistent or potentially erroneous values.	
ED, emergency department; VA, Veterans Affairs.					
*Any drug code (DrugsD, DrugsE, or DrugsP) where DrugsD = 693.0 (dermatitis due to drugs) or 995.2 (unspecified adverse effect of drug), DrugsE = E930–E949 (drugs and medicinal and biological substances causing adverse effects in therapeutic use), excluding E934.6 (gamma globulin) and E934.7 (natural blood products); and DrugsP = 960–969 (poisoning by drugs, medicinal and biological substances), E850 (accidental poisoning by analgesics, antipyretics, and antirheumatics), E950 (suicide and self-inflicted poisoning by solid or liquid substances), E962 (assault by poisoning), or E980 (poisoning by solid or liquid substances, undetermined whether accidentally or purposely inflicted).					
[†] Dermatological manifestations: 708.0, 708.1, 708.9 (urticaria, allergic, idiopathic, unspecified), and 995.1 (angioneurotic edema).					
[‡] Respiratory manifestations: 478.75 (laryngeal spasm), 478.8 (upper respiratory tract hypersensitivity, site unspecified), 786.05 (shortness of breath), 786.07 (wheezing), 786.09 (respiratory insufficiency, distress), and 786.1 (stridor).					
[§] Cardiovascular manifestations: 458.9 (hypotension) and 785.0 (tachycardia, unspecified).					

West *et al.*¹⁸ used the South Carolina Emergency Room Hospital Discharge Data to examine drug-related anaphylaxis in children and adolescents. They developed an intricate algorithm that included ICD-9 diagnostic codes representing acute allergic reactions (i.e. 995.0 [anaphylactic shock], 995.1 [angioneurotic edema]) or codes representing dermatological, respiratory, and cardiovascular manifestations (two of three systems must have been present), in combination with drug-related ICD-9 diagnostic or external cause-of-injury codes. Details of algorithms and corresponding PPVs are provided in Table 1 (with the number of subjects used to calculate each PPV in parentheses). The PPVs were 38% for 'probable or possible anaphylaxis' and 15% for 'other drug-related allergic reactions'; the combined PPV was 32%.

DISCUSSION

This literature review identified several validation studies on coding algorithms for anaphylaxis. These studies used the following anaphylaxis-specific coding algorithms: ICD-9 codes 995.0 (anaphylactic shock), 995.6 (anaphylactic shock caused by adverse food reaction), 999.4 (anaphylactic shock caused by serum), and 995.4 (shock caused by anesthesia), and 'nonspecific codes' such as 989.5 (toxic effect of venom), 708.0 (allergic urticaria), 708.9 (urticaria unspecified), 995.1 (angioneurotic edema), 995.2 (unspecified adverse effect of drug, medicinal and biological substance), 995.3 (allergy, unspecified), and 695.1 (erythema multiforme). *Current Procedural Terminology (CPT)* code 92950 (cardiopulmonary resuscitation) and the Healthcare Common Procedure Coding System (HCPCS) code for adrenaline injection (J7640) were also used as part of the coding algorithm for anaphylaxis.

The codes most commonly used in the studies with validation estimates (each in four of the six validated studies) were the anaphylaxis-specific code 995.0 (anaphylactic shock) and the nonspecific code 995.1 (angioneurotic edema). These codes are also the basis of the 'probable anaphylaxis' and 'other drug-related allergic reactions' definitions used by West *et al.*,¹⁸ each of which incorporated multiple additional diagnosis or injury codes that are incorporated as footnotes to Table 1.

The PPV of the latter of these codes, 995.1 (angioneurotic edema), varied greatly. The PPV was poor when examining all-cause anaphylaxis (PPV = 7.4%)¹¹ and when used as the basis of an intricate algorithm aimed to identify any drug-related anaphylaxis in children and adolescents (PPV = 15.4%).¹⁸ In contrast, PPVs of 90%

and 95.3% were obtained when the focus was on ACE inhibitor-associated angioedema.^{9,16} Angioneurotic edema is characterized by a subcutaneous edema of sudden onset and short duration that most often involves the larynx, tongue, lips, and face. When the airways are affected, it can be a life-threatening condition.¹⁶ Because of these clear clinical symptoms, we are not surprised by these high PPVs, as misdiagnosis of angioneurotic edema is very unlikely. However, despite these high PPVs, detection of angioedema via diagnostic codes in retrospective administrative and claims data is not likely to have been sensitive. Both Brown *et al.*⁹ and Miller *et al.*¹⁶ suggest that mild cases may not seek medical attention and that physicians may neglect to code a diagnosis of angioedema in outpatient settings. In addition, because the clinical manifestations of anaphylaxis are broad, mild cases may be more difficult to diagnose as anaphylaxis. For these reasons, administrative and claims-based algorithms may underestimate the true incidence of ACE inhibitor-associated angioedema. The overall incidence rates in these studies were estimated at 1.60 and 1.97 per 1000 person-years, respectively.^{9,16} These are considerably lower than the rates reported from a large-scale clinical trial (Omapatrilat Cardiovascular Treatment Assessment vs. Enalapril [OCTAVE] Trial) with more than 25 000 subjects that featured prospective adjudication of cases and probably included many mild cases that may have been missed in these administrative and claims-based studies.¹⁹

The other algorithm used in multiple studies was ICD-9 code 995.0 (anaphylactic shock). Both Bohlke *et al.*¹¹ and Johannes *et al.*¹⁵ used similar data (i.e. from commercially based insurance carriers) yet examined very different outcomes (all-cause anaphylaxis versus serious allergic reactions to fluoroquinolone antibacterials). Despite this, the reported PPVs for ICD-9 code 995.0 were very similar: 55.4% and 57.1%, respectively. These numbers are not high, but they provide better identification of anaphylaxis cases than other codes used in these reports. The PPV of other diagnostic and procedural codes (for resuscitation or adrenaline injection) used to identify anaphylaxis-related conditions in these two studies never exceeded 10%. Iribarren *et al.*¹⁷ also used code 995.0 to identify all-cause anaphylaxis and reported a higher PPV of 72% when using comparable categorizations to that of Bohlke *et al.*¹¹ (i.e. probable or possible criteria). In contrast to the other studies using ICD-9 code 995.0, West *et al.*¹⁸ used the code as the basis of their 'probable anaphylaxis' definition. When combined with their 'possible anaphylaxis' definition, which incorporated drug-related diagnosis codes, adverse drug-effect injury codes, and diagnosis and injury codes indicating drug poisonings, a PPV of 38% was achieved.

The reported PPV in Bohlke *et al.*¹¹ may, however, be an underestimate, as these values are derived from calculations where the denominator is based on the number of visits with a particular code rather than the number of cases. Inclusion of follow-up and consultation visits with anaphylaxis-related codes in the denominator is likely to reduce PPV estimates. The authors noted that most (95%) of the rejected diagnoses of ICD-9 code 995.6 (anaphylactic shock caused by adverse food reaction) were follow-up visits and/or allergy/immunology consultations.¹¹ The recent study by Iribarren *et al.*¹⁷ used a case-based denominator instead of a diagnosis-based denominator and reported a higher PPV when other validation factors (e.g. algorithms, categorization criteria) were similar to those of Bohlke *et al.*¹¹ This suggests that the true PPV of ICD-9 code 995.0 may be higher than reported in the studies that used the number of visits with a diagnosis code as the denominator for validation calculations.

The diagnosis-based denominator in Bohlke *et al.*,¹¹ however, provides a look into the frequency of how often individual diagnostic codes are used when interest lies in all-cause anaphylaxis. Of the 29 035 distinct instances of any anaphylaxis-related diagnostic code in their data, 69% ($n = 20\,055$) had ICD-9 code 995.3 (allergy, unspecified), which had a PPV of only 1.3%. By contrast, less than 0.4% ($n = 106$) distinct occurrences of ICD-9 code 995.0 (anaphylactic shock) appeared in their data. As ICD-9 code 995.0 was the only code in Bohlke *et al.*¹¹ with a PPV of greater than 50%, it well illustrates that a high PPV in itself may not be adequate to identify anaphylaxis and anaphylaxis-related conditions via administrative and claims-based definitions. Incorporation of more complicated algorithms making use of procedural codes in combination with anaphylaxis-related diagnostic codes may assist in improved identification of this outcome.

CONCLUSION

Our review found that among the few studies validating the algorithms for anaphylaxis and related conditions, ICD-9 code 995.0 (anaphylactic shock) was the most commonly used anaphylaxis-specific diagnostic code; the corresponding PPV ranged from 38.0% to 72.0%. Among diagnostic codes not specific to anaphylaxis conditions, ICD-9 code 995.1 (angioneurotic edema) was most commonly validated and had a PPV ranging from 90% to 95.3% when limited to ACE inhibitor angioedema but exhibited substantially lower PPV when applied to the broader all-cause anaphylaxis or all drug-related anaphylaxis outcomes.

Our review highlights limited literature focusing on anaphylaxis and related conditions that also provided validated algorithms and prediction estimates. Of those studies fulfilling these criteria, differences in the study populations and outcomes of interest hinder direct comparisons of PPVs. Furthermore, diagnostic codes producing high PPVs are seemingly not commonly used in administrative and claims data or produce these high PPVs only when applied to a very specific condition after a very specific exposure.

Further research needs to be conducted on the development and validation of a comprehensive anaphylaxis algorithm to be used to identify anaphylaxis cases from administrative and claims databases. The algorithms in the reviewed studies were simplistic; administrative and claims-based identification of anaphylaxis and related conditions was dependent on diagnostic or procedural codes that were applied individually. Improvement may be possible by incorporating more complicated algorithms that use combinations of diagnostic and procedural codes. For example, the procedural codes used by Johannes *et al.*¹⁵ (for resuscitation or adrenaline injection) in combination with applicable diagnostic codes may improve PPV. If interest lies in the more severe end of the anaphylaxis spectrum, limiting administrative and claims-based definitions to hospitals and emergency rooms may be warranted because this is where patients are likely to seek care. When interest lies in anaphylaxis following a specified trigger, administrative and claims-based algorithms should also incorporate these exposures (e.g. prescribed medication) whenever possible.

CONFLICT OF INTEREST

The authors declare no conflict of interest. This is not product-specific or privately funded research. The views expressed in this document do not necessarily reflect the official policies of the Department of Health and Human Services nor does mention of trade names, commercial practices, or organizations imply endorsement by the US government.

KEY POINTS

- There is limited literature focusing on anaphylaxis that provides administrative and claims data-based coding algorithms and validation estimates.
- Additional research is needed regarding the use of administrative and claims data-based coding algorithms to identify anaphylaxis.

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