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

ERYTHEMA MULTIFORME MAJOR/MINOR/NOT OTHERWISE SPECIFIED, STEVENS-JOHNSON SYNDROME, OR TOXIC EPIDERMAL NECROLYSIS REPORT

Prepared by: Gary Schneider, ScD, MSPH, Sumesh Kachroo, PhD, MS, B. Pharmacy, Natalie Jones, BS, Sheila Crean, MPH, Ruzan Avetisyan, MD, MPH, and Matthew W. Reynolds, PhD

Author Affiliations: United BioSource Corporation, Epidemiology and Database Analytics

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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

Erythema Multiforme Major/Minor/Not Otherwise Specified, Stevens-Johnson Syndrome, or Toxic Epidermal Necrolysis Report

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 erythema multiforme and related conditions algorithm review.

B. SUMMARY OF FINDINGS

Our search revealed limited literature focusing on erythema multiforme and related conditions that provided validated algorithms and validation estimates. We came across 4 studies that provided the codes for erythema multiforme and related conditions and employed some method of validation. Two of these studies reported on identical study cohorts, while the cohort from another was very similar, albeit slightly expanded, to that reported in the other 2. The validation estimates of these 3 papers are therefore very similar, but correspond to the validation estimates in the fourth study, which used an entirely different cohort. We also included 2 additional studies that only provided information on the codes employed, with no validation.

All studies showed consistency in defining erythema multiforme and related conditions. One study[1] used International Classification of Diseases-Adapted, Eighth Modification (ICDA-8) code 695.1, while the remaining studies used ICD-9-CM code 695.1.

Two studies[1, 2] focused on combined conditions (erythema multiforme [EM], Stevens-Johnson syndrome [SJS], and toxic epidermal necrolysis [TEN]), 3 studies[3-5] that were related publications focused on EM and SJS, and 1 study[6] focused on TEN.

Clinical experts frequently disagreed with the discharge diagnosis, with only approximately 50% of cases being consistent with EM, SJS, and TEN. At the time of these studies, EM, SJS, and TEN were defined by the 4-digit ICD-9-CM code 695.1, which also included staphylococcus scalded-skin syndrome (SSSS). Effective as of FY2009, SSSS was eliminated from ICD-9-CM code 695.1. We therefore calculated positive predictive values (PPVs) of ICD-9-CM code 695.1 with and without SSSS. With SSSS, PPVs ranged from 61% to 66%; without SSSS, PPVs ranged from approximately 54% to 60%.

C. RECOMMENDATION FOR ALGORITHMS AND SUGGESTION FOR FUTURE RESEARCH

At the time of this current report, the most recent data identified in our search were 25 years old and therefore did not incorporate changes to the diagnostic coding of these conditions that became effective as of FY2009. The newly defined ICD-9-CM code 695.1 eliminates SSSS and also includes a fifth digit, providing specific codes for the various conditions previously under the umbrella of the 4-digit ICD-9-CM code 695.1. These more stringent diagnostic coding definitions should be leveraged to aid future examination of coding algorithms for erythema multiforme and related conditions. Updated research

needs to be conducted on development and validation of coding algorithms for EM, SJS, and TEN to identify cases in administrative databases.

II. PROJECT OBJECTIVES

The primary objective of this project was to identify studies that used validated algorithms 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 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 were identified in a textbook chapter reviewing the validity of drug and diagnosis data used in pharmacoepidemiologic studies,[7] 2) a list of designated medical events from a proposed FDA rule on the safety-reporting requirements for human drug and biological products,[8] and 3) the Observational Medical Outcomes Partnership (OMOP)'s[i] commissioned reports on algorithms used to identify the health outcomes using administrative data.[9]

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.

Erythema multiforme and related conditions was one of the 20 HOIs selected for review. This report describes the review process and findings for the erythema multiforme and related conditions 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 articles, OMOP investigators reviewed the PubMed indexing of the articles deemed useful in final

[i] For more information about OMOP, see http://omop.fnih.org

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)[4,5] 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 erythema multiforme and related conditions 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 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 1 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 following summarizes the search results obtained from PubMed, EMBASE, and IDIS searches. The PubMed search identified 34 citations (Table 1), the EMBASE search identified 691 citations (Table 2), and the IDIS search identified 19 citations (Table 3). The total number of unique citations from the combined searches was 714. An additional PubMed search was conducted at a later date to amend the original search strategy with names of relevant databases that were not included in the original search. This search identified 1 citation (Table 4), bringing the total number of unique citations from the combined searches to 715.

