

MINI-SENTINEL SYSTEMATIC EVALUATION OF HEALTH OUTCOME OF INTEREST DEFINITIONS FOR STUDIES USING ADMINISTRATIVE DATA

ANAPHYLAXIS, INCLUDING ANAPHYLACTIC SHOCK AND ANGIONEUROTIC EDEMA REPORT

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Mini-Sentinel is a pilot project sponsored by the [U.S. Food and Drug Administration \(FDA\)](#) to inform and facilitate development of a fully operational active surveillance system, the Sentinel System, for monitoring the safety of FDA-regulated medical products. Mini-Sentinel is one piece of the [Sentinel Initiative](#), a multi-faceted effort by the FDA to develop a national electronic system that will complement existing methods of safety surveillance. Mini-Sentinel Collaborators include Data and Academic Partners that provide access to health care data and ongoing scientific, technical, methodological, and organizational expertise. The Mini-Sentinel Coordinating Center is funded by the FDA through the Department of Health and Human Services (HHS) Contract number HHSF223200910006I.

Mini-Sentinel Systematic Evaluation Of Health Outcome Of Interest Definitions For Studies Using Administrative Data

Anaphylaxis, Including Anaphylactic Shock and Angioneurotic Edema Report

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I. EXECUTIVE SUMMARY

A. OVERVIEW OF PROJECT

The Food and Drug Administration (FDA) Mini-Sentinel contract is a pilot program that aims to conduct active surveillance to detect and refine safety signals that emerge for marketed medical products. To perform this active surveillance, it is necessary to develop and understand the validity of algorithms for identifying health outcomes of interest in administrative data. Thus, the goal of this project was to identify algorithms used to detect selected health outcomes of interest using administrative data sources and describe the performance characteristics of these algorithms as reported by the studies in which they were used. This report summarizes the process and findings of the anaphylaxis algorithm review.

B. SUMMARY OF FINDINGS

We came across 8 studies that provided the codes for anaphylaxis-related conditions and also employed some method of validation. Of these 8 studies, 4 provided some validation statistics.

Bohlke, et al.¹ found that ICD-9 code 995.0 (anaphylactic shock) had relatively higher positive predictive value (PPV 55%) compared to the other ICD-9 codes to predict “probable” or “possible” anaphylaxis. No other codes in Bohlke, et al.¹ produced PPVs that exceeded 10%. The study by Johannes, et al.,² however, produced a very similar PPV for ICD-9 code 995 (57.1%).

Studies by Miller, et al.³ and Brown, et al.⁴ focused on ICD-9 code 995.1 (angioneurotic edema) to predict angioneurotic edema. The PPV of this code to predict angioedema was high (95.3% and 90.0% in these studies, respectively).

C. RECOMMENDATION FOR ALGORITHMS AND SUGGESTION FOR FUTURE RESEARCH

Among the validation studies, the codes for anaphylaxis and related conditions included those specifically for anaphylaxis: ICD-9 codes 995.0 (anaphylactic shock), 999.4 (anaphylactic shock because of serum), 995.6 (anaphylactic shock caused by adverse food reaction), 995.4 (shock caused by anesthesia), and 995.1 (angioneurotic edema); and codes not specific to anaphylaxis: 989.5 (toxic effect of venom), 708.0 (allergic urticaria), 708.9 (urticaria unspecified), 995.3 (allergy, unspecified), and 695.1 (erythema multiforme).

Our review found that, among the few studies validating the algorithms for anaphylaxis and related conditions, ICD-9 code 995.0 (anaphylactic shock) was more commonly used and had a PPV ranging from 55% to 57.1%. Among anaphylaxis-related conditions, angioneurotic edema was most commonly validated; it 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 outcome.

Our review highlights limited literature focusing on anaphylaxis and related conditions that has provided validated algorithms and prediction estimates. 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.

II. PROJECT OBJECTIVES

The primary objective of this project was to identify studies that have validated algorithms used to identify various health outcomes of interest (HOIs) using administrative data from the United States or Canada, and to summarize the results of those validation studies. If fewer than five validation studies were identified, a secondary objective was to identify non-validated algorithms that were used to identify the HOIs using administrative data.

III. BACKGROUND

The Food and Drug Administration (FDA) Mini-Sentinel contract is a pilot program that aims to conduct active surveillance to detect and refine safety signals that emerge for marketed medical products. In order to perform this work, the program needed to identify algorithms used to detect various health outcomes of interest using administrative data sources and identify the performance characteristics of these algorithms as measured in the studies in which they were used. The data sources of interest were limited to those from the United States or Canada to increase their relevance to the Mini-Sentinel data sources, which are all from the United States. The Mini-Sentinel Protocol Core developed a preliminary list of approximately 140 potential health outcomes of interest, based on several criteria. These criteria included: 1) previous validation studies that had been identified in a textbook chapter reviewing the validity of drug and diagnosis data used in pharmacoepidemiologic studies,⁵ 2) a list of designated medical events developed from a proposed FDA rule on the safety-reporting requirements for human drug and biological products,⁶ and 3) the Observational Medical Outcomes Partnership (OMOP)'sⁱ commissioned reports on algorithms used to identify the health outcome using administrative data.⁷

From the original list of 140 HOIs, the Protocol Core worked with the FDA to select 20 for which reviews of algorithms would be completed. HOIs for which OMOP had already commissioned reports were purposefully excluded in order to avoid duplication of effort.

Anaphylaxis was one of the 20 HOIs selected for review. This report describes the review process and findings for the anaphylaxis definition algorithms.

IV. METHODS

A. SEARCH STRATEGY

The general search strategy was developed based on prior work by OMOP and its contractors, and modified slightly for these reports. Originally, OMOP contracted with two organizations to perform reviews of 10 HOIs. Because the search strategies used by each organization resulted in very different sets of articles, OMOP investigators reviewed the PubMed indexing of the articles deemed useful in final reports and developed a strategy that would identify the majority of these citations while maintaining efficiency in the number of abstracts that would need to be reviewed. Mini-Sentinel investigators made minor changes to this strategy that would result in the identification of more citations, and confirmed

ⁱ For more information, visit the [OMOP website](#).

empirically that the majority of relevant articles from one set of OMOP reports (angioedema)^{4,8} would be identified using this approach. The base search strategy was then combined with PubMed terms representing the HOIs. Medical subject heading (MeSH) terms were generally preferred as HOI search terms due to their likely specificity. Text word searches were sometimes used, particularly when the MeSH search resulted in a small number of citations for review. The workgroup also searched the database of the Iowa Drug Information Service (IDIS) using a similar search strategy to identify other relevant articles that were not found in the PubMed search. For a limited number of outcomes where very few citations were identified from PubMed and IDIS searches, EMBASE searches were conducted. Search results were restricted to articles published on or after January 1, 1990.

University of Iowa investigators compiled the search results from different databases and eliminated duplicate results using a citation manager program. The results were then output into two sets of files, one containing the abstracts for review and the other for documenting abstract review results.

The search strategy and results for anaphylaxis are detailed in the Results section. The PubMed and IDIS searches were conducted on May 10, 2010.

B. ABSTRACT REVIEW

1. Abstract Review Methods

Each abstract was reviewed independently by 2 investigators to determine whether the full-text article should be reviewed. Exclusion criteria were documented sequentially (i.e., if exclusion criterion 1 was met, then the other criteria were not documented). If the reviewers disagreed on whether the full text should be reviewed, then it was selected for review. Inter-rater agreement on whether to include or exclude an abstract was calculated using Cohen's kappa statistic. The goal was to review any administrative database study that used data from the United States or Canada and studied the HOI, as validation components of studies are not necessarily included in the abstract and other relevant citations might be identified from the references of such studies.

2. Abstract Exclusion Criteria

1. Did not study the HOI.
2. Not an administrative database study. Eligible sources included insurance claims databases as well as other secondary databases that identify health outcomes using billing codes.
3. Data source not from the United States or Canada.

C. FULL-TEXT REVIEW

1. Full-text Review Methods

Full-text articles were reviewed independently by 2 investigators, with a goal of identifying validation studies described in the article itself or from the reference section of the article. Citations from the article's references were selected for full-text review if they were cited as a source for the HOI algorithm, or were otherwise deemed likely to be relevant. Full-text review exclusion criteria were applied sequentially, because if fewer than 5 validation studies were identified, up to 10 of the articles

excluded based on the second criterion would need to be incorporated into the final report. If there was disagreement on whether a study should be included, the 2 reviewers attempted to reach consensus on inclusion by discussion. If the reviewers could not agree, a third investigator was consulted to make the final decision.

2. Full-text Exclusion Criteria

1. Poorly described HOI identification algorithm that would be difficult to operationalize.
2. No validation of outcome definition or reporting of validity statistics.

D. MINI-SENTINEL INVESTIGATOR SURVEY

Mini-Sentinel investigators were surveyed to request information on any published or unpublished studies that validated an algorithm to identify an HOI in administrative data. Studies that would not be excluded by one of the aforementioned criteria were included in the final report.

E. EVIDENCE TABLE CREATION

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.

F. CLINICIAN OR TOPIC-EXPERT CONSULTATION

A clinician or topic expert was consulted to review the results of the evidence table and discuss how they compare 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 to diagnostic criteria currently used in clinical practice. A summary of this consultation was included in the results.

