

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

HYPERSENSITIVITY REACTIONS OTHER THAN ANAPHYLAXIS (FEVER, RASH, AND LYMPHADENOPATHY) 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

Hypersensitivity Reactions Other Than Anaphylaxis (Fever, Rash, and Lymphadenopathy) 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 (HOIs) 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 hypersensitivity-reactions (HSR) algorithm review.

B. SUMMARY OF FINDINGS

We came across 7 studies that provided codes for different types of HSR and employed some method of validation. Of these 7 studies, 5 studies provided some validation estimates.

Among the reviewed studies, both Nordstrom, et al.¹ and West, et al.² developed and validated comprehensive algorithms for HSR. Other studies provided codes for specific types of HSR. The most frequent reactions that were included across the reviewed studies were specific codes such as International Classification of Disease, Ninth Revision (ICD-9) codes 995.1 (angioneurotic edema), 995.2 (unspecified adverse effect of drug), and 995.3 (allergy unspecified). Anaphylaxis (ICD-9 codes 995.0 and 995.6) was also included in reviewed studies as an HSR. 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. For validation statistics, Nordstrom, et al.'s¹ algorithm demonstrated 95% sensitivity and 90% specificity when tested using a bootstrap resampling approach. West, et al.² reported PPVs of 3% and 15% for "Probable or possible anaphylaxis" and "Other drug-related allergic reactions", respectively. Brown, et al.³ reported that of the 91 patients reviewed, 82 met their definition of angioedema, which included swelling of the face, lips, mouth, or airway. Thus, there were 82 patients with verified angioedema, giving an overall positive predictive value (PPV) of 90% (82 of 91). Miller, et al.⁴ reported that 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. The PPVs reported by Johannes, et al.⁵ that coincided with this HOI did not exceed 3%.

C. RECOMMENDATION FOR ALGORITHMS AND SUGGESTION FOR FUTURE RESEARCH

Our review found that there is no single specific ICD-9 code to identify HSR, but rather several specific and non-specific codes referring to separate types of HSR. Nordstrom, et al.¹ developed and validated a comprehensive algorithm for identifying HSR cases from administrative databases. The algorithm demonstrated 95% sensitivity and 90% specificity. The most frequent types of HSR that were studied included ICD-9 codes 995.1 (angioneurotic edema), 995.2 (unspecified adverse effect of drug), and 995.3 (allergy unspecified inflammatory conditions of skin and subcutaneous tissue).

Our search highlighted a dearth of literature focusing on HSR that provided validated algorithms and validation estimates. Nordstrom, et al.'s¹ algorithm showed high validation estimates in the context of

abacavir-related HSR identification, and it is merited to apply and validate their approach in other patients and care settings. Further research is recommended for the development and validation of algorithms for HSR.

II. PROJECT OBJECTIVES

The primary objective of this project was to identify studies that 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 5 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 HOIs 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 HOIs, based on several criteria. These criteria included: 1) previous validation studies that were identified in a textbook chapter reviewing the validity of drug and diagnosis data used in pharmacoepidemiologic studies,⁶ 2) a list of designated medical events from a proposed FDA rule on the safety-reporting requirements for human drug and biological products,⁷ and 3) the Observational Medical Outcomes Partnership (OMOP)'s¹ commissioned reports on algorithms used to identify the health outcomes using administrative data.⁸

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 to avoid duplication of effort.

Hypersensitivity reaction was one of the 20 HOIs selected for review. This report describes the review process and findings for the HSR 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 2 organizations to perform reviews of 10 HOIs. Because the search strategies used by each organization resulted in very different sets of

¹ For more information, visit the [OMOP website](#).

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 empirically that the majority of relevant articles from one set of OMOP reports (angioedema)^{9, 10} 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 2 sets of files, 1 containing the abstracts for review and the other for documenting abstract-review results.

The search strategy and results for HSR are detailed in the Results section. The initial PubMed search was conducted on May 8, 2010, and the IDIS searches on June 12, 2010. A second PubMed search to update the original search with additional database names was performed on July 6, 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 the 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 to 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 is included in the Results section.

V. RESULTS

A. SEARCH STRATEGY AND RESULTS

The PubMed and IDIS searches identified 342 (Table 1) and 42 citations (Table 2), respectively. A subsequent PubMed search was conducted to amend the original search strategy with relevant databases that were not originally included; this search identified 8 citations (Table 3). The total number of unique citations from the combined searches was 389.