Table 1. PubMed Search Strategy and Results (34): Performed on 05/10/10

Search	Query	Results
#1	("Erythema Multiforme"[Mesh] OR "Erythema Multiforme"[All] OR "Toxic Epidermolysis"[All] OR "Toxic Epidermal Necrolysis"[All] OR "Stevens-Johnson Syndrome"[All] OR "Fiessinger-Rendu Syndrome"[All] OR "Lyell's Syndrome"[All] OR "Lyell Syndrome"[All] OR "Badder's Syndrome"[All] OR "Badder Syndrome"[All] OR "Rowell's Syndrome"[All] OR "Rowell Syndrome"[All] OR "Staphylococcal Scalded Skin Syndrome"[All])	6651
#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])	774739
#3	#1 and #2	117
#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 Topic"[Mesh] OR "Sensitivity and Specificity"[Mesh] OR "Predictive Value of Tests"[Mesh] OR	3586178

	"Reproducibility of Results"[Mesh])	
#5	#3 and #4	86
#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])	4484867
#7	#5 NOT #6	40
#8	("humans"[MeSH Terms] AND English[lang] AND ("1990/01/01"[PDAT] : "2010/06/1"[PDAT]))	6112373
#9	#7 and #8	34

Table 2. EMBASE Search Strategy and Results (691): Performed on 06/23/10

1) 'premier':ab,ti OR 'solucient':ab,ti OR 'cerner':ab,ti OR 'ingenix':ab,ti OR 'labrx':ab,ti OR 'ihcis':ab,ti OR 'marketscan':ab,ti OR 'market scan':ab,ti OR 'medstat':ab,ti OR 'thomson':ab,ti OR 'pharmetrics':ab,ti OR 'healthcore':ab,ti OR 'united healthcare':ab,ti OR 'unitedhealthcare':ab,ti OR 'uhc':ab,ti OR 'research database':ab,ti OR 'group health':ab,ti OR 'hcup':ab,ti OR ('healthcare cost':ab,ti AND 'utilization project':ab,ti) OR ('health care cost':ab,ti AND 'utilization project':ab,ti) OR 'meps':ab,ti OR 'medical expenditure panel survey':ab,ti OR 'namcs':ab,ti OR 'national hospital ambulatory medical care survey':ab,ti OR 'national ambulatory medical care survey':ab,ti OR 'nhis':ab,ti OR 'national health interview survey':ab,ti OR 'kaiser':ab,ti OR 'health maintenance organization':de,ab,ti OR 'hmo':ab,ti OR 'cleveland clinic':ab,ti OR 'lovelace':ab,ti OR 'department of defense':ab,ti OR 'henry ford':ab,ti OR ('denmark':ab,ti AND 'epidemiology':ab,ti) OR 'i3':ab,ti OR 'aetna':ab,ti OR 'humana':ab,ti OR 'wellpoint':ab,ti OR 'ims':ab,ti OR 'intercontinental marketing services':ab,ti OR 'geisinger':ab,ti OR 'ge healthcare':ab,ti OR 'mqic':ab,ti OR 'pharmo':ab,ti OR 'pilgrim':ab,ti OR 'puget sound':ab,ti OR 'regenstrief':ab,ti OR 'saskatchewan':ab,ti OR 'tayside':ab,ti OR 'memo':ab,ti OR 'veterans affairs':ab,ti OR 'partners healthcare':ab,ti OR 'mayo clinic':ab,ti OR 'rochester epidemiology':ab,ti OR 'indiana health':ab,ti OR 'intermountain':ab,ti OR 'blue cross':ab,ti OR 'health partners':ab,ti OR 'health plan':ab,ti OR 'health services':ab,ti OR 'nationwide inpatient sample':ab,ti OR 'national inpatient sample':ab,ti OR 'medicaid':de,ab,ti OR 'medicare':de,ab,ti OR 'mediplus':ab,ti OR 'outcome assessment':de,ab,ti OR 'insurance database':ab,ti OR 'insurance databases':ab,ti OR 'data warehouse':ab,ti OR 'disease classification'/exp OR 'icd-9':ab,ti OR 'international statistical classification':ab,ti OR 'international classification of diseases':ab,ti OR 'icd-10':ab,ti OR 'current procedural terminology':de,ab,ti OR 'cpt':ab,ti OR 'medical information system'/exp OR 'drug surveillance program'/exp OR 'drug surveillance':ab,ti OR ('claims':ab AND 'administrative':ab) OR ('data':ab AND 'administrative':ab) OR 'factual database'/exp OR 'data base'/exp OR 'electronic medical record'/exp OR 'diagnosis related group'/exp OR 'tenncare':ab,ti OR 'ramq':ab,ti OR 'cigna':ab,ti OR (british AND columbia:ab,ti AND health:ab,ti) OR 'cihi' OR (manitoba:ab,ti AND center AND for AND 'health'/exp AND 'policy'/exp) OR (ontario:ab,ti AND population:ab,ti) OR ohip:ab,ti OR (registered AND 'persons'/exp AND database:ab,ti) OR ('health'/exp AND insurance:ab,ti) OR ices OR (institute AND for AND clinical AND evaluative AND sciences) OR (alberta:ab,ti AND health:ab,ti) OR data:ab,ti OR database:ab,ti OR population:ab,ti OR ('alberta'/exp AND 'health'/exp AND 'wellness'/exp) AND [embase]/lim
2) 'validation study'/exp OR 'sensitivity and specificity'/exp OR 'prediction and forecasting'/exp OR 'reproducibility'/exp OR 'predictive validity'/exp OR 'predictive value':ab,ti OR 'algorithm'/exp OR 'drug therapy'/exp OR 'adverse drug reaction'/exp OR 'drug toxicity and intoxication'/exp OR 'drug safety'/de OR 'chemically induced disorder'/de OR 'pharmacoepidemiology'/de AND [embase]/lim
3) #1 AND #2
4) 'clinical trial'/exp OR 'meta analysis'/exp OR 'prospective study'/exp OR 'pilot study'/exp AND 'review'/exp OR 'double blind procedure'/exp OR 'letter'/exp OR 'editorial'/exp AND [embase]/lim
5) #3 NOT #4
6) 'erythema multiforme'/exp OR 'toxic epidermolysis'/exp OR 'toxic epidermal necrolysis'/exp OR 'stevens-johnson syndrome'/exp OR 'fiessinger-rendu syndrome' OR 'lyells syndrome' OR 'lyell syndrome'/exp OR 'badders syndrome' OR 'badder syndrome' OR 'rowells syndrome' OR 'rowell syndrome' OR 'staphylococcal scalded skin syndrome'/exp AND [embase]/lim
7) #5 AND #6
8) #5 AND #6 AND [humans]/lim AND [english]/lim AND [embase]/lim AND [1990-2010]/py