V. RESULTS

A. SEARCH STRATEGY AND RESULTS

The PubMed and IDIS searches identified 124 (Table 1) and 14 (Table 2) citations, respectively. A subsequent PubMed search was conducted to supplement the original search strategy with relevant databases that were not originally included; this search identified 1 citation (Table 3). The total number of unique citations from the combined searches was 134. Mini-Sentinel investigators provided no additional published or unpublished reports of validation studies.

Table 1. PubMed Search Strategy and Results (124): Performed on 05/10/10

Search	Query	Results
#1	("anaphylaxis"[MeSH Terms] OR "anaphylaxis"[All Fields] OR ("anaphylactic"[All Fields] AND "shock"[All Fields]) OR "anaphylactic shock"[All Fields]) OR ("angioneurotic oedema"[All Fields] OR "angioedema"[MeSH Terms] OR "angioedema"[All Fields] OR ("angioneurotic"[All Fields] AND "edema"[All Fields]) OR "angioneurotic edema"[All Fields] OR ("Angioneurotic"[All Fields] AND "Edema"[All Fields]) OR "Angioneurotic Edema"[All Fields] OR ("angioneurotic"[All Fields] AND "edema"[All Fields]))	26143
#2	("Premier"[All] OR "Solucient"[All] OR "Cerner"[All] OR "Ingenix"[All] OR "LabRx"[All] OR "IHCIS"[All] OR "marketscan"[All] OR "market scan"[All] OR "Medstat"[All] OR "Thomson"[All] OR "pharmetrics"[All] OR "healthcore"[All] OR "united healthcare"[All] OR "UnitedHealthcare"[All] OR "UHC"[All] OR "GPRD"[All] OR "general practice research database"[All] OR "Research Database"[All] OR "Group Health"[All] OR "HCUP"[All] OR ("Healthcare Cost"[All] AND "Utilization Project"[All]) OR ("Health Care Cost"[All] AND "Utilization Project"[All]) OR "MEPS"[All] OR "Medical Expenditure Panel Survey"[All] OR "NAMCS"[All] OR "National Hospital Ambulatory Medical Care Survey"[All] OR "National Ambulatory Medical Care Survey"[All] OR "NHIS"[All] OR "National Health Interview Survey"[All] OR "Kaiser"[All] OR "HMO Research"[All] OR "Health Maintenance Organization"[All] OR "HMO"[All] OR "Cleveland Clinic"[All] OR "Lovelace"[All] OR "Department of Defense"[All] OR "Henry Ford"[All] OR ("Denmark"[All] AND "Epidemiology"[All]) OR "i3 Drug Safety"[All] OR "i3"[All] OR "Aetna"[All] OR "Humana"[All] OR "Wellpoint"[All] OR "IMS"[All] OR "Intercontinental Marketing Services"[All] OR "IMS Health"[All] OR "Geisinger"[All] OR "GE Healthcare"[All] OR "MQIC"[All] OR "PHARMO"[All] OR "Institute for Drug Outcome Research"[All] OR "Pilgrim"[All] OR "Puget Sound"[All] OR "Regenstrief"[All] OR "Saskatchewan"[All] OR "Tayside"[All] OR "MEMO"[All] OR "Medicines Monitoring Unit"[All] OR "Veterans Affairs"[All] OR "Partners Healthcare"[All] OR "Mayo Clinic"[All] OR "Rochester Epidemiology"[All] OR "Indiana Health Information Exchange"[All] OR "Indiana Health"[All] OR "Intermountain"[All] OR "THIN"[All] OR "The health improvement network"[All] OR "blue cross"[All] OR "health partners"[All] OR "health plan"[All] OR "health services"[All] OR "Nationwide Inpatient Sample"[All] OR "National Inpatient Sample"[All] OR "medicaid"[All] OR "medicare"[All] OR "MediPlus"[All] OR "Outcome Assessment"[All] OR "insurance database"[All] OR "insurance databases"[All] OR "Data Warehouse"[All] OR "ICD-9"[All] OR "international statistical classification"[All] OR "international classification of diseases"[All] OR "ICD-10"[All] OR "Database Management Systems"[Mesh] OR "Medical Records"[Mesh] OR "Medical Records Systems, Computerized"[Mesh] OR "CPT"[All] OR "Current procedural terminology"[All] OR "drug surveillance" [All] OR ("claims"[tw] AND "administrative"[tw]) OR ("data"[tw] AND "administrative"[tw]) OR "Databases, Factual"[Mesh] OR "Databases as topic"[Mesh] OR "Medical Record Linkage"[Mesh] OR "ICD-9-CM"[All Fields] OR "ICD-10-CM"[All Fields])	881983
#3	#1 and #2	431
#4	("Pharmaceutical preparations/adverse effects"[Mesh] OR "Pharmaceutical preparations/contraindications"[Mesh] OR "Pharmaceutical preparations/poisoning"[Mesh] OR "Pharmaceutical preparations/therapeutic use"[Mesh] OR "Pharmaceutical preparations/toxicity"[Mesh] OR "Pharmaceutical preparations/therapy"[Mesh] OR "Pharmaceutical preparations/analysis"[Mesh] OR "Chemical actions and uses/adverse effects"[Mesh] OR "Chemical actions and uses/contraindications"[Mesh] OR "Chemical actions and uses/poisoning"[Mesh] OR "Chemical actions and uses/therapeutic use"[Mesh] OR "Chemical actions and uses/toxicity"[Mesh] OR "Chemical actions and uses/therapy"[Mesh] OR "Chemical actions and uses/analysis"[Mesh] OR "Chemical actions and uses/epidemiology"[Mesh] OR "Drug toxicity"[Mesh] OR "Diseases Category/chemically induced"[Mesh] OR "Diseases Category/drug therapy"[Mesh] OR "Diseases Category/epidemiology"[Mesh] OR "Validation Studies"[pt] OR "Validation Studies as	35821263

	Topic"[Mesh] OR "Sensitivity and Specificity"[Mesh] OR "Predictive Value of Tests"[Mesh] OR "Reproducibility of Results"[Mesh] OR "Predictive Value" [tw])	
#5	#3 and #4	273
#6	("Clinical Trials"[pt] OR "Editorial"[pt] OR "Letter"[pt] OR "Meta-Analysis"[pt] OR "Randomized Controlled Trial"[pt] OR "Clinical Trial, Phase I"[pt] OR "Clinical Trial, Phase II"[pt] OR "Clinical Trial, Phase III"[pt] OR "Clinical Trial, Phase IV"[pt] OR "Comment"[pt] OR "Controlled Clinical Trial"[pt] OR "case reports"[pt] OR "Clinical Trials as Topic"[Mesh] OR "double-blind"[All] OR "placebo-controlled"[All] OR "pilot study"[All] OR "pilot projects"[Mesh] OR "Review"[pt] OR "Prospective Studies"[Mesh])	4546100
#7	#5 NOT #6	152
#8	("humans"[MeSH Terms] AND English[lang] AND ("1990/01/01"[PDAT] : "2010/06/1"[PDAT]))	7582731
#9	#7 and #8	124

Table 2. IDIS Search Strategy and Results (14): Performed on 05/10/10

Disease:

"SHOCK, ANAPHYLACTIC 995.0" OR "EDEMA, ANGIONEUROTIC 995.1"

NOT Author:

("(Editorial)" OR "Letter to Ed")

NOT Descriptor:

("CASE REPORT ADULT 0" OR "CASE REPORT PEDIATRIC 1" OR "CASE REPORT GERIATRIC 2" OR "REVIEW ADULT 6" OR "STUDY NON-CLINICAL 8" OR "REVIEW PEDIATRIC 21" OR "REVIEW GERIATRIC 23" OR "STUDY RANDOMIZE ADULT 135" OR "STUDY RANDOMIZE PEDIATRIC 136" OR "STUDY RANDOMIZE GERIATRIC 137" OR "CROSS-OVER 144" OR "META-ANALYSIS 145" OR "N-OF-ONE TRIAL 146" OR "PRACTICE GUIDELINE 156" OR "SYSTEMATIC REVIEW 161" OR "ANNOTATED BIBLIOGRAPHY 167" OR "PRIORITY CLIN PRACT GUIDE 168") AND ("SIDE EF IMMUNOLOGIC 90")

AND Abstract:

((("anaphylactic" AND "shock") OR ("angioneurotic" AND "edema") OR "Premier" OR "Solucient" OR "Cerner" OR "Ingenix" OR "LabRx" OR "IHClS" OR "marketscan" OR "market scan" OR "Medstat" OR "Thomson" OR "pharmetrics" OR "healthcore" OR "united healthcare" OR "UnitedHealthcare" OR "UHC" OR "GPRD" OR "general practice research database" OR "Research Database" OR "Group Health" OR "HCUP" OR ("Healthcare Cost" AND "Utilization Project") OR ("Health Care Cost" AND "Utilization Project") OR "MEPS" OR "Medical Expenditure Panel Survey" OR "NAMCS" OR "National Hospital Ambulatory Medical Care Survey" OR "National Ambulatory Medical Care Survey" OR "NHIS" OR "National Health Interview Survey" OR "Kaiser" OR "HMO Research" OR "Health Maintenance Organization" OR "HMO" OR "Cleveland Clinic" OR "Lovelace" OR "Department of Defense" OR "Henry Ford" OR ("Denmark" AND "Epidemiology") OR "i3 Drug Safety" OR "i3" OR "Aetna" OR "Humana" OR "Wellpoint" OR "IMS" OR "Intercontinental Marketing Services" OR "IMS Health" OR "Geisinger" OR "GE Healthcare" OR "MQIC" OR "PHARMO" OR "Institute for Drug Outcome Research" OR "Pilgrim" OR "Puget Sound" OR "Regenstrief" OR "Saskatchewan" OR "Tayside" OR "MEMO" OR "Medicines Monitoring Unit" OR "Veterans Affairs" OR "Partners Healthcare" OR "Mayo Clinic" OR "Rochester Epidemiology" OR "Indiana Health Information Exchange" OR "Indiana Health" OR "Intermountain" OR "THIN" OR "The health improvement network" OR "blue cross" OR "health partners" OR "health plan" OR "health services" OR "Nationwide Inpatient Sample" OR "National Inpatient Sample" OR "medicaid" OR "medicare" OR "MediPlus" OR "Outcome Assessment" OR "insurance database" OR "insurance databases" OR "Data Warehouse" OR "ICD-9" OR "international statistical classification" OR "international classification of diseases" OR "ICD-10" OR "Database Management Systems" OR "Medical Records Systems, Computerized" OR "CPT" OR "Current procedural terminology" OR "drug surveillance" OR ("claims" AND "administrative") OR ("data" AND "administrative") OR "Databases, Factual" OR "Databases as topic" OR "Medical Record Linkage" OR "ICD-9-CM" OR "ICD-10-CM")

Table 3. Search to Update the Original PubMed Search with Additional Database Names: Performed on 07/06/10, Results = 1

Search	Query	Results
#1	("Pharmaceutical preparations/adverse effects"[Mesh] OR "Pharmaceutical preparations/contraindications"[Mesh] OR "Pharmaceutical preparations/poisoning"[Mesh] OR "Pharmaceutical preparations/therapeutic use"[Mesh] OR "Pharmaceutical preparations/toxicity"[Mesh] OR "Pharmaceutical preparations/therapy"[Mesh] OR "Pharmaceutical preparations/analysis"[Mesh] OR "Chemical actions and uses/adverse effects"[Mesh] OR "Chemical actions and uses/contraindications"[Mesh] OR "Chemical actions and uses/poisoning"[Mesh] OR "Chemical actions and uses/therapeutic use"[Mesh] OR "Chemical actions and uses/toxicity"[Mesh] OR "Chemical actions and uses/therapy"[Mesh] OR "Chemical actions and uses/analysis"[Mesh] OR "Chemical actions and uses/epidemiology"[Mesh] OR "Drug toxicity"[Mesh] OR "Diseases Category/chemically induced"[Mesh] OR "Diseases Category/drug therapy"[Mesh] OR "Diseases Category/epidemiology"[Mesh] OR "Validation Studies"[pt] OR "Validation Studies as Topic"[Mesh] OR "Sensitivity and Specificity"[Mesh] OR "Predictive Value of Tests"[Mesh] OR "Reproducibility of Results"[Mesh] OR "Predictive Value"[tw])	1867752
#2	("Premier"[All] OR "Solucient"[All] OR "Cerner"[All] OR "Ingenix"[All] OR "LabRx"[All] OR "IHCS"[All] OR "marketscan"[All] OR "market scan"[All] OR "Medstat"[All] OR "Thomson"[All] OR "pharmetrics"[All] OR "healthcore"[All] OR "united healthcare"[All] OR "UnitedHealthcare"[All] OR "UHC"[All] OR "GPRD"[All] OR "general practice research database"[All] OR "Research Database"[All] OR "Group Health"[All] OR "HCUP"[All] OR ("Healthcare Cost"[All] AND "Utilization Project"[All]) OR ("Health Care Cost"[All] AND "Utilization Project"[All]) OR "MEPS"[All] OR "Medical Expenditure Panel Survey"[All] OR "NAMCS"[All] OR "National Hospital Ambulatory Medical Care Survey"[All] OR "National Ambulatory Medical Care Survey"[All] OR "NHIS"[All] OR "National Health Interview Survey"[All] OR "Kaiser"[All] OR "HMO Research"[All] OR "Health Maintenance Organization"[All] OR "HMO"[All] OR "Cleveland Clinic"[All] OR "Lovelace"[All] OR "Department of Defense"[All] OR "Henry Ford"[All] OR ("Denmark"[All] AND "Epidemiology"[All]) OR "i3 Drug Safety"[All] OR "i3"[All] OR "Aetna"[All] OR "Humana"[All] OR "Wellpoint"[All] OR "IMS"[All] OR "Intercontinental Marketing Services"[All] OR "IMS Health"[All] OR "Geisinger"[All] OR "GE Healthcare"[All] OR "MQIC"[All] OR "PHARMO"[All] OR "Institute for Drug Outcome Research"[All] OR "Pilgrim"[All] OR "Puget Sound"[All] OR "Regenstrief"[All] OR "Saskatchewan"[All] OR "Tayside"[All] OR "MEMO"[All] OR "Medicines Monitoring Unit"[All] OR "Veterans Affairs"[All] OR "Partners Healthcare"[All] OR "Mayo Clinic"[All] OR "Rochester Epidemiology"[All] OR "Indiana Health Information Exchange"[All] OR "Indiana Health"[All] OR "Intermountain"[All] OR "THIN"[All] OR "The health improvement network"[All] OR "blue cross"[All] OR "health partners"[All] OR "health plan"[All] OR "health services"[All] OR "Nationwide Inpatient Sample"[All] OR "National Inpatient Sample"[All] OR "medicaid"[All] OR "medicare"[All] OR "MediPlus"[All] OR "Outcome Assessment"[All] OR "insurance database"[All] OR "insurance databases"[All] OR "Data Warehouse"[All] OR "ICD-9"[All] OR "international statistical classification"[All] OR "international classification of diseases"[All] OR "ICD-10"[All] OR "Database Management Systems"[Mesh] OR "Medical Records Systems, Computerized"[Mesh] OR "CPT"[All] OR "Current procedural terminology"[All] OR "drug surveillance"[All] OR ("claims"[tw] AND "administrative"[tw]) OR ("data"[tw] AND "administrative"[tw]) OR "Databases, Factual"[Mesh] OR "Databases as topic"[Mesh] OR "Medical Record Linkage"[Mesh] OR "ICD-9-CM"[All Fields] OR "ICD-10-CM"[All Fields])	399576
#3	("Clinical Trial"[pt] OR "Editorial"[pt] OR "Letter"[pt] OR "Meta-Analysis"[pt] OR "Randomized Controlled Trial"[pt] OR "Clinical Trial, Phase I"[pt] OR "Clinical Trial, Phase II"[pt] OR "Clinical Trial, Phase III"[pt] OR "Clinical Trial, Phase IV"[pt] OR "Comment"[pt] OR "Controlled Clinical Trial"[pt] OR "case reports"[pt] OR "Clinical Trials as Topic"[Mesh] OR "double-blind"[All] OR "placebo-controlled"[All] OR "pilot study"[All] OR "pilot projects"[Mesh] OR "Review"[pt] OR	2729582

	"Prospective Studies"[Mesh]	
#4	#1 NOT #2	1748136
#5	#4 NOT #3	819148
#6	(TennCare [tiab]) OR (RAMQ [tiab]) OR (Cigna [tiab]) OR ((british columbia[tiab]) AND ((health[tiab]) OR (data[tiab]) OR (database[tiab]) OR (population[tiab]))) OR (CIHI [All Fields]) OR ((manitoba[tiab]) AND ((center for health policy[all fields]) OR (population[tiab]) OR (health insurance[tiab]))) OR ((ontario[tiab]) AND ((population[tiab]) OR (OHIP[tiab]) OR (registered persons database[tiab]) OR (health insurance [tiab]) OR (ICES[All Fields]) OR (Institute for Clinical Evaluative Sciences[All Fields]))) OR ((Alberta[tiab]) AND ((health[tiab]) OR (data[tiab]) OR (database[tiab]) OR (population[tiab]) OR (Alberta Health and Wellness[All Fields])))	5128
#7	#5 AND #6	1579
#8	#7 AND (("anaphylaxis"[MeSH Terms] OR "anaphylaxis"[All Fields] OR ("anaphylactic"[All Fields] AND "shock"[All Fields]) OR "anaphylactic shock"[All Fields]) OR ("angioneurotic oedema"[All Fields] OR "angioedema"[MeSH Terms] OR "angioedema"[All Fields] OR ("angioneurotic"[All Fields] AND "edema"[All Fields]) OR "angioneurotic edema"[All Fields]) OR ("Angioneurotic"[All Fields] AND "Edema"[All Fields]) OR "Angioneurotic Edema"[All Fields] OR ("angioneurotic"[All Fields] AND "edema"[All Fields])))	1

B. ABSTRACT REVIEWS

Of the 134 abstracts reviewed, we accepted 24 for full-text review. The 2 reviewers generally agreed on acceptance/rejection status of abstracts for full-text review (i.e., Cohen's kappa = 0.97). There was, however, limited agreement on the reason for rejection. Among the 111 abstracts rejected, inter-rater agreement (via kappa coefficient) was 0.00, 0.24, and 0.70 for 1) examination of the HOI of interest, 2) use of administrative database, and 3) study conducted in the United States or Canada, respectively. These seemingly low agreement rates result from only a single reject 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 than a true lack of agreement; they also illustrate that many rejected articles fulfilled multiple exclusion criteria.

C. FULL-TEXT REVIEWS

Of the 24 full-text articles reviewed, 15 were excluded: 8 for not including validation of the outcome of interest or not reporting validity statistics, 5 for not including ICD-9 codes, 1 for not using data from the US or Canada, and 1 for not focusing on the HOI of interest.

Of the 9 papers identified by either or both reviewers, 5 were determined not to fulfill all inclusion criteria. One did not provide validation estimates⁸ but used the same cohort as an earlier study by the same author⁴; 1 did not provide validation estimates⁹ but described the algorithm used in another paper by the same author that did provide validation estimates¹; 1 did not have validation estimates and used death certificates, a data source that is non-applicable to the Mini-Sentinel objective of surveillance of automated health care data¹⁰; 1 validated several anaphylaxis-specific and non-specific codes in the

context of developing a broader hypersensitivity reaction (HSR) algorithm¹¹; and 1 provided validation but did not define the specific algorithm used,¹² and this paper was therefore not included in the evidence table.

Reviewers identified no additional citations for review from full-text article references. This left 8 articles to include in the evidence table, only 4 of which had reported validation of the anaphylaxis coding algorithm directly in the article or within a reference cited in the article.¹⁻⁴ Cohen's kappa for agreement between reviewers on inclusion vs. exclusion of full-text articles reviewed was 0.75.

D. MINI-SENTINEL INVESTIGATOR SURVEY

Mini-Sentinel investigators provided no published or unpublished reports of validation studies that had been completed by their teams. They did not provide any published reports that they were familiar with but not directly involved in, either.

E. EVIDENCE INCLUDED IN TABLE

Of the 8 studies included in the table, all were identified from the initial search strategy. None were identified through references of articles that underwent full-text review or were provided by Mini-Sentinel investigators.

F. SUMMARY AND DISCUSSION OF ALGORITHMS AND VALIDATION

Codes Used in Algorithms. We came across 8 studies that provided the codes for anaphylaxis and related conditions and also employed some method of validation. Of these 8 studies, only 4 studies provided validation estimates for codes of anaphylaxis and related conditions.

Of the studies with validation statistics, the most commonly used codes for anaphylaxis and related conditions were: ICD-9 codes 995.0 (anaphylactic shock),^{1,2} 995.1 (angioneurotic edema),^{1,3,4} and 995.3 (allergy, unspecified).^{1,2}

The less commonly used codes among the studies with validation statistics included procedure codes consistent with resuscitation (i.e., CPT 92950, cardiopulmonary resuscitation and HCPCS J7640, adrenaline injection) that were used by Johannes, et al.² The Bohlke, et al.¹ paper also used the following codes specific to anaphylaxis: 999.4 (anaphylactic shock because of serum), 995.6 (anaphylactic shock caused by adverse food reaction), and 995.4 (shock caused by anesthesia), as well as the following non-anaphylaxis-specific conditions: 995.1 (angioneurotic edema), 708.0 (allergic urticaria), 708.9 (urticaria unspecified), 995.3 (allergy, unspecified), 695.1 (erythema multiforme), and 995.2 (unspecified adverse effect of drug, medicinal and biological substance).

Among the articles with codes but without validation statistics, Brown, et al.⁸ incorporated the same cohort as another paper by the same author.⁴ Bohlke, et al.⁹ described the algorithm used in the above-referenced Bohlke, et al.¹ article. Simon, et al.¹⁰ used ICD-9 codes 995.0 and 999.4 as well as the following ICD-10 codes: T50.9 (overdose or wrong substance given), T63.2 (scorpion sting), T63.4 (insect sting), T63.6 (marine animal sting), T63.9 (sting), T78.0 (food), T78.2 (anaphylactic shock), T80.5 (serum), and T88.6 (correct substance properly administered). Nordstrom, et al.¹¹ used data-mining approaches to define HSR that consisted of a variety of ICD-9-CM codes consistent with HSR-related symptoms, as well as ICD-9-CM codes 995.0, 995.2, and 995.3.¹¹ However, as the focus of Nordstrom, et al.¹¹ was to

define a broader hypersensitivity algorithm, they focus on the related validation statistics within the report corresponding to that HOI.

Validation Algorithms. Bohlke, et al.¹ 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 in this study was ICD-9 code 995.6 (anaphylactic shock caused by adverse food reaction), although only 10 of 102 visits (10%) with this code were accepted as anaphylaxis. Among the non-specific codes, higher PPV (7.4%) was related to ICD-9 code 995.1 (angioneurotic edema) to predict anaphylaxis.

The Brown, et al.⁸ and Miller, et al.³ papers both used the same ICD-9 code, 995.1 (angioneurotic edema), specific to the angioedema outcome. Brown, et al.⁸ performed validation of this code to confirm cases of angioedema identified in the administrative database and estimated an overall PPV of 90% (82 of 91). The PPV was 98% in black subjects and 78% in white subjects. Miller, et al.³ performed chart reviews to validate this code and found a comparable PPV of 95.3% (828 of 869).

Johannes, et al.² obtained medical records for 64 of 77 (83.1%) patients, and confirmed anaphylaxis in 1 of 35 (2.9%) patients on the basis of a procedure code for resuscitation. Clinical review confirmed that 16 of 28 (57.1%) patients with ICD-9 code 995.0 (anaphylactic shock) had anaphylaxis.

The remaining studies did not perform validation of the coding algorithms for anaphylaxis and its related conditions.

Selected Patient Populations. Bohlke, et al.¹ validated an algorithm for anaphylaxis in a study assessing incidence of anaphylaxis from all causes in children and adolescents under the age of 18 who were enrolled at Group Health Cooperative for any duration between 1991 and 1997. The Brown, et al.⁸ and Miller, et al.³ papers are similar in that they both examined angiotensin-converting enzyme (ACE) inhibitor–associated angioedema. Brown, et al.⁸ evaluated the risk among Medicaid program enrollees age 15 and older, while Miller, et al.³ assessed the incidence of angioedema in new users of ACE inhibitors among a cohort enrolled in the Veterans Affairs Health Care System (VA) between 1998 and 2000. Johannes, et al.² aimed to evaluate drug-specific incidence of serious allergic reactions after fluoroquinolone, cephalosporin, phenoxymethylpenicillin, and potassium exposure among privately insured patients between 2000 and 2004.

G. SUMMARY OF EXCLUDED POPULATIONS AND DIAGNOSES

As indicated in section F above, of the 4 studies with validation estimates, 2 focused on cohorts extracted from state-specific databases. Brown, et al.⁴ used Tennessee Medicaid beneficiary data on patients aged 15 years or older with at least 1 year of Medicaid enrollment, while Bohlke, et al.¹ extracted data on children and adolescents under the age of 18 with enrollment of any duration from the Group Health Cooperative, which is based in Seattle, Washington. The remaining 2 studies used data that encompassed a more national breadth. Johannes, et al.² examined a population with no age restriction but with at least 197 days of enrollment (183 baseline, 14 follow-up) from the Ingenix Research Database, while the population studied by Miller, et al.³ excluded individuals with an antihypertensive prescription during the first 6 months of data collected from the US Veterans Health Care System.

Three of the 4 studies with algorithms but without validation used state-specific or regional data. Brown, et al.⁸ used the same Tennessee Medicaid beneficiary data as the earlier Brown, et al.⁴ paper. Bohlke, et al.⁹ used data on patients aged 0–17 years with at least 1 day of enrollment from 4 West Coast HMOs. Simon, et al.¹⁰ used the death certificate data of Florida residents identified from the Florida Department of Health, Office of Vital Statistics. The last article, Nordstrom, et al.,¹¹ examined patients initiating abacavir treatment with no less than 6 months of continuous enrollment prior to their first dispensing, identified from the Ingenix Research Database.

H. EVIDENCE TABLE

Table 4. Positive Predictive Values by Algorithm

Citation	Study Population and Time Period	Description of Outcome Studied	Algorithm	Validation/Adjudication Procedure and Operational Definition	Validation Statistics
Bohlke, et al. 2004 ¹	<p>Group Health Cooperative data, 1991–1997.</p> <p>The study population consisted of the 229,422 children and adolescents under the age of 18 years.</p> <p>From 753 chart reviews, 67 definite cases of anaphylaxis were accepted (ages 0–4: 15; 5–9: 13; 10–14: 22; and 15–17: 17), of which 27 were females and 40 were males.</p>	Incidence of anaphylaxis from all causes.	<p>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).</p> <p>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).</p>	<p>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 bronchiolitis, other allergies, or use of albuterol or another inhaler. To classify episodes as “probable” or “possible” anaphylaxis, the authors considered the number and type of organ systems involved, the rapidity with which signs and symptoms appeared after exposure to a precipitating agent, and treatment. The decision to incorporate treatment was based on the knowledge that prompt treatment of an anaphylactic episode can stop progression to >1 organ system. Cases defined as “probable” anaphylaxis required manifestations involving >1 organ system (cutaneous, respiratory, cardiovascular, and/or gastrointestinal) occurring within 4 hours of exposure to a precipitating agent, with subsequent treatment. “Possible” anaphylaxis included 3 groups: 1) those with involvement of >1 organ system (described above), with</p>	<p>PPVs for codes specific to anaphylaxis:</p> <p>995.0 (anaphylactic shock) = 55.4%.</p> <p>995.6 (anaphylactic shock caused by adverse food reaction) = 9.8%.</p> <p>999.4 (anaphylactic shock caused by serum) = 0%.</p> <p>995.4 (shock caused by anesthesia) = 0%.</p> <p>PPVs for codes not specific to anaphylaxis:</p> <p>989.5 (toxic effect of venom) = 4.7%.</p> <p>708.0 (allergic urticaria) = 5.6%.</p> <p>708.9 (urticaria unspecified) = 0%.</p> <p>995.1 (angioneurotic edema) = 7.4%.</p> <p>995.3 (allergy, unspecified) = 1.3%.</p> <p>695.1 (erythema multiforme) = 0%.</p>

				<p>signs and symptoms developing within 4 hours of exposure and untreated; 2) those with involvement of >1 organ system, occurring >4 hours (or an indeterminate time period) after exposure, who were treated; and 3) those with involvement of only 1 organ system, with symptoms developing within 4 hours of exposure, who were treated.</p> <p>Operational definition: Provided in the article as a figure.</p>	
Brown, et al. 1996 ⁴	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 angiotensin-converting enzyme (ACE) inhibitor–associated angioedema .	Angioneurotic edema (ICD-9-CM code of 995.1): based on first paid claim with a coded diagnosis of angioneurotic edema while receiving an ACE inhibitor.	<p>Medical record review.</p> <p>Angioedema was defined as swelling of the face, lips, mouth, or airway.</p>	<p>PPV = 90% (82 of 91).</p> <p>PPV was 98% in black subjects and 78% in white subjects.</p>
Johannes, et al. 2007 ²	Ingenix Research Data Mart. The study population comprised patients receiving at least 1 dispensing of moxifloxacin, ciprofloxacin, levofloxacin, gatifloxacin, phenoxymethylpenicillin potassium, or a	Drug-specific incidence of serious allergic reactions after fluoroquinolone, cephalosporin, and phenoxymethylpenicillin potassium exposure. The authors	A serious allergic reaction was defined as the presence of at least 1 claim for services occurring during the index inpatient or ED visit bearing ICD-9 diagnosis codes of 995.0 (anaphylactic shock), 995.2	<p>Medical record review.</p> <p>An abstraction form recorded information in a standardized format 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</p>	<p>PPV for 995.0 (anaphylactic shock) = 57.1% (16 of 28).</p> <p>PPVs for 995.3 (allergy, unspecified) and 995.2 (unspecified adverse effect of drug) were not reported.</p> <p>PPV for CPT 92950 (cardiopulmonary resuscitation) and HCPCS J7640 (adrenaline injection) combined = 2.9% (1 of 35).</p>

	<p>combined group of first-, second-, and third-generation cephalosporins. Patients who were dispensed more than 1 study drug were placed into each relevant drug group and thus could appear in 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 July 1, 2000 to June 30, 2004.</p>	<p>followed each person for 14 days after each study drug dispensing and counted the first emergency department (ED) or hospitalization (inpatient) visit during this time.</p>	<p>(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).</p>	<p>determination of case status, date of onset, and any exposure noted as presumed to precipitate the event.</p>	
<p>Miller, et al. 2008³</p>	<p>Veterans Affairs Health Care System (VA) data; cohort consisted of all VA patients who received VA prescriptions for antihypertensive medications (N=869), October 1, 1998 through December 31, 2000.</p>	<p>Incidence of angioedema in new users of ACE inhibitors.</p>	<p>ICD-9-CM code 995.1 (angioedema).</p>	<p>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.</p>	<p>PPV = 95.3% (82 of 91).</p>

Table 5. Non-Validated Algorithms

Citation	Study Population and Time Period	Description of Outcome Studied	Algorithm
<p>Bohlke, et al. 2003⁹</p>	<p>The 4 HMOs participating in the study were: Group Health Cooperative, Seattle, Washington; Northern California Kaiser Permanente, Oakland, California; Northwest Kaiser Permanente, Portland, Oregon; and Southern California Kaiser Permanente, Los Angeles, California. The study cohort consisted of children and adolescents aged 0 through 17 years at 3 sites and aged 0 through 6 years at 1 site. A total of 2,226,907 children and adolescents in this cohort were enrolled in their respective HMO for at least 1 day between 1991 (for 3 of the sites) or 1992 (for 1 site) and the end of 1997. Five of the 657 episodes reviewed were accepted as probable or possible anaphylaxis.</p>	<p>Risk of anaphylaxis after vaccination of children and adolescents.</p>	<p>ICD-9 code 995.0 (anaphylactic shock), E948.0 through E948.9 (adverse reaction from bacterial vaccines), E949.0 through E949.9 (adverse reaction from other vaccines and biological substances).</p> <p>Review was restricted to diagnoses occurring on days 0 to 2 after vaccination (day 0 was defined as the same day as vaccination) for ICD-9 code 995.0 and day 0 for ICD-9 codes E948.0 to E948.9 and E949.0 to E949.9. Chart reviews were performed on all day 0 diagnoses of 708.0 (allergic urticaria), 708.9 (urticaria unspecified), 995.1 (angioneurotic edema), 995.3 (allergy unspecified), 695.1 (erythema multiforme), and 995.2 (unspecified adverse effect of drug, medicinal and biological substance).</p>
<p>Brown, et al. 1997⁸</p>	<p>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.</p>	<p>Recurrence rate of angioedema associated with continued use of angiotensin-converting enzyme (ACE) inhibitor.</p>	<p>Angioneurotic edema (ICD-9-CM code 995.1).</p>
<p>Nordstrom, et al. 2007¹¹</p> <p><i>Note: This is included in the non-validated algorithm table, as no separate validation was conducted for the individual anaphylaxis codes.</i></p>	<p>Ingenix Research Database; patients who received their first dispensing of abacavir (n=934), from whom 22 hypersensitivity reactions (HSRs) were confirmed, 1 January 1999–31 July 2003.</p>	<p>Abacavir-associated HSR.</p>	<p>For a data-mining exercise, a lengthy list of codes, including HSR-related symptoms; diagnoses; and procedures as well as common non-HSR-related diagnoses were 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.</p> <p>See Appendix D for details.</p>

Simon, et al. 2008 ¹⁰	The source population was identified from the Florida Department of Health, Office of Vital Statistics, for the years 1996–2005. The study population included 89 anaphylactic deaths among Florida residents, 84 of which had available death certificates (42 males and 42 females).	Ten-year incidence of death from anaphylaxis in Florida and its descriptive epidemiology.	ICD-9 codes 995.0 (anaphylactic shock) and 999.4 (anaphylactic shock because of serum). ICD-10 codes T50.9 (overdose or wrong substance given), T63.2 (scorpion sting), T63.4 (insect sting), T63.6 (marine animal sting), T63.9 (sting), T78.0 (food), T78.2 (anaphylactic shock), T80.5 (serum), and T88.6 (correct substance properly administered).
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I. CLINICIAN OR TOPIC-EXPERT CONSULTATION

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), as well as “non-specific 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 code most commonly used in the studies with validation estimates (3 of the 4 validated studies) was the non-specific code of 995.1 (angioneurotic edema). The PPV of this code varied greatly. The PPV was poor (7.4%) when examining all-cause anaphylaxis,¹ but PPVs of 90% and 95.3% were obtained when the focus was on ACE inhibitor–associated angioedema^{3,4}; these represent the best PPVs of any of the anaphylaxis-related algorithms with validation estimates.

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.³ 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 claims data is not likely to have been sensitive. Both Brown, et al.⁴ and Miller, et al.³ suggest that mild cases may not seek medical attention and that physicians may neglect to code a diagnosis of angioedema in outpatient settings. Claims-based algorithms may therefore 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 1,000 person-years, respectively.^{3,4} 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 claims-based studies.¹³

The other algorithm used in multiple studies was ICD-9 code 995.0 (anaphylactic shock). Both Bohlke, et al.¹ and Johannes, et al.² used similar data (i.e., from commercially based insurance carriers) yet examined very different outcomes (all-cause anaphylaxis vs. 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 2 studies never exceeded 10%.

The reported PPV in Bohlke, et al.¹ 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.¹ A recent study by Iribarren, et al.¹⁴ that was unavailable in PubMed when the searches were conducted used a case-based denominator instead of a diagnosis-based denominator. Using comparable categorization to that of Bohlke, et al.¹ (i.e., probable or possible criteria), they report a PPV of 72% for ICD-9 code 995.0 (anaphylactic shock). This suggests that the true PPV of ICD-9 code 995.0 may be higher than reported in the studies that are formally part of this review.

The diagnosis-based denominator in Bohlke, et al.,¹ however, provides a look at 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.¹ with a PPV of greater than 50%, it illustrates well that a high PPV in itself may not be adequate to identify anaphylaxis and anaphylaxis-related conditions via 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.

It is worth noting here that on October 1, 2013, medical coding in US health care settings will change from ICD-9 to ICD-10. The transition will imply business and systems changes throughout the health care industry, including health plans and health care practice and research. All HIPAA transactions, including outpatient claims with dates of service and inpatient claims with dates of discharge, will use ICD-10 codes starting in October 2013. The ICD-10 sections for T78.2 (anaphylactic shock, unspecified) and T80.5 (anaphylactic shock due to serum) refer to anaphylaxis and related conditions. These codes will provide an opportunity to identify anaphylaxis, including anaphylactic shock and angioneurotic edema.

VI. SUMMARY AND CONCLUSIONS

A. RECOMMENDATIONS FOR ALGORITHMS

We came across 8 studies that provided the codes for anaphylaxis and related conditions and also employed some method of validation. Of these 8 studies, only 4 studies provided some validation estimates.

Among the validation studies, the codes for anaphylaxis and related conditions included those specifically for anaphylaxis: ICD-9 codes 995.0 (anaphylactic shock), 999.4 (anaphylactic shock because of serum), 995.6 (anaphylactic shock caused by adverse food reaction), 995.4 (shock caused by anesthesia), and 995.1 (angioneurotic edema); and codes not specific to anaphylaxis: 989.5 (toxic effect

of venom), 708.0 (allergic urticaria), 708.9 (urticaria unspecified), 995.3 (allergy, unspecified), and 695.1 (erythema multiforme).

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 55.4% to 57.1%. 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 outcome.

B. SUGGESTIONS FOR FUTURE RESEARCH BASED ON EVIDENCE GAPS

Our review highlights limited literature focusing on anaphylaxis and related conditions that also provided validated algorithms and predictive 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 claims data, or produce these high PPVs only when applied to a very specific condition subsequent to 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 claims databases. The algorithms in the reviewed studies were simplistic; 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 employ combinations of diagnostic and procedural codes. For example, the procedural codes used by Johannes, et al.² (for resuscitation or adrenaline injection) in combination with applicable diagnostic codes may improve PPV. When interest lies in anaphylaxis following a specified trigger, claims-based algorithms should also incorporate these exposures (e.g., prescribed medication) whenever possible.

VII. REFERENCES

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VIII. APPENDICES

A. APPENDIX A: ABSTRACTS OF STUDIES INCLUDED IN EVIDENCE TABLE

Bohlke K, Davis RL, DeStefano F, Marcy SM, Braun MM, Thompson RS. Epidemiology of anaphylaxis among children and adolescents enrolled in a health maintenance organization. *The Journal of Allergy and Clinical Immunology*. 2004; 113(3): 536–542.

BACKGROUND: There is little information about the incidence of anaphylaxis from all causes. **OBJECTIVE:** The objects of this study were (1) to estimate the incidence of anaphylaxis; (2) to explore the range of diagnoses attributed to an anaphylactic episode; and (3) to describe the clinical features of anaphylaxis. **METHODS:** The study population consisted of children and adolescents enrolled at a health maintenance organization. We identified potential episodes of anaphylaxis occurring between 1991 and 1997 from automated databases and reviewed the medical record to confirm the diagnosis. We reviewed all diagnoses specific for anaphylaxis (e.g., ICD-9 995.0, anaphylactic shock) and sampled from among other related diagnoses (e.g., ICD-9 995.3, allergy unspecified). Estimation of the incidence of provider-diagnosed anaphylaxis was based on cases confirmed from among the specific diagnosis codes. Description of the clinical features of anaphylaxis involved all confirmed cases regardless of diagnosis. **RESULTS:** We identified 67 episodes of anaphylaxis among children with diagnosis codes specific for anaphylaxis (10.5 episodes per 100,000 person-years). There was no increase in incidence over time. Review of samples of diagnoses not specific for anaphylaxis yielded an additional 18 episodes. Among all identified episodes (n = 85), mucocutaneous and respiratory manifestations were the most common. Seventy-one percent of episodes were treated in the emergency department. Nine episodes (11%) resulted in hospitalization. **CONCLUSIONS:** The incidence of anaphylaxis did not increase during these years. A majority of episodes were treated in the emergency department. Anaphylaxis in this population was frequently diagnosed as another related condition, and the basis and implications of diagnostic practices in this disorder warrant further exploration

Bohlke K, Davis RL, Marcy SM, Braun MM, DeStefano F, Black SB, Mullooly JP, Thompson RS. Risk of anaphylaxis after vaccination of children and adolescents. *Pediatrics*. 2003; 112(4): 815–820.

OBJECTIVE: To quantify the risk of anaphylaxis after vaccination of children and adolescents. **METHODS:** The study population consisted of children and adolescents who were enrolled at 4 health maintenance organizations that participated in the Vaccine Safety Datalink Project. For the period 1991-1997, we identified potential cases by searching for occurrences of International Classification of Diseases, Ninth Revision (ICD-9) code 995.0 (anaphylactic shock), E948.0 through E948.9 (adverse reaction from bacterial vaccines), and E949.0 through E949.9 (adverse reaction from other vaccines and biological substances). At 1 study site, we also included a range of other allergy codes. We restricted to diagnoses on days 0 to 2 after vaccination (ICD-9 995.0) or day 0 (all other ICD-9 codes). We then reviewed the medical record to confirm the diagnosis. **RESULTS:** We identified 5 cases of potentially vaccine-associated anaphylaxis after administration of 7 644 049 vaccine doses, for a risk of 0.65 cases/million doses (95% confidence interval: 0.21-1.53). None of the episodes resulted in death. Vaccines that were administered before the anaphylactic episodes were generally given in combination and included measles-mumps-rubella, hepatitis B, diphtheria-tetanus, diphtheria-tetanus-pertussis, Haemophilus influenzae type b, and oral polio vaccine. One case of anaphylaxis followed measles-mumps-rubella vaccine alone. At the site at which we reviewed additional allergy codes, we identified 1 case after 653 990 vaccine doses, for a risk of 1.53 cases/million doses (95% confidence interval: 0.04-8.52). **CONCLUSIONS:** Patients and health care

providers can be reassured that vaccine-associated anaphylaxis is a rare event. Nevertheless, providers should be prepared to provide immediate medical treatment should it occur.

Brown NJ, Ray WA, Snowden M, Griffin MR. Black Americans have an increased rate of angiotensin converting enzyme inhibitor-associated angioedema. *Clinical Pharmacology and Therapeutics*. 1996; 60(1): 8–13.

OBJECTIVE: To study the association of race and other patient characteristics associated with angiotensin converting enzyme (ACE) inhibitor-associated angioedema. **METHODS:** This was a retrospective cohort study of participants in the Tennessee Medicaid Program (≥ 15 years of age) to whom ACE inhibitors had been prescribed from 1986 through 1992. **RESULTS:** We identified 82 patients with confirmed angioedema during 51,752 person-years of ACE inhibitor use, giving an overall rate of angioedema of 1.6 per 1000 person-years of ACE inhibitor use. After potential confounding factors were controlled for, the adjusted relative risk (RR) of angioedema among black American users of ACE inhibitors was 4.5 (95% confidence interval [CI] 2.9 to 6.8) compared with white subjects. In addition to race, other factors associated with a significantly increased relative risk in the entire population were the first 30 days of ACE inhibitor use (RR, 4.6; 95% CI, 2.5 to 8.5) compared to > 1 year of use, use of either lisinopril (RR, 2.2; 95% CI, 1.2 to 3.9) or enalapril (RR, 2.2; 95% CI, 1.4 to 3.5) compared to captopril, and previous hospitalization for any diagnosis within 30 days (RR, 2.0; 95% CI, 1.1 to 3.6). Neither ACE inhibitor dose nor concurrent diuretic use was associated with the risk of angioedema. **CONCLUSIONS:** These data suggest that black Americans have a substantially increased risk of ACE inhibitor-associated angioedema compared with white subjects and that this increased risk cannot be attributed to an effect of dose, specific ACE inhibitor, or concurrent medications.

Brown NJ, Snowden M, Griffin MR. Recurrent angiotensin-converting enzyme inhibitor--associated angioedema. *JAMA: The Journal of the American Medical Association*. 1997; 278(3): 232–233.

CONTEXT: Angiotensin-converting enzyme (ACE) inhibitors are associated with an increased risk of angioedema, but the risk of recurrent angioedema if treatment is continued is not known. **OBJECTIVE:** To test the hypothesis that the association between ACE inhibitor use and angioedema may not be recognized and to determine characteristics of angioedema associated with continued use of ACE inhibitors. **DESIGN:** Retrospective cohort study. **SETTING:** Tennessee Medicaid program. **PATIENTS:** Medicaid enrollees aged 15 years or older who used an ACE inhibitor and had a first documented episode of angioedema between 1986 and 1992 were followed up for recurrent episodes through June 1993. **MEASUREMENTS AND MAIN RESULTS:** We previously identified 82 patients with a first confirmed diagnosis of angioedema during 51 752 person-years of ACE inhibitor use in this population (1.6 per 1000 person-years). Among these 82 patients, there were 16 outpatient recurrences of angioedema among 13 patients during 189 patient-years of follow-up (8.5 per 100 patient-years). The rate of angioedema was much higher in users of ACE inhibitors with continued exposure (18.7 per 100 patient-years) than in those whose use of the drug was discontinued (1.8 per 100 patient-years) ($P=.001$). Review of the medical records for patients taking ACE inhibitors who had recurrent angioedema revealed that physicians attributed angioedema to a number of causes not related to ACE inhibitor use, even after multiple recurrences. **CONCLUSION:** Continuing use of ACE inhibitors in spite of angioedema results in a markedly increased rate of angioedema recurrence with serious morbidity.

Johannes CB, Ziyadeh N, Seeger JD, Tucker E, Reiter C, Faich G. Incidence of allergic reactions associated with antibacterial use in a large, managed care organization. *Drug Safety: An International Journal of Medical Toxicology and Drug Experience*. 2007; 30(8): 705–713.

BACKGROUND: Data on the incidence of serious allergic reactions to fluoroquinolone antibacterials are mainly derived from spontaneous reports that cannot be used to accurately estimate incidence. **METHODS:** This study estimated the drug-specific incidence of serious allergic reactions after fluoroquinolone, cephalosporin and phenoxymethylpenicillin potassium exposure, using claims for healthcare services with confirmation through medical record abstraction within a large health insurer database. Cohorts exposed to each antibacterial of interest (moxifloxacin, levofloxacin, ciprofloxacin, gatifloxacin, cephalosporins and penicillin) were identified, and followed for 14 days for anaphylaxis (9th revision of the International Classification of Diseases [ICD-9] code 995.0), other allergic drug reactions (ICD-9 995.2, 995.3) or cardiopulmonary resuscitation. **RESULTS:** The incidence per 10,000 first dispensings of any allergic diagnosis made in the hospital or emergency department was similar for moxifloxacin (4.3; 95% CI 3.5, 5.3), penicillin (4.7; 95% CI 3.8, 5.7) and ciprofloxacin (5.4; 95% CI 4.4, 6.5). The incidence for moxifloxacin was lower than that for levofloxacin (8.7; 95% CI 7.4, 10.0), gatifloxacin (6.7; 95% CI 5.6, 7.9) and the cephalosporins (7.5; 95% CI 6.3, 8.8). The incidence of anaphylaxis/anaphylactoid reactions after first dispensings was similar for the fluoroquinolones: 0.1 (95% CI 0.0, 0.3) for ciprofloxacin, 0.3 (95% CI 0.1, 0.5) for moxifloxacin, 0.3 (95% CI 0.1, 0.6) for gatifloxacin and 0.5 (95% CI 0.3, 0.9) for levofloxacin; and comparable with that of the cephalosporins (0.2; 95% CI 0.0, 0.4) and penicillin (0.1; 95% CI 0.0, 0.3). **CONCLUSIONS:** Anaphylactic reactions were rare and their incidence did not differ substantially among the drug groups studied. By determining the occurrence of reactions following defined exposures, these results provide a context for the interpretation of spontaneous reports of allergic reactions.

Miller DR, Oliveria SA, Berlowitz DR, Fincke BG, Stang P, Lillienfeld DE. Angioedema incidence in US veterans initiating angiotensin-converting enzyme inhibitors. *Hypertension*. 2008; 51(0194-911; 6): 1624–1630.

Angioedema is a rare but potentially serious complication of angiotensin-converting enzyme inhibitor (ACE) use. We conducted a study to estimate incidence of ACE-related angioedema and explore its determinants in a large racially diverse patient population. We used linked medical and pharmacy records to identify all patients in the US Veterans Affairs Health Care System from April 1999 through December 2000 who received first prescriptions for antihypertensive medications. We studied 195 192 ACE initiators and 399 889 patients initiating other antihypertensive medications (OAH). New angioedema was identified by diagnosis codes using methods validated in a national sample of 869 angioedema cases with confirmation for over 95% of cases. Overall, 0.20% of ACE initiators developed angioedema while on the medication and the incidence rate was 1.97 (1.77 to 2.18) cases per 1000 person years. This compares with a rate of 0.51 (0.43 to 0.59) in OAH initiators and the adjusted relative risk estimate was 3.56 (2.82 to 4.44). Fifty five percent of cases occurred within 90 days of first ACE use but risk remained elevated with prolonged use, even beyond 1 year. We estimate that 58.3% of angioedema in patients starting antihypertensives was related to ACE. We also found that angioedema rates were nearly 4-fold higher in blacks, 50% higher in women, and 12% lower in those with diabetes. This study provides a reliable estimate of angioedema incidence associated with ACE use in a diverse nontrial patient population, confirming that the incidence is low, but finding substantial variation by race, sex, and diabetes status.

Nordstrom BL, Norman HS, Dube TJ, Wilcox MA, Walker AM. Identification of abacavir hypersensitivity reaction in health care claims data. *Pharmacoepidemiology and Drug Safety*. 2007; 16(3): 289–296.

PURPOSE: Abacavir is associated with an infrequent but potentially serious hypersensitivity reaction (HSR) that can include a wide range of signs and symptoms. Identification of this reaction through medical insurance claims could provide a simple and efficient means of monitoring the incidence of abacavir hypersensitivity in large populations of patients. **METHODS:** Using data from a safety study of 948 abacavir users with 22 hypersensitivity events identified from claims and validated through medical record review, we used a recursive partitioning analysis to construct an algorithm to differentiate between patients with and without validated adverse events. Bootstrap resampling techniques provided validation for the analysis. **RESULTS:** The analysis produced a classification tree with three decision nodes that comprised the best indicators of HSRs. The predictors included any one 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 prior to completing a 90-day course of therapy. The algorithm demonstrated 95% sensitivity and 90% specificity when tested using a bootstrap resampling approach with the current data. **CONCLUSIONS:** A sensitive and specific algorithm for identifying abacavir hypersensitivity from claims was created. This algorithm would permit efficient identification of charts for medical review. Further testing of the algorithm with additional medical claims data for abacavir users will be required to ascertain its validity across databases.

Simon MR, Mulla ZD. A population-based epidemiologic analysis of deaths from anaphylaxis in Florida. *Allergy*. 2008; 63(8): 1077–1083.

BACKGROUND: Previous US population-based epidemiologic studies of anaphylactic deaths have been limited by small populations and/or few deaths. The objective of this study was to determine the 10-year incidence of death from anaphylaxis in Florida and its descriptive epidemiology. **METHODS:** Patients who died from anaphylaxis from 1996 to 2005 were identified from ICD-9 and ICD-10 codes on death certificates statewide. Age, race and gender-specific anaphylactic death rates were calculated. **RESULTS:** There were 89 deaths among Florida residents. The individuals with autopsy confirmed diagnoses, and those with clinical diagnoses only, did not differ with regard to race, anaphylactic triggers or the clinical variables of lung and heart disease. Annual death rate for anaphylaxis in Florida was 5.02/10 000 000. The relative risk of death from anaphylaxis was 14.09 for individuals ≥ 65 years old ($P = 0.0000002$) and 6.38 for individuals 35-64 years old ($P = 0.0019$) compared with those who were 5-14 years of age. Deaths among Florida residents that occurred in emergency rooms or outpatient settings were 2.11 times as likely to be anaphylactic deaths than deaths that occurred in inpatient settings ($P = 0.0026$). The ratios of anaphylactic deaths to total deaths in March and April and in July and August were greater than the ratios for the other bimonthly periods ($P = 0.02$). **CONCLUSION:** Death from anaphylaxis in Florida was more likely to occur in older individuals, in an emergency department, and in the months of March and April and July and August.

B. APPENDIX B: LIST OF CITATIONS SELECTED FOR FULL-TEXT REVIEW BUT NOT INCLUDED, BY REASONS FOR EXCLUSION

1. Studies Excluded Due to Poorly Defined Algorithms

Golden WE, Cleves MA, Heard JK, Brasher R, McKinney P, Johnston JC. Frequency and recognition of angiotensin-converting enzyme inhibitor-associated angioneurotic edema. *Clinical Performance and Quality Health Care*. 1993; 1(4): 205–207.

Manivannan V, Campbell RL, Bellolio MF, Stead LG, Li JTC, Decker WW. Factors associated with repeated use of epinephrine for the treatment of anaphylaxis. *Annals of Allergy, Asthma & Immunology: Official Publication of the American College of Allergy, Asthma, & Immunology*. 2009; 103(5): 395–400.

Piromrat K, Chinratanapisit S, Trathong S. Anaphylaxis in an emergency department: a 2-year study in a tertiary-care hospital. *Asian Pacific Journal of Allergy and Immunology (launched by the Allergy and Immunology Society of Thailand)*. 2008; 26(0125-877; 0125-877; 2-3): 121–128.

Simons FE, Peterson S, Black CD. Epinephrine dispensing for the out-of-hospital treatment of anaphylaxis in infants and children: a population-based study. *Annals of Allergy, Asthma & Immunology: Official Publication of the American College of Allergy, Asthma, & Immunology*. 2001; 86(6): 622–626.

Simons FE, Peterson S, Black CD. Epinephrine dispensing patterns for an out-of-hospital population: a novel approach to studying the epidemiology of anaphylaxis. *The Journal of Allergy and Clinical Immunology*. 2002; 110(4): 647–651.

Yocum MW, Butterfield JH, Klein JS, Volcheck GW, Schroeder DR, Silverstein MD. Epidemiology of anaphylaxis in Olmsted County: a population-based study. *The Journal of Allergy and Clinical Immunology*. 1999; 104(2): 452–456.

2. Studies Excluded Due to Lack of Validation or Reporting of Validation Statistics

Bohlke K, Davis RL, Marcy SM, Braun MM, DeStefano F, Black SB, Mullooly JP, Thompson RS. Risk of anaphylaxis after vaccination of children and adolescents. *Pediatrics*. 2003; 112(4): 815–820.

Brown NJ, Snowden M, Griffin MR. Recurrent angiotensin-converting enzyme inhibitor--associated angioedema. *JAMA: The Journal of the American Medical Association*. 1997; 278(3): 232–233.

Demain JG, Gessner BD, McLaughlin JB, Sikes DS, Foote JT. Increasing insect reactions in Alaska: is this related to changing climate? *Allergy and Asthma Proceedings: The Official Journal of Regional and State Allergy Societies*. 2009; 30(3): 238–243.

Gaeta TJ, Clark S, Pelletier AJ, Camargo CA. National study of US emergency department visits for acute allergic reactions, 1993 to 2004. *Annals of Allergy, Asthma & Immunology*. 2007; 98(4): 360–365.

Lin RY, Anderson AS, Shah SN, Nurruzzaman F. Increasing anaphylaxis hospitalizations in the first 2 decades of life: New York State, 1990–2006. *Annals of Allergy, Asthma & Immunology*. 2008; 101(4): 387–393.

Meropol SB, Chan KA, Chen Z, Finkelstein JA, Hennessy S, Lautenbach E, Platt R, Schech SD, Shatin D, Metlay JP. Adverse events associated with prolonged antibiotic use. *Pharmacoepidemiology and Drug Safety*. 2008; 17(5): 523–532.

Mulla ZD, Ebrahim MS, Gonzalez JL. Anaphylaxis in the obstetric patient: analysis of a statewide hospital discharge database. *Annals of Allergy, Asthma & Immunology*. 2010; 104(1): 55–59.

Mulla ZD, Simon MR. Hospitalizations for anaphylaxis in Florida: epidemiologic analysis of a population-based dataset. *International Archives of Allergy and Immunology*. 2007; 144(2): 128–136.

Yocum MW, Khan DA. Assessment of patients who have experienced anaphylaxis: a 3-year survey. *Mayo Clinic Proceedings*. 1994; 69(1): 16–23.

Zinderman CE, Landow L, Wise RP. Anaphylactoid reactions to Dextran 40 and 70: reports to the United States Food and Drug Administration, 1969 to 2004. *Journal of Vascular Surgery: Official Publication of the Society for Vascular Surgery [and] International Society for Cardiovascular Surgery, North American Chapter*. 2006; 43(5): 1004–1009.

3. Other Excluded Studies – Not HOI of Interest

Johnson TL, Parker AL. Rates of retrieval of self-injectable epinephrine prescriptions: a descriptive report. *Annals of Allergy, Asthma & Immunology: Official Publication of the American College of Allergy, Asthma, & Immunology*. 2006; 97(5): 694–697.

Nordstrom BL, Norman HS, Dube TJ, Wilcox MA, Walker AM. Identification of abacavir hypersensitivity reaction in health care claims data. *Pharmacoepidemiology and Drug Safety*. 2007; 16(3): 289–296.

4. Other Excluded Studies – Not Administrative or US/Canada Data

Simon MR, Mulla ZD. A population-based epidemiologic analysis of deaths from anaphylaxis in Florida. *Allergy*. 2008; 63(8): 1077–1083.

Poachanukoon O, Paopairochanakorn C. Incidence of anaphylaxis in the emergency department: a 1-year study in a university hospital. *Asian Pacific Journal of Allergy and Immunology (launched by the Allergy and Immunology Society of Thailand)*. 2006; 24(0125-877; 0125-877; 2-3): 111–116.

C. APPENDIX C: LIST AND DEFINITIONS OF ICD OR PROCEDURAL CODES INCLUDED IN ALGORITHMS

Type of Code	Code	Description
ICD-9	995.0	Anaphylactic shock
ICD-9	995.6	Anaphylactic shock caused by adverse food reaction
ICD-9	999.4	Shock caused by anesthesia
ICD-9	989.5	Toxic effect of venom
ICD-9	708.0	Allergic urticaria
ICD-9	708.9	Urticaria unspecified
ICD-9	995.1	Angioneurotic edema
ICD-9	995.3	Allergy, unspecified
ICD-9	695.1	Erythema multiforme
ICD-9	E948.0–E948.9	Adverse reaction from bacterial vaccines
ICD-9	E949.0–E949.9	Adverse reaction from other vaccines and biological substances
ICD-9	995.2	Unspecified adverse effect of drug, medicinal and biological substance
ICD-9	995.60–995.69	Anaphylactic shock due to an adverse reaction to a nonpoisonous food, such as peanuts or crustaceans
ICD-10	T50.9	Overdose or wrong substance given
ICD-10	T63.2	Scorpion sting
ICD-10	T63.4	Insect sting
ICD-10	T63.6	Marine animal sting
ICD-10	T63.9	Sting
ICD-10	T78.0	Food
ICD-10	T78.2	Anaphylactic shock
ICD-10	T80.5	Serum
ICD-10	T88.6	Correct substance properly administered

D. APPENDIX D: ADDITIONAL INFORMATION FROM TABLE 4

Citation	Algorithm
<p>Nordstrom, et al.¹¹</p>	<p>Diagnostic and procedure codes for identification of possible HSR from medical claims data:</p> <p><i>HSR-relevant symptoms:</i> 462, acute pharyngitis; 719.4, arthralgia; 729.1, myalgia; 780.6, fever; 780.7, malaise and fatigue; 780.9, chills; 782.1, rash; 784.0, headache; 786.0, dyspnea; 786.2, cough; 787.0, nausea and vomiting; 787.91, diarrhea; 789.0, abdominal pain</p> <p><i>Syncope and collapse:</i> 780.2, syncope and collapse</p> <p><i>Sudden death:</i> 798.1, sudden death, cause unknown</p> <p><i>Acute allergic reactions/adverse drug events:</i> 961.7, poisoning by antiviral drugs; 977.9, poisoning by unspecified drug; 995.0, other anaphylactic shock; 995.2, unspecified adverse effect of drug; 995.3, allergy unspecified</p> <p><i>Inflammatory conditions of skin and subcutaneous tissue:</i> 693.0, dermatitis due to drugs and medicines; 695.0, toxic erythema; 695.1, erythema multiforme; 695.8, other erythematous conditions; 695.9, unspecified erythematous conditions; 698, pruritus and related conditions</p> <p><i>Acute respiratory syndromes:</i> 518.8, acute respiratory failure; 799.1, respiratory arrest</p> <p><i>Liver disease codes likely to lead to medical record abstraction:</i> 570, acute and subacute necrosis of liver; 571, chronic liver disease and cirrhosis; 572.2, hepatic coma; 573, other disorders of liver, including 573.3: hepatitis unspecified, including toxic (noninfectious) hepatitis; 782.4, jaundice unspecified, not of newborn; 790.4, nonspecific elevation of transaminase or LDH</p> <p><i>Other liver disease codes worth investigating:</i> 017.9, tuberculous hepatitis; 070, viral hepatitis; 091.62, secondary syphilitic hepatitis; 095.3, syphilis of liver; 130.5, hepatitis due to toxoplasmosis; 275.0, disorders of iron metabolism (e.g., pigmentary cirrhosis of liver, hemochromatosis, bronzed diabetes); 572.3, portal hypertension; 572.4, hepatorenal syndrome; 789.1, hepatomegaly; 789.5, ascites; 794.8, abnormal liver scans</p> <p><i>Procedure codes for diagnosis and treatment of liver disease:</i> CPT 47000–47015, biopsy of liver, percutaneous, liver incision; 47100–47136, wedge biopsy of liver, liver excision; 47300–47362, liver repair; 47399, other liver procedures</p> <p><i>Intubation, ventilation, and ambulance service:</i> CPT 30600–31601, tracheostomy, planned; 31603–31605, tracheostomy, emergency procedure; 31500, intubation, endotracheal, emergency procedure; 31610, tracheostomy, fenestration procedure with flaps; 31612, tracheal puncture, percutaneous with transtracheal aspiration and/or injection; 69433, ventilating tube insertion; 94656, ventilation assist and management, first day; 94657, ventilation assist and</p>

	management, subsequent day; ICD-9 v3 96.01, insertion of nasopharyngeal airway; 96.02, insertion of oropharyngeal airway; 96.04, insertion of endotracheal tube; 96.05, other intubation of respiratory tract; 96.7, other continuous mechanical ventilation; 96.70, continuous mechanical ventilation of unspecified duration; 96.71, continuous mechanical ventilation for <96 consecutive hours; 96.72, continuous mechanical ventilation for 96+ consecutive hours; 93.93, nonmechanical methods of resuscitation; HCPCS A0021–A0050, ambulance service; A0225–A0999, ambulance service, specialized services, and supplies
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