Table 1. PubMed Search Strategy and Results (342): Performed on 05/08/10

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]) Limits: Humans, English, Publication Date from 1990/01/01 to 2011/01/01	1844889
#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 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] Limits: Humans, English, Publication Date from 1990/01/01 to 2011/01/01	395147
#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	2701948

	"placebo-controlled"[All] OR "pilot study"[All] OR "pilot projects"[Mesh] OR "Review"[pt] OR "Prospective Studies"[Mesh]) Limits: Humans, English, Publication Date from 1990/01/01 to 2011/01/01	
#4	Search #1 AND #2 Limits: Humans, English, Publication Date from 1990/01/01 to 2011/01/01	117951
#5	Search #4 NOT #3 Limits: Humans, English, Publication Date from 1990/01/01 to 2011/01/01	71403
#6	((((((((("Drug Hypersensitivity"[Mesh] OR ("Hypersensitivity, Delayed/chemically induced"[Mesh] OR "Hypersensitivity, Delayed/classification"[Mesh] OR "Hypersensitivity, Delayed/drug effects"[Mesh] OR "Hypersensitivity, Delayed/epidemiology"[Mesh])) OR ("Conjunctivitis, Allergic/chemically induced"[Mesh] OR "Conjunctivitis, Allergic/classification"[Mesh] OR "Conjunctivitis, Allergic/epidemiology"[Mesh])) OR ("Dermatitis, Atopic/chemically induced"[Mesh] OR "Dermatitis, Atopic/classification"[Mesh] OR "Dermatitis, Atopic/epidemiology"[Mesh])) OR ("Urticaria/chemically induced"[Mesh] OR "Urticaria/classification"[Mesh] OR "Urticaria/epidemiology"[Mesh])) OR ("Vasculitis, Leukocytoclastic, Cutaneous/chemically induced"[Mesh] OR "Vasculitis, Leukocytoclastic, Cutaneous/classification"[Mesh] OR "Vasculitis, Leukocytoclastic, Cutaneous/epidemiology"[Mesh])) OR ("Immune Complex Diseases/chemically induced"[Mesh] OR "Immune Complex Diseases/classification"[Mesh] OR "Immune Complex Diseases/epidemiology"[Mesh])) OR ("Wissler's Syndrome/chemically induced"[Mesh] OR "Wissler's Syndrome/classification"[Mesh] OR "Wissler's Syndrome/epidemiology"[Mesh])) OR ("Histiocytosis/chemically induced"[Mesh] OR "Histiocytosis/classification"[Mesh] OR "Histiocytosis/epidemiology"[Mesh])) OR ("Lymphadenitis/chemically induced"[Mesh] OR "Lymphadenitis/classification"[Mesh] OR "Lymphadenitis/epidemiology"[Mesh])) OR ("Lymphangiectasis/chemically induced"[Mesh] OR "Lymphangiectasis/classification"[Mesh] OR "Lymphangiectasis/epidemiology"[Mesh])) OR ("Lymphangitis/chemically induced"[Mesh] OR "Lymphangitis/diagnosis"[Mesh] OR "Lymphangitis/epidemiology"[Mesh])) OR ("Lymphedema/chemically induced"[Mesh] OR "Lymphedema/classification"[Mesh] OR "Lymphedema/epidemiology"[Mesh])) OR ("Mucocutaneous Lymph Node Syndrome/chemically induced"[Mesh] OR "Mucocutaneous Lymph Node Syndrome/classification"[Mesh] OR "Mucocutaneous Lymph Node Syndrome/epidemiology"[Mesh])) OR ("Pseudolymphoma/chemically induced"[Mesh] OR "Pseudolymphoma/classification"[Mesh] OR "Pseudolymphoma/epidemiology"[Mesh]) Limits: Humans, English, Publication Date from 1990/01/01 to 2011/01/01	16550
#7	Search #6 AND #5 Limits: Humans, English, Publication Date from 1990/01/01 to 2011/01/01	342

Table 2. IDIS Search Strategy and Results (42): Performed on 06/12/10

<p><u>Search 1: 11 Results</u></p> <p>ADVANCED SEARCH</p> <p>All Fields:</p> <p>"Premier" OR "Solucient" OR "Cerner" OR "Ingenix" OR "LabRx" OR "IHCIS" 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" OR "Medical Record Linkage" OR "ICD-9-CM" OR "ICD-10-CM"</p> <p>AND Disease(s):</p> <p>995.* (NOTE: REACTION, ALLERGIC, DRUG 995.2 , ALLERGY NEC 995.3)</p> <p>AND NOT Descriptor(s):</p> <p>"CASE REPORT ADULT 0" or "FDA APPROVAL PACKAGE 155" OR "FDA BLACK BOX WARNING 165" OR "PIVOTAL STUDY 162" OR "FDA ADVISORY COMMITTEE 164" 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"</p> <p>AND NOT Author(s):</p> <p>"(EDITORIAL)"</p> <p>Years: 1990-2010</p>
<p><u>Search 2: 38 Results</u></p> <p>ADVANCED SEARCH</p> <p>All Fields:</p> <p>"Premier" OR "Solucient" OR "Cerner" OR "Ingenix" OR "LabRx" OR "IHCIS" 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</p>

"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" OR "Medical Record Linkage" OR "ICD-9-CM" OR "ICD-10-CM"

AND Descriptor:

"SIDE EF IMMUNOLOGIC 90" not ("CASE REPORT ADULT 0" or "FDA APPROVAL PACKAGE 155" OR "FDA BLACK BOX WARNING 165" OR "PIVOTAL STUDY 162" OR "FDA ADVISORY COMMITTEE 164" 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 NOT Author:

"(EDITORIAL)" or "(LETTER TO ED)"

Years: 1990-2010

Table 3. Search to Update the Original PubMed Search with Additional Database Names: Performed on 07/06/10, Results = 8

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 "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 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 "Prospective Studies"[Mesh])	2729582
#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	Search #7 AND (((((((((((("Drug Hypersensitivity"[Mesh] OR ("Hypersensitivity, Delayed/chemically induced"[Mesh] OR "Hypersensitivity, Delayed/classification"[Mesh] OR "Hypersensitivity, Delayed/drug effects"[Mesh] OR "Hypersensitivity, Delayed/epidemiology"[Mesh])) OR ("Conjunctivitis, Allergic/chemically induced"[Mesh] OR "Conjunctivitis, Allergic/classification"[Mesh] OR "Conjunctivitis, Allergic/epidemiology"[Mesh])) OR ("Dermatitis, Atopic/chemically induced"[Mesh] OR "Dermatitis, Atopic/classification"[Mesh] OR "Dermatitis, Atopic/epidemiology"[Mesh])) OR ("Urticaria/chemically induced"[Mesh] OR "Urticaria/classification"[Mesh] OR "Urticaria/epidemiology"[Mesh])) OR ("Vasculitis, Leukocytoclastic, Cutaneous/chemically induced"[Mesh] OR "Vasculitis, Leukocytoclastic, Cutaneous/classification"[Mesh] OR "Vasculitis, Leukocytoclastic, Cutaneous/epidemiology"[Mesh])) OR ("Immune Complex Diseases/chemically induced"[Mesh] OR "Immune Complex Diseases/classification"[Mesh] OR "Immune Complex Diseases/epidemiology"[Mesh])) OR ("Wissler's Syndrome/chemically induced"[Mesh] OR "Wissler's Syndrome/classification"[Mesh] OR "Wissler's Syndrome/epidemiology"[Mesh])) OR ("Histiocytosis/chemically induced"[Mesh] OR "Histiocytosis/classification"[Mesh] OR "Histiocytosis/epidemiology"[Mesh])) OR ("Lymphadenitis/chemically induced"[Mesh] OR "Lymphadenitis/classification"[Mesh] OR "Lymphadenitis/epidemiology"[Mesh])) OR ("Lymphangiectasis/chemically induced"[Mesh] OR "Lymphangiectasis/classification"[Mesh] OR "Lymphangiectasis/epidemiology"[Mesh])) OR ("Lymphangitis/chemically induced"[Mesh] OR "Lymphangitis/epidemiology"[Mesh] OR "Lymphangitis/diagnosis"[Mesh] OR "Lymphangitis/epidemiology"[Mesh])) OR ("Lymphedema/chemically induced"[Mesh] OR "Lymphedema/classification"[Mesh] OR "Lymphedema/epidemiology"[Mesh])) OR ("Mucocutaneous Lymph Node Syndrome/chemically induced"[Mesh] OR "Mucocutaneous Lymph Node Syndrome/classification"[Mesh] OR "Mucocutaneous Lymph Node Syndrome/epidemiology"[Mesh])) OR ("Pseudolymphoma/chemically induced"[Mesh] OR "Pseudolymphoma/classification"[Mesh] OR "Pseudolymphoma/epidemiology"[Mesh]))	8

C. ABSTRACT REVIEWS

Of the 389 abstracts reviewed, we accepted 46 for full-text review. Because of the straightforward inclusion criteria, which consisted of: 1) examination of the HOI, 2) use of an administrative database, and 3) study conducted in the United States or Canada, the 2 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, inter-rater agreement (via kappa coefficient) was 0.07, 0.19, and 0.42 for the 3 inclusion criteria, respectively. This seemingly low agreement results 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 rather than a true lack of agreement. They also illustrate that many rejected articles fulfilled multiple exclusion criteria.

D. FULL-TEXT REVIEWS

Of the 46 full-text articles reviewed, 41 were excluded. Thirty-six were excluded during full-text review: 2 were excluded because the HOI identification algorithm was poorly defined, 14 were excluded because they did not include validation of the outcome definition or report validity statistics, and 20 were excluded for other reasons (15: no ICD-9 code; 3: not an administrative database; 2: no codes for the HOI). Cohen's kappa for agreement between reviewers on inclusion vs. exclusion of full-text articles reviewed was 0.38.

Of the 10 papers identified by either or both reviewers, 5 were excluded upon additional review: 3 due to lack of ICD-9 codes¹⁰⁻¹² and 2 due to lack of validation,^{13,14} reducing the total number of articles fulfilling all criteria to 5.