Table 3. IDIS Search Strategy and Results (19): Performed on 05/10/10

Disease:

"ERYTHEMA, MULTIFORME 695.1"

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 SKIN 86")

AND **Abstract:**

(("erythema" AND "multiforme") OR ("toxic" AND "epidermal" AND "necrosis") OR "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 as topic" OR "Medical Record Linkage" OR "ICD-9-CM" OR "ICD-10-CM")

Table 4. 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 "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 (("Erythema Multiforme"[Mesh] OR "Erythema Multiforme"[All] OR "Toxic Epidermolysis"[All] OR "Toxic Epidermal Necrolysis"[All] OR "Stevens-Johnson Syndrome"[All] OR "Fiessinger-Rendu Syndrome"[All] OR "Lyell's Syndrome"[All] OR "Lyell Syndrome"[All] OR "Badder's Syndrome"[All] OR "Badder Syndrome"[All] OR "Rowell's Syndrome"[All] OR "Rowell Syndrome"[All] OR "Staphylococcal Scalded Skin Syndrome"[All]))	1

B. ABSTRACT REVIEWS

Of the 715 abstracts reviewed, we accepted 8 for full-text review. Because of the straightforward inclusion criteria, which consisted of: 1) examination of the HOI of interest, 2) use of administrative database, and 3) study conducted in the United States or Canada, the level of agreement between the 2 reviewers in regard to acceptance/rejection status of an abstract for full-text review could be considered high (Cohen's kappa = 0.77). Agreement on the reason of rejection was also generally high; among the 707 abstracts rejected, inter-rater agreement (via kappa coefficient) was 0.89, 0.86, and 0.32 for the 3 inclusion criteria, respectively. As only a single rejection reason was captured in our abstract review database, this overwhelming consensus illustrates that the classification process was generally not complicated.

C. FULL-TEXT REVIEWS

Of the 8 full-text articles reviewed, 4 were determined to fulfill all inclusion criteria[1, 3-5]; Cohen's kappa for agreement between reviewers on inclusion vs. exclusion of full-text articles reviewed was 1.0 (i.e., perfect inter-rater agreement). Of the 4 excluded studies, all did not contain validation estimates,[2, 6, 10, 11] 1 did not include ICD-9 codes,[10] and 1 was not from the US or Canada.[11] Reviewers identified no additional citations for review from full-text article references. Although 4 articles were determined to have reported validation of the coding algorithm directly in the article, 2 reported results from the same study,[3, 4] leaving 3 unique studies that fulfilled inclusion criteria.

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 4 validation 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.

Because fewer than 5 validation studies were identified, 2 studies that did not include validation of the outcome or reporting of validity estimates were reviewed and included in the evidence table. A complete list of studies with clear HOI definitions that were eligible to be selected for inclusion is available in Appendix B.

F. SUMMARY AND DISCUSSION OF ALGORITHMS AND VALIDATION

Codes Used in Algorithms. We identified 4 studies fulfilling all inclusion criteria,[1, 3-5] and another 2 with algorithms but with no validation.[2, 6] All studies showed consistency in defining erythema multiforme and related conditions. One study used International Classification of Diseases-Adapted, Eighth Modification (ICDA-8) code 695.1,[1] while the remaining 5 used ICD-9-CM code 695.1.[2-6]

Validation Algorithms. Through FY2008, ICD-9-CM code 695.1 incorporated the erythema multiforme (EM) conditions of erythema iris and herpes iris, Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN)/Lyell's syndrome, and staphylococcus scalded-skin syndrome (SSSS).[12] As this code is multi-diagnostic, reporting a PPV statistic for each unique disease under its umbrella would be deceptive. We therefore report proportions of ICD-9-CM code 695.1 that were considered consistent with EM, SJS, and/or TEN via expert review (Appendix D). The proportions of common misdiagnoses are also presented. The PPV estimates incorporate all diagnoses within ICD-9-CM code 695.1 at the time of these studies (i.e., including SSSS).

Between 45% and 51% of instances of ICD-9-CM code 695.1 were validated cases of EM, SJS, or TEN (Appendix D). The classification of diseases within this diagnostic code, however, differs between the Chan, et al.[1] paper and the 3 Strom, et al.[3-5] papers. The former specifies EM, SJS, and TEN. By contrast, 1 of the Strom , et al. papers reports a group defined as "SJS and EM Major"[5]; the other 2 Strom , et al. papers report this as well as a group defined as "EM Minor and EM NOS."[3, 4] In these 2 papers, the aggregate of these groups equals their overall EM proportion.[3, 4]

All of the validated studies reported common misdiagnoses (i.e., not EM, SJS, or TEN). Other skin diseases, SSSS, and truly misclassified (i.e., not a skin disease) cases were generally responsible for 30%, 15%, and 5% of the misdiagnoses, respectively (Appendix D). There was little study-to-study variation. By subtracting the aggregated percentage of the non-SSSS misdiagnoses from 100%, we were able to calculate the PPV of ICD-9-CM code 695.1 in the 2 studies that did not directly report them.[1, 5] Generally, between 61% and 66% of patients with ICD-9-CM code 695.1 had a condition consistent with that diagnostic code at the time of these studies (i.e., EM, SJS, TEN, or SSSS).

Selected Patient Populations. Three of the 4 studies with validation used cohorts extracted from the Computerized On-Line Medicaid Pharmaceutical Analysis and Surveillance System (COMPASS), a database composed of Medicaid billing data; 2 of these are nearly identical reports in different journals,[3, 4] while the third uses a slightly larger cohort than the other 2 (i.e., data from 5 states as opposed to 3).[5] Of these 3 studies, only 1 reports demographic information. Of the 273 potential cases, the majority were from Michigan (67%) and aged 0–19 years (60.4%); males comprised 39%, and 55% resided in urban areas.[3] Medical records were obtained for 128 (47%) of these potential cases. All 3 of these studies used COMPASS data from the early 1980s.[3-5] The fourth study with validation estimates used data among patients of any age from Group Health Cooperative (GHC) of Puget Sound, Seattle, Washