

A systematic review of validated methods for identifying hypersensitivity reactions other than anaphylaxis (fever, rash, and lymphadenopathy), using administrative and claims data

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ABSTRACT

Purpose The Food and Drug Administration's Mini-Sentinel pilot program 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 hypersensitivity reactions.

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

Results We identified five studies that provided validated hypersensitivity-reaction algorithms. Algorithm positive predictive values (PPVs) for various definitions of hypersensitivity reactions ranged from 3% to 95%. PPVs were high (i.e. 90%–95%) when both exposures and diagnoses were very specific. PPV generally decreased when the definition of hypersensitivity was expanded, except in one study that used data mining methodology for algorithm development.

Conclusions The ability of coding algorithms to identify hypersensitivity reactions varied, with decreasing performance occurring with expanded outcome definitions. This examination of hypersensitivity-reaction coding algorithms provides an example of surveillance bias resulting from outcome definitions that include mild cases. Data mining may provide tools for algorithm development for hypersensitivity and other health outcomes. Research needs to be conducted on designing validation studies to test hypersensitivity-reaction algorithms and estimating their predictive power, sensitivity, and specificity. Copyright © 2012 John Wiley & Sons, Ltd.

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

INTRODUCTION

Mini-Sentinel is the Food and Drug Administration's pilot program that aims to conduct active surveillance using 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. In this article, we describe the algorithm review process and findings for 1 of the 20 HOIs selected for review by the Food and Drug Administration: hypersensitivity reactions (HSRs).

Drug hypersensitivity is defined as an immune-mediated response to a drug agent in a sensitized patient that is inappropriate or excessive.¹ HSRs account for 5% to 10% of all adverse drug reactions, which as a group are responsible for 2% to 5% of all hospital admissions, cause more than 100 000 deaths per year, and impose an economic burden of \$1.5 to \$4 billion per year in the United States.^{1,2}

The Gell and Coombs system is the most common method of classifying drug hypersensitivity. This classification system consists of four types of immunological reactions: IgE mediated (type I), cytotoxic (type II),

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immune complex (type III), and delayed, cell mediated (type IV).³ Some HSRs, however, may not fit into any of these classes. Such reactions include Stevens–Johnson syndrome, toxic epidermal necrolysis, lupus-like syndrome, anticonvulsant hypersensitivity syndrome, and maculopapular rashes,¹ a class of reactions that was the focus of an alternative HOI selected for review.

Type I reactions, also termed drug allergies or immediate hypersensitivity, occur minutes to hours after drug exposure and manifest most commonly with cutaneous symptoms (e.g. angioedema, urticaria, pruritus) but can also feature anaphylaxis, bronchospasm, and flulike symptoms.^{1,4} A common example of a type I HSR is an allergy to beta-lactam antibiotics, including penicillin, which can result in anaphylaxis.^{1,2}

Type II reactions are mediated by the binding of cytotoxic antibodies, primarily immunoglobulin M and immunoglobulin G, to antigens on cell surfaces.⁴ The time of onset for type II reactions and their clinical manifestations varies from immediate to days after exposure.^{1,4} Common clinical manifestations include hemolytic anemia, thrombocytopenia, and agranulocytosis, and frequent causative agents include sulfonamides, penicillin, and heparin.^{1,3,5}

Type III reactions occur when antigens and immunoglobulin G or immunoglobulin M antibodies are present in equal amounts and cross-link to form immune complexes, which deposit in tissues and induce inflammation.^{1,2} These reactions can occur hours, days, or weeks after drug exposure and can manifest as conditions such as systemic lupus erythematosus, serum sickness, vasculitis, or glomerulonephritis, with symptoms including lymphadenopathy, cutaneous reactions, fever, and arthralgia.^{1,4,5} Hydralazine-induced systemic lupus erythematosus is a prominent example of type III hypersensitivity.²

Type IV reactions differ from the other three types in that they are cell mediated rather than mediated by antibodies; they occur when T lymphocytes recognize antigens in major histocompatibility complexes and induce the release of cytokines and inflammatory mediators.⁴ An example of a type IV reaction is allergic contact dermatitis.^{1,2}

METHODS

The general search strategy originated from prior work by the Observational Medical Outcomes Partnership (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 Moores⁶. In brief, the base PubMed

search was combined with the following terms to represent the HOI: ‘drug hypersensitivity’, ‘hypersensitivity, delayed’, ‘conjunctivitis allergic’, ‘dermatitis, atopic’, ‘urticaria’, ‘vasculitis, leukocytoclastic, cutaneous’, ‘immune complex diseases’, ‘Wissler’s syndrome’, ‘histiocytosis’, ‘lymphadenitis’, ‘lymphangiectasis’, ‘lymphangitis’, ‘lymphedema’, ‘mucocutaneous lymph node syndrome’, and ‘pseudolymphoma’. With the exception of ‘drug hypersensitivity’, each of these was searched in conjunction with the following terms: ‘chemically induced’, ‘classification’, ‘drug effects’, and ‘epidemiology’.

To identify other relevant articles that were not found in the PubMed search, the Iowa Drug Information Service Web (IDIS/Web) was also searched using a similar search strategy. The PubMed and IDIS searches were conducted on 8 May 2010 and 12 June 2010, respectively. An additional PubMed search was conducted on 6 July 2010 to amend the original search strategy with additional databases. All searches were restricted to articles published in 1990 or later. The details of these searches can be found in the full report on the Mini-Sentinel Web site at http://mini-sentinel.org/foundational_activities/related_projects/default.aspx.

The search results from different databases were compiled and duplicate results were eliminated. The results were then output and provided to organizations contracted to conduct the literature reviews. Mini-Sentinel collaborators were also asked to help identify any 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 Cohen’s kappa statistic. 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 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 total number of citations identified from the combined searches was 392 (PubMed, 342; IDIS, 42; additional PubMed, 8); excluding overlap, the total number

of unique citations from the combined searches was 389. Mini-Sentinel collaborators provided no additional published or unpublished reports of validation studies.

Of the 389 abstracts reviewed, we accepted 46 for full-text review. Because of the straightforward inclusion criteria, which consisted of (i) the examination of the HOI, (ii) the use of an administrative and claims database, and (iii) the 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=0.98). There was, however, limited agreement on the reasons for rejection. Among the 343 rejected abstracts, interrater agreement (via kappa coefficient) was 0.07, 0.19, and 0.42 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 a function of the different reviewers focusing on different criteria rather than a true lack of agreement; they also illustrate that many rejected articles fulfilled multiple exclusion criteria.

Of the 46 full-text articles reviewed, 41 were excluded. Thirty-six articles were excluded during full-text review: 2 articles were excluded because the HOI identification algorithm was poorly defined, 14 articles were excluded because they did not include validation of the outcome definition or report validity statistics, and 20 articles were excluded for other reasons (15 articles, no *International Classification of Diseases, Ninth Revision [ICD-9]*, code; 3 articles, not an administrative and claims database; and 2 articles, no codes for the HOI). Cohen's kappa for agreement between reviewers on inclusion versus exclusion of full-text articles reviewed was 0.38. Of the 10 articles identified by either or both reviewers, 5 articles were excluded upon additional review: 3 articles due to lack of *ICD-9* codes⁷⁻⁹ and 2 articles due to lack of validation,^{10,11} reducing the total number of articles fulfilling all criteria to 5.

SUMMARY OF ALGORITHMS

We came across five studies that provided codes for HSRs and provided validation estimates. Summaries of the study populations, outcomes, coding algorithms, and validation methods with corresponding positive predictive values (PPVs) of the five citations are presented in Table 1. As can be seen, coding algorithms for HSRs were straightforward, consisting of codes representative of acute allergic reactions or HSR-

relevant symptoms as well as sophisticated, using combinations of diagnostic codes.

The articles of Brown *et al.*¹² and Miller *et al.*¹³ 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 claims-identified angioedema cases, respectively.

Johannes *et al.*¹⁴ 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); however, note that this code is a generalized type I HSR and does not belong to this HOI, which is defined as HSRs other than anaphylaxis. Johannes *et al.*¹⁴ also confirmed serious allergic reaction in 1 of 35 (2.9%) patients on the basis of a procedure code consistent with resuscitation; PPVs for code 995.3 (allergy, unspecified) and code 995.2 (unspecified adverse effect of drug) were not reported.

Nordstrom *et al.*¹⁵ examined abacavir hypersensitivity during the interval from the date of the last dispensing through 14 days after the end of supply. Medical records of 934 subjects were reviewed, from which 22 HSR cases were confirmed. They examined a lengthy list of codes, including HSR-related symptoms, diagnoses, and procedures as well as common non-HSR-related diagnoses, and reported the number of patients with and without an HSR event who presented 31 groupings of these codes (sometimes a grouping consisted of multiple codes). From this information, we calculated PPVs, which are presented in Table 1 (with the number of subjects used to calculate each PPV in parentheses). Among six subjects with the *ICD-9* code 995.3 (allergy, unspecified), the PPV was 83.3%. Groupings of *ICD-9* codes including 995.3 and/or 995.2 (unspecified adverse effect of drug) in aggregate with 995.0 (anaphylactic shock) resulted in PPVs between 61% and 64%. Note that anaphylactic shock is a generalized type I HSR not belonging to this HOI.

Although we were able to calculate PPVs from the descriptive information in Nordstrom *et al.*,¹⁵ the intent of their research was to develop sophisticated HSR-identifying algorithms via two data-mining analyses (recursive partitioning and random forests). In fact, the PPVs from Nordstrom *et al.*¹⁵ presented in Table 1 represent only the *ICD-9* codes used in the final classification trees aimed at identifying the 22 HSR

Table 1. Hypersensitivity 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> ¹²	Tennessee Medicaid Program; 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 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
Miller <i>et al.</i> ¹³	VA Health Care System data; cohort consisted of all VA patients who received VA prescriptions for antihypertensive medications ($n=869$), 1 October 1998 to 31 December, 2000	Incidence of angioedema in new users of ACE inhibitors	<i>ICD-9-CM</i> code 995.1 (angioedema)	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)
Johannes <i>et al.</i> ¹⁴	Ingenix Research Data Mart. The study population comprised patients receiving at least one dispensing of moxifloxacin, ciprofloxacin, levofloxacin, gatifloxacin, phenoxymethylpenicillin 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 more than one treatment group. Approximately 200 000 initiators were in each treatment group. Sixty-four possible cases of serious allergic reactions were identified between 1 July 2000 and 30 June 2004	Drug-specific incidence of serious allergic reactions after fluoroquinolone, cephalosporin, and phenoxymethylpenicillin 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 995.0 (anaphylactic shock), 995.2 (unspecified adverse effect of drug), 995.3 (allergy, unspecified), a <i>CPT</i> code of 92950 for cardiopulmonary resuscitation, or an HCPCS code for adrenaline injection (J7640).	Medical record review. An abstraction form was used to record 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 determination of case status, date of onset, and any exposure noted as presumed to precipitate the event.	PPV for code 995.0 (anaphylactic shock) = 57.1% (16 of 28). PPVs for code 995.3 (allergy, unspecified) and code 995.2 (unspecified adverse effect of drug) were not reported. PPV for <i>CPT</i> 92950 (cardiopulmonary resuscitation) and HCPCS J7640 (adrenaline injection) combined = 2.9% (1 of 35).
Nordstrom <i>et al.</i> ¹⁵	Ingenix Research Database; patients who received their first dispensing of abacavir ($n=934$), for whom 22 HSRs were confirmed	Abacavir-associated HSR	For a data-mining exercise, a lengthy list of codes, including HSR-related symptoms, diagnoses, and procedures as well as	Potential events identified from the claims were validated through review of medical claims, medical record abstraction, and review	From the list of codes, we calculated PPVs.

(Continues)

Table 1. (Continued)

Citation	Study population and time period	Description of outcome studied	Algorithm	Validation/adjudication procedure and operational definition	Validation statistics
	from 1 January 1999 to 31 July 2003.		common non-HSR-related diagnoses was examined. The number of patients with and without an HSR event who presented 31 groupings of these codes (sometimes a grouping consisted of multiple codes) were examined.	by a panel of four clinical HIV specialists. Development and of an algorithm via data mining approaches identified 22 HSR events identified from claims and was validated through medical record review. The analysis produced a classification tree with three decision nodes that comprised the best indicators of HSRs. The predictors included any 1 of several specific symptoms commonly found with this reaction; a claims diagnosis of adverse effect of drug, anaphylactic shock, or unspecified allergy; and a discontinuation in abacavir before completing a 90-day course of therapy.	Acute allergic reactions PPV for code 995.0 (anaphylactic shock) and code 995.2 (unspecified adverse effect of drug) combined = 61.1% (11 of 18). PPV for code 995.3 (allergy, unspecified) = 83.3% (5 of 6). PPV for codes 995.0, 995.2, and 995.3 combined = 63.6% (14 of 22). Selected HSR-relevant symptoms PPV for code 780.6 (fever) = 37.9% (11 of 29). PPV for code 780.7 (malaise) = 21.9% (7 of 32). PPV for code 787.0 (nausea [with or without vomiting]) = 25.0% (4 of 16). PPV for code 784.0 (headache) = 37.5% (3 of 8). PPV for code 782.1 (rash) = 25.0% (3 of 12). Data-mining approach The classification tree algorithm demonstrated 95% sensitivity and 90% specificity when tested using a bootstrap resampling approach with the current data.
West <i>et al.</i> ¹⁶	South Carolina EDs for patients <19 years (<i>n</i> = 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 (dermatologic, [†] respiratory, [‡] and/or cardiovascular [§]) and any drug code Other drug-related allergic reactions: 995.1 (angioneurotic edema)	Two nurses were responsible for abstracting the medical records, with the primary focus of determining whether the <i>ICD-9-CM</i> codes in the South Carolina Emergency Room Hospital Discharge Data for drug-related anaphylaxis could be substantiated by the clinical notes. A standard	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
			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*	abstraction process was used, including abstractor training with extensive data checks to correct inconsistent or potentially erroneous values.	

CPT, Current Procedural Terminology; ED, emergency department; HCPCS, Healthcare Common Procedure Coding System; ICD-9-CM, International Classification of Diseases, Ninth Revision, Clinical Modification; 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, 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 anti-rheumatics), 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).

cases. The classification tree was initiated with a dichotomy of HSR-relevant symptoms. Among those with any HSR-relevant symptom, those with abacavir discontinuation were considered to have an HSR. Among those with no HSR-relevant symptoms, those with ICD-9 codes 995.3 (allergy, unspecified), 995.2 (unspecified adverse effect of drug), or 995.0 (anaphylactic shock) were considered to have an HSR. This algorithm identified 21 of the 22 HSR cases, of which 18 were identified from the ‘with HSR-relevant symptom’ branch that did not incorporate the anaphylactic shock diagnostic code, which is a generalized type I HSR not belonging to this HOI. Both data-mining methods resulted in the same classification trees and demonstrated in excess of 95% sensitivity and 90% specificity when tested via a bootstrap resampling approach.¹⁵

The final article fulfilling all inclusion criteria, West *et al.*,¹⁶ 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 PPV

for ‘probable or possible anaphylaxis’ was 38% and was 15% for ‘other drug related allergic reactions’; the combined PPV was 32%.

DISCUSSION

This literature review identified several validation studies for hypersensitivity coding algorithms. The basis of algorithms consisted of the following ICD-9 codes: 995.0 (other anaphylactic shock), 995.1 (angioneurotic edema), 995.2 (unspecified adverse effect of drug), and 995.3 (allergy, unspecified). Although the simpler algorithms consisted of a single code,^{12–14} the more complicated algorithms used combinations of these codes in conjunction with additional codes representing HSR-related symptoms, clinical manifestations, and/or adverse event drug codes.^{15,16} As a result, it was impossible to segregate this HOI’s formal definition of hypersensitivity, which was not meant to include anaphylaxis, from the definition of hypersensitivity used in these more complicated algorithms.

The highest PPVs identified, 90% and 95.3%, were related to ICD-9 code 995.1 (angioneurotic edema) when the focus was on ACE inhibitor-associated angioedema.^{12,13} 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.¹³ These clear clinical symptoms suggest that angioedema misdiagnosis is

very unlikely; we are therefore not surprised by the corresponding high PPVs.

Despite these high PPVs, the detection of angioedema via diagnostic codes in administrative and claims data is not likely to have been sensitive. Both Brown *et al.*¹² and Miller *et al.*¹³ used administrative and claims data consisting of inpatient and outpatient claims. This is the genesis of a potential surveillance bias that presents when using such data to examine outcomes that include mild cases. Namely, although these data reliably capture billable interactions between a patient and the healthcare system, mild cases may not seek medical attention. Claims-based algorithms will therefore underestimate the true incidence of diseases that include mild cases.

As it relates to this report, the noncapture of such mild cases in combination with the possibility that physicians may neglect to code a diagnosis of angioedema in outpatient settings may result in an underestimate of the true incidence of ACE inhibitor–associated angioedema. The overall incidence in these studies was estimated at 1.60 and 1.97 per 1000 person-years, respectively.^{12,13} These are considerably lower than the rates reported from a large-scale clinical trial (Omapatrilat Cardiovascular Treatment Assessment vs. Enalapril [OCTAVE] Trial), where a rate of 6.8 per 1000 for more than 24 weeks of follow-up among 12 557 Enalapril subjects was estimated. OCTAVE was conducted using prospective adjudication of cases, 75% of which were the least severe type 1 reactions—cases that may have been largely missed in claims-based studies.¹⁷

By contrast, in West *et al.*,¹⁶ where the focus was on emergency room data, all confirmed cases of drug-related anaphylaxis were identified (i.e. sensitivity = 1.0); however, a large proportion of false-positives was also identified, leading to a low specificity (0.28) and a low overall PPV of 32%.

The validation study by Nordstrom *et al.*¹⁵ is unique in that the algorithm was built via a data-mining approach. Despite the often low PPV of each individual code, their data-driven algorithm, which used a multitude of diagnostic and procedure codes, was proven to be highly sensitive and specific via bootstrap resampling. This contrasts with other algorithms developed via the *a priori* beliefs of investigators, and we believe it may be an efficient method to identify this and other HOIs. Even *a priori* algorithms of equal or greater complexity, such as that in West *et al.*,¹⁶ did not achieve similarly promising results. Of course, validation of external data would be the true test of such methodology.

The operational definition of HSRs is obviously wide. It captures several distinct symptoms and

syndromes that result from hypersensitivity. The PPVs reported in this review range from very good to quite poor, with the latter generally focusing on HSR as a whole and the former focusing on very specific diagnoses and drug reactions. This suggests that HSR coding algorithms may not be able to focus on the full gamut of HSRs as a single phenomenon. However, when a specific HSR is of interest, narrower definitions can be developed and, subsequently, more specific coding algorithms can be built.

Although specific diagnoses and drug reactions yielded high PPVs, HSR coding algorithms are further hindered because HSRs other than serious hypersensitivities are nonemergency conditions that can be treated in both inpatient and outpatient settings. When the HSR is serious, healthcare providers are more likely to document appropriate codes. However, the conditions with less serious HSRs, even if recognized and treated, sometimes may not be documented with diagnostic codes for HSRs. In these cases, the development of more sophisticated coding algorithms that include important symptoms of HSRs, in addition to more specific ICD codes and information on drug discontinuations (if drug-related hypersensitivity) or appropriate procedural and diagnostic test codes, may enhance the predictive power of the algorithms.

CONCLUSION

Our review found that there is no specific ICD-9 code to identify HSRs but rather several specific and nonspecific codes referring to separate types of HSRs. When interest lies in a very specific HSR diagnosis and a very specific drug group, high PPV is possible. This was demonstrated in the studies by Brown *et al.*¹² and Miller *et al.*,¹³ who determined PPVs of greater than 90% for ACE inhibitor–associated angioedema. By contrast, as shown by West *et al.*,¹⁶ when the HSR definition is more general, even highly sophisticated algorithms may exhibit low PPV.

Despite the potential of high PPV, we illustrated that because of the noncapture of mild cases, the detection of angioedema is not likely to be sensitive. Such surveillance bias is a likely scenario when using administrative and claims data to examine any disease process that may include mild cases because these cases may not seek medical care and will not be incorporated into the billable interactions that are captured by these data. This limitation should be considered when using these types of data for pharmacoepidemiologic examinations.

There is limited literature focusing on HSRs 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 limited to algorithms applied to a very specific condition after a very specific exposure. The algorithm of Nordstrom *et al.*¹⁵ is a partial exception. Their work produced high validation estimates about a general HSR definition within the context of a specific exposure (i.e. abacavir). We believe it is merited to apply and validate their approach in other patients and care settings. Further research is recommended to develop and validate algorithms for HSRs.

CONFLICT OF INTEREST

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

KEY POINTS

- There is limited literature focusing on hypersensitivity that provides administrative and claims data-based coding algorithms and validation estimates.
- Algorithm development via data mining methods may outperform methods on the basis of *a priori* knowledge of disease process.
- Additional research is needed regarding the use of administrative and claims data-based coding algorithms to identify hypersensitivity.

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