E. MINI-SENTINEL INVESTIGATOR SURVEY

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

F. EVIDENCE INCLUDED IN TABLE

Of the 7 studies included in the table, all were identified from the initial search strategy, and none were identified through references of articles that underwent full-text review or were provided by Mini-Sentinel investigators. Two of these studies, Jackson, et al.¹³ and Brown, et al.,¹⁴ did not include validity statistics; the latter, however, incorporates the same cohort as another paper by the same author.³ A complete list of studies with clear HOI definitions that were eligible to be selected for inclusion is available in Appendix B.

G. SUMMARY AND DISCUSSION OF ALGORITHMS AND VALIDATION

Codes Used in Algorithms. We came across 5 studies that provided codes for HSRs and provided validation estimates. Coding algorithms for HSRs varied in complexity, but generally were based upon similar ICD-9-CM codes representative of acute allergic reactions, such as 995.0 (anaphylactic shock),

995.1 (angioneurotic edema), 995.2 (unspecified adverse effect of drug), and 995.3 (allergy, unspecified).

Brown, et al.³ and Miller, et al.⁴ simply used ICD-9-CM code 995.1. Johannes, et al.⁵ used ICD-9-CM codes 995.0, 995.3, and 995.2 as well as procedure codes consistent with resuscitation. West, et al.² developed a more complicated algorithm that was based on ICD-9-CM codes 995.1 and 995.0. Nordstrom, et al.¹ used data-mining approaches to create a definition of 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.

We should note that one of these diagnostic codes, ICD-9 995.0 (anaphylactic shock), does not belong to this HOI, which is defined as HSRs other than anaphylaxis. This code was included in our review because it was often used in combination with other codes within the identified algorithms.

Validation Algorithms. The Brown, et al.³ and Miller, et al.⁴ papers 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.⁵ examined serious allergic reactions to fluoroquinolone antibacterials. The only PPV confirmed via clinical review that exceeded 3% from this study was anaphylaxis (57.1%) but its corresponding diagnostic code, ICD-9 995.0 (anaphylactic shock), does not belong to this HOI. Johannes, et al.⁵ also examined 2 additional ICD-9 diagnostic codes and 2 procedure codes. The additional ICD-9 codes used were: 995.3 (allergy, unspecified) and 995.2 (unspecified adverse effect of drug); PPVs were not reported. They did, however, confirm serious allergic reactions in 1 of 35 (2.9%) patients on the basis of a procedure code consistent with resuscitation.

West, et al.² used the South Carolina Emergency Room Hospital Discharge Data (SCERHDD) 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 [2 of 3 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 4 (with the number of subjects used to calculate each PPV in parentheses). The PPV for “probable or possible anaphylaxis” was 38% and the PPV for “other drug related allergic reactions” was 15%; the combined PPV was 32%.

The final article fulfilling all inclusion criteria, Nordstrom, et al.,¹ 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 4 (with the number of subjects used to calculate each PPV in parentheses). Among 6 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.,¹ the intent of their research was to develop sophisticated HSR-identifying algorithms via 2 data-mining analyses (recursive partitioning and random forests). In fact, the PPVs from Nordstrom, et al.¹ presented in Table 4 represent only the ICD-9 codes used in the final classification trees aimed at identifying the 22 HSR cases. The classification tree was initiated with a dichotomy of the HSR-relevant symptoms listed in Table 4. 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 of 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.¹

Selected Patient Populations. The studies also varied with respect to patient population. Beyond the demographic differences described below, clinical differences were evident. Brown, et al.³ and Miller, et al.⁴ studied ACE inhibitor–associated angioedema; however, the source populations and study intervals greatly varied. Johannes, et al.⁵ and Nordstrom, et al.¹ both used the same source data, but they examined serious allergic reactions to fluoroquinolone antibacterials and abacavir HSR, respectively. West, et al.² examined general drug-related anaphylaxis.

The 2 papers with algorithms included in the evidence table but without algorithm validation statistics are Brown, et al.¹⁴ and Jackson, et al.¹³ The Brown, et al.¹⁴ paper examined ACE inhibitor–associated angioedema, as did the other study by the same lead author.³ Jackson, et al.¹³ studied children who received 1 or more doses of diphtheria-tetanus toxoids-acellular pertussis (DTaP) vaccine.

H. SUMMARY OF EXCLUDED POPULATIONS AND DIAGNOSES

As indicated in section F above, the demographic characteristics of subjects included in the 5 studies with validation estimates varied. Brown, et al.³ and West, et al.² focused on cohorts extracted from state-specific databases. Brown, et al.³ used Tennessee Medicaid beneficiary data from 1986–1992 on patients aged 15 years or older with at least 1 year of Medicaid enrollment, while West, et al.² made use of data from the 2000–2002 interval extracted from the South Carolina Emergency Room Hospital discharge database among patients aged <19 years.

The remaining 3 studies used data that encompassed more national breadths. Johannes, et al.⁵ and Nordstrom, et al.¹ both used the Ingenix Research Database. The former examined a population with no age restriction but with at least 197 days of enrollment (183 baseline, 14 follow-up), while the latter was limited to newly treated abacavir patients. The corresponding intervals of data were similar: 2000–2004 and 1999–2003, respectively. Miller, et al.⁴ were restricted to US Veterans Health Care System patients who received VA prescriptions for antihypertensive medications during the 1998–2000 interval.

The 2 papers with algorithms included in the evidence table but without algorithm validation statistics are Brown, et al.¹⁴ and Jackson, et al.¹³ The Brown, et al.¹⁴ paper used the same data as the Brown, et al.³ paper referred to above. Jackson, et al.¹³ used Group Health Cooperative data from 1997–2000 among children <7 years of age who received 1 or more doses of DTaP vaccine.

I. 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
Brown, et al. 1996 ³	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 angiotensin-converting enzyme (ACE) inhibitor–associated angioedema.	Angioneurotic edema (ICD-9-CM 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, et al. 2008 ⁴	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–December 31, 2000.	Incidence of angioedema in new users of ACE inhibitors.	ICD-9-CM 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).
West, et al. 2007 ²	South Carolina (SC) emergency departments (EDs) for patients <19 years (N=63), 2000–2002.	Drug-related anaphylaxis.	<i>Probable or possible anaphylaxis:</i> 995.0 (anaphylactic shock) and any drug code* OR	Two CMR nurses were responsible for abstracting the medical records, with the primary focus of determining whether the ICD-9-CM codes	Probable or possible anaphylaxis: PPV = 38.0% (19 of 50). Other drug-related allergic reactions:

			<p>involvement of at least 2 systems (dermatologic*, respiratory***, and/or cardiovascular****) and any drug code</p> <p><i>Other drug-related allergic reactions:</i></p> <p>995.1 (angioneurotic edema) and a code from the DrugsE category* and at least 1 of the following: allergic reaction or allergy unspecified, another dermatologic code, or an ICD-9-CM code from DrugsD*.</p> <p>See Appendix D for details on:</p> <p>*Any drug code</p> <p>**Dermatological</p> <p>***Respiratory</p> <p>****Cardiovascular manifestations.</p>	<p>in the SCERHDD for drug-related anaphylaxis could be substantiated by the clinical notes. A standard abstraction process was used, including abstractor training with extensive data checks to correct inconsistent or potentially erroneous values.</p>	<p>PPV = 15.0% (2 of 13).</p>
<p>Johannes, et al. 2007⁵</p>	<p>Ingenix Research Data Mart. The study population comprised patients receiving at least 1 dispensing of moxifloxacin, ciprofloxacin, levofloxacin, gatifloxacin, phenoxymethylpenicillin potassium, or a</p>	<p>Drug-specific incidence of serious allergic reactions after fluoroquinolone, cephalosporin, and phenoxymethylpenicillin potassium exposure. The authors followed each</p>	<p>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</p>	<p>Medical record review.</p> <p>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</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</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 between July 1, 2000 and June 30, 2004.</p>	<p>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>shock), 995.2 (unspecified adverse effect of drug), 995.3 (allergy, unspecified), a Current Procedural Terminology (CPT) code of 92950 for cardiopulmonary resuscitation, or a Healthcare Common Procedure Coding System (HCPCS) code for adrenaline injection (J7640).</p>	<p>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.</p>	<p>(adrenaline injection) combined = 2.9% (1 of 35).</p>
<p>Nordstrom, et al. 2007¹</p>	<p>Ingenix Research Database; patients who received their first dispensing of abacavir (n=934), for whom 22 hypersensitivity reactions (HSRs) were confirmed from January 1, 1999–July 31, 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, 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. See Appendix D for details.</p>	<p>Potential events identified from the claims were validated through review of medical claims, medical record abstraction, and review by a panel of 4 clinical HIV specialists.</p> <p>Development and validation of an algorithm identified 22 HSR events identified from claims and validated through medical record review. Recursive partitioning analysis was used to construct an algorithm to differentiate patients with and without validated adverse events. The analysis produced a</p>	<p>From the list of codes, we calculated PPVs.</p> <p>Acute Allergic Reactions</p> <p>PPV for 995.0 (anaphylactic shock) AND 995.2 (unspecified adverse effect of drug) combined = 61.1% (11 of 18).</p> <p>PPV for 995.3 (allergy, unspecified) = 83.3% (5 of 6).</p> <p>PPV for 995.0, 995.2, and 995.3 combined = 63.6% (14 of 22).</p> <p>Selected HSR-relevant Symptoms</p> <p>PPV for 780.6 (fever) = 37.9% (11 of 29).</p> <p>PPV for 780.7 (malaise) = 21.9% (7</p>

				<p>classification tree with 3 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 prior to completing a 90-day course of therapy.</p>	<p>of 32). PPV for 787.0 (nausea [with or without vomiting]) = 25.0% (4 of 16). PPV for 784.0 (headache) = 37.5% (3 of 8). PPV for 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.</p>
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Table 5. Non-Validated Algorithms

Citation	Study Population and Time Period	Description of Outcome Studied	Algorithm
Brown, et al. 1997 ¹⁴	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.	Recurrence rate of angioedema associated with continued use of angiotensin-converting enzyme (ACE) inhibitor.	Angioneurotic edema (ICD-9-CM code 995.1).
Jackson, et al. 2002 ¹³	Group Health Cooperative data, 1997–2000. Children <7 years of age who received 1 or more doses of diphtheria-tetanus toxoids-acellular pertussis (DTaP) vaccine at a Group Health clinic from January 1997 through December 2000.	Injection site reactions (ISRs), seizures, allergic responses within 7 days after DTaP vaccines, and febrile episodes within 3 days after vaccination.	ICD-9 codes were defined as 323, 345, 427.5, 458, 465.9, 682, 695.1, 708.0, 708.9, 729.8, 779.0, 780.0, 780.2, 780.3, 780.6, 780.7, 782.5, 785.51, 785.9, 798, 995.0, 995.1, 995.2, 995.3, 999.4, 999.5, 999.9, E948.5, and E948.6.

J. CLINICIAN OR TOPIC-EXPERT CONSULTATION

The literature includes a wide range of codes used to identify “hypersensitivity reactions other than anaphylaxis (fever, rash, and lymphadenopathy).” 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,^{3,5} 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.^{1,2} 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.^{3,4} 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.⁴ These clear clinical symptoms suggest that angioedema misdiagnosis is very unlikely; we therefore are not surprised by the corresponding high PPVs.

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.³ and Miller, et al.,⁴ who both used claims data consisting of inpatient and outpatient claims, suggested 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 in these studies was 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) of over 25,000 subjects that was conducted using prospective adjudication of cases and probably included many mild cases that may have been missed in these claims-based studies.¹⁵

By contrast, in West, et al.,² 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.¹ is unique in that the algorithm was built via a data-mining approach. Using a multitude of diagnostic and procedure codes, their data-driven algorithm was proven to be highly sensitive and specific via bootstrap resampling, despite the often low PPV of each code on an individual basis. 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 HOI and others. Even a priori algorithms of equal or greater complexity, such as that in West, et al.,² 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. If any specific HSR is of interest, narrower definitions can be developed and, subsequently, more specific coding algorithms can be built. HSRs other than serious hypersensitivities are non-emergency conditions and can be treated in both inpatient and outpatient settings. When the HSR is serious, care providers are more likely to document appropriate codes. However, the conditions with less serious HSRs, even if recognized and treated, sometimes do not get documented with diagnostic codes for HSRs. In these cases, development of broader 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, will enhance the predictive power of the algorithms.

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 result in 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 includes several codes that can be used to identify different types of HSR.

VI. SUMMARY AND CONCLUSIONS

A. RECOMMENDATIONS FOR ALGORITHMS

Our review found that there is no specific ICD-9 code to identify HSRs, but rather several specific and non-specific 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.³ and Miller, et al.,⁴ who determined PPVs of greater than 90% for ACE inhibitor–associated angioedema. By contrast, as shown by West, et al.,² when the HSR definition is more general, even highly sophisticated algorithms may exhibit low PPV.

B. SUGGESTIONS FOR FUTURE RESEARCH BASED ON EVIDENCE GAPS

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 subsequent to a very specific exposure. Nordstrom, et al.'s¹ algorithm is the exception. Their work produced high validation estimates in the context of a general HSR definition and 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.

VII. REFERENCES

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VIII. APPENDICES

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

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.

Jackson LA, Carste BA, Malais D, Froeschle J. Retrospective population-based assessment of medically attended injection site reactions, seizures, allergic responses and febrile episodes after acellular pertussis vaccine combined with diphtheria and tetanus toxoids. *The Pediatric Infectious Disease Journal*. 2002; 21(8): 781–786.

BACKGROUND: Since 1997 diphtheria-tetanus toxoids-acellular pertussis (DTaP) vaccines have been recommended for the five dose pertussis vaccination series. To assess rates of medically attended injection site reactions (ISRs), seizures, allergic responses and febrile episodes after Tripedia DTaP vaccine administered in the context of routine care, we conducted a retrospective assessment among the population of Group Health Cooperative from 1997 through 2000. **METHODS:** Administrative databases were used to identify medical visits linked with diagnostic codes potentially indicative of ISRs, seizures, allergic responses and febrile episodes after DTaP vaccine. Outcomes were confirmed by medical record review. **RESULTS:** During the study period 76,133 doses of DTaP were administered. Of the 26 ISRs identified, 6 followed DTaP given as the fourth dose and 18 followed DTaP given as the fifth dose, for rates of 1 per 2779 and 1 per 900 vaccinations, respectively. During the study period nearly all children receiving DTaP as the fifth dose had received whole cell pertussis vaccine for their primary series, and all of the fifth dose ISRs were among that group. Four of those reactions involved the entire upper arm. The rate of febrile seizures within 2 days of DTaP among children <2 years of age was 1 per 19,496 vaccinations. **CONCLUSIONS:** The low rate of febrile seizures and other serious events confirms the safety of DTaP vaccine. The risk of medically attended ISRs was highest with DTaP given as the fifth dose, and whole arm reactions were reported, but medically attended ISRs were relatively uncommon and were self-limited.

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(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

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 organisation. *Drug Saf*. 2007; 30(8): 705-13.

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.

West SL, D'Aloisio AA, Ringel-Kulka T, Waller AE, Clayton Bordley W. Population-based drug-related anaphylaxis in children and adolescents captured by South Carolina Emergency Room Hospital Discharge Database (SCERHDD) (2000-2002). *Pharmacoepidemiol Drug Saf.* 2007 Dec; 16(12): 1255-67.

PURPOSE: Anaphylaxis is a life-threatening condition; drug-related anaphylaxis represents approximately 10% of all cases. We assessed the utility of a statewide emergency department (ED) database for identifying drug-related anaphylaxis in children by developing and validating an algorithm composed of ICD-9-CM codes. **METHODS:** There were 1 314,760 visits to South Carolina (SC) emergency departments (EDs) for patients <19 years in 2000-2002. We used ICD-9-CM disease or external cause of injury codes (E-codes) that suggested drug-related anaphylaxis or a severe drug-related allergic reaction. We found 50 cases classifiable as probable or possible drug-related anaphylaxis and 13 as drug-related allergic reactions. We used clinical evaluation by two pediatricians as the 'alloyed gold standard'¹ for estimating sensitivity, specificity, and positive predictive value (PPV) of our algorithm. **RESULTS:** ED-treated drug-related anaphylaxis in the SC pediatric population was 1.56/100,000 person-years based on the algorithm and 0.50/100,000 person-years based on clinical evaluation. Assuming the disease codes we used identified all potential anaphylaxis cases in the database, the sensitivity was 1.00 (95%CI: 0.79, 1.00), specificity was 0.28 (95%CI: 0.16, 0.43), and the PPV was 0.32 (0.20, 0.47) for the algorithm. Sensitivity analyses improved the measurement properties of the algorithm. **CONCLUSIONS:** E-codes were invaluable for developing an anaphylaxis algorithm although the frequently used code of E947.9 was often incorrectly applied. We believe that our algorithm may have over-ascertained drug-related anaphylaxis patients seen in an ED, but the clinical evaluation may have under-represented this diagnosis due to limited information on the offending agent in the abstracted ED records. Post-marketing drug surveillance using ED records may be viable if clinicians were to document drug-related anaphylaxis in the charts so that billing codes could be assigned properly.

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.

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

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

Type of Code	Code	Description
ICD- 9-CM	576.1	Primary sclerosing cholangitis (PSC)
ICD- 9-CM	720.x	Ankylosing spondylitis
ICD- 9-CM	364.x	Iritis/uveitis
ICD- 9-CM	686.0	Pyoderma gangrenosum
ICD- 9-CM	695.2	Erythema nodosum
ICD- 9-CM	477.1	Allergic rhinitis attributable to food
ICD- 9-CM	558.3	Allergic gastroenteritis and colitis
ICD- 9-CM	V15.01	General food allergy according to specific type of food Peanuts
ICD- 9-CM	V15.02	General food allergy according to specific type of food Milk products
ICD- 9-CM	V15.03	General food allergy according to specific type of food Eggs
ICD- 9-CM	V15.04	General food allergy according to specific type of food Seafood
ICD- 9-CM	V15.05	General food allergy according to specific type of food Other foods
ICD- 9-CM	692.5	Contact dermatitis attributable to food in contact with skin
ICD- 9-CM	693.1	Dermatitis attributable to food taken internally
ICD- 9-CM	988.0	Toxic effect of fish and shellfish
ICD- 9-CM	995.6	Anaphylactic shock attributable to adverse food reaction, specifically for
ICD- 9-CM	995.60	Anaphylactic shock attributable to adverse food reaction, specifically for Unspecified food
ICD- 9-CM	995.61	Anaphylactic shock attributable to adverse food reaction, specifically for Peanuts
ICD- 9-CM	995.62	Anaphylactic shock attributable to adverse food reaction, specifically for Crustaceans
ICD- 9-CM	995.63	Anaphylactic shock attributable to adverse food reaction, specifically for Fruits and vegetables
ICD- 9-CM	995.64	Anaphylactic shock attributable to adverse food reaction,

		specifically for Tree nuts and seeds
ICD- 9-CM	995.65	Anaphylactic shock attributable to adverse food reaction, specifically for Fish
ICD- 9-CM	995.66	Anaphylactic shock attributable to adverse food reaction, specifically for Food additives
ICD- 9-CM	995.67	Anaphylactic shock attributable to adverse food reaction, specifically for Milk products
ICD- 9-CM	995.68	Anaphylactic shock attributable to adverse food reaction, specifically for Eggs
ICD- 9-CM	995.69	Anaphylactic shock attributable to adverse food reaction, specifically for Other specified food
ICD- 9-CM	995.7	Other adverse food reactions, not elsewhere classified
ICD- 9-CM	988.0	Toxic effects of fish or shellfish eaten
ICD- 9-CM	691.8	Other atopic dermatitis and related conditions
ICD- 9-CM	692.9	Contact dermatitis and other eczema when no cause is specified
ICD- 9-CM	446.1	Kawasaki disease
ICD- 9-CM	373.3	Noninfectious dermatoses of eyelid
ICD- 9-CM	995.0	Other anaphylactic shock
ICD- 9-CM	995.1	Angioneurotic edema
ICD- 9-CM	995.2	Unspecified adverse effect of drug, medicinal, and biological substance [due] to correct medicinal substance properly administered
ICD- 9-CM	995.3	Allergy, unspecified
ICD- 9-CM	995.6	Anaphylactic shock due to adverse food reaction
ICD- 9-CM	003.1, 036.2, and 038.0–038.9	Sepsis
ICD- 9-CM	708.0 to 708.9	Urticaria
ICD- 9-CM	323, 345, 427.5, 458, 465.9, 682, 695.1, 708.0, 708.9, 729.8, 779.0, 780.0, 780.2, 780.3, 780.6, 780.7, 782.5, 785.51, 785.9, 798, 995.0, 995.1, 995.2, 995.3, 999.4, 999.5, 999.9, E948.5, and E948.6	Injection site reactions (ISRs), seizures, allergic responses and febrile episodes
ICD- 9-CM	078.3	Catscratch disease
ICD- 9-CM	078.00, 078.10, 078.11, 110.00, 110.10, 110.20, 110.30, 110.40, 110.50, 110.80, 110.90, 111.00, 111.80, 111.90, 112.00, 112.10, 112.30, 112.90, 172.40,	Dermatologic or skin condition

	172.50, 172.60, 172.70, 172.90, 173.10, 173.20, 173.30, 173.40, 173.50, 173.60, 173.70, 173.90, 216.10, 216.20, 216.30, 216.40, 216.50, 216.60, 216.70, 216.90, 238.20, 680.20, 680.90, 681.00, 681.01, 681.02, 681.10, 681.90, 682.00, 682.20, 682.30, 682.40, 682.60, 682.70, 682.90, 684.00, 685.00, 685.10, 686.00, 686.10, 686.90, 690.10, 691.00, 691.80, 692.30, 692.40, 692.60, 692.70, 692.71, 692.72, 692.74, 692.79, 692.90, 693.00, 693.10, 694.50, 695.10, 695.30, 695.40, 695.89, 695.90, 696.00, 696.10, 696.20, 696.30, 696.50, 697.00, 697.90, 698.00, 698.10, 698.30, 698.90, 700.00, 701.00, 701.10, 701.30, 701.40, 701.50, 701.80, 701.90, 702.00, 702.11, 702.19, 702.80, 703.00, 703.80, 704.00, 704.01, 704.02, 704.09, 704.20, 704.80, 704.90, 705.81, 705.83, 706.00, 706.10, 706.20, 706.30, 706.80, 706.90, 707.10, 707.80, 707.90, 708.10, 708.50, 708.80, 708.90, 709.00, 709.01, 709.09, 709.20, 709.30, 709.80, and 709.90	
ICD- 9-CM	284	Aplastic anemia
ICD-9-CM	478.75	Laryngeal spasm
ICD- 9-CM	478.8	Upper respiratory tract hypersensitivity
ICD- 9-CM	786.05	Shortness of breathe
ICD- 9-CM	786.07	Wheezing
ICD- 9-CM	786.09	Respiratory insufficiency distress
ICD- 9-CM	786.1	Stridor

D. APPENDIX D: ADDITIONAL INFORMATION FROM TABLE 4

Citation	Algorithm
West, et al. ²	<p>* Any drug code = (DrugsD, DrugsE, or DrugsP) where: Drugs D = 693.0 (dermatitis due to drugs) or 995.2 (unspecified adverse effect of drug); Drugs E = 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 Drugs P = 960–969 (poisoning by drugs, medicinal and biological substances), E850 (accidental poisoning by analgesics, antipyretics, and antirheumatics), E950 (suicide and self-inflicted poisoning by solid or liquid substances), E962 (assault by poisoning), or E980 (poisoning by solid or liquid substances, undetermined whether accidentally or purposely inflicted)</p> <p>**Dermatological manifestations: 708.0, 708.1, 708.9 (urticaria, allergic, idiopathic, unspecified), 995.1 (angioneurotic edema)</p> <p>***Respiratory manifestations: 478.75 (laryngeal spasm), 478.8 (upper respiratory tract hypersensitivity, site unspec.), 786.05 (shortness of breath), 786.07 (wheezing), 786.09 (respiratory insufficiency, distress), 786.1 (Stridor)</p> <p>****Cardiovascular manifestations: 458.9 (hypotension), 785.0 (tachycardia, unspecified)</p>
Nordstrom, et al. ¹	<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,</p>

	<p>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 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</p>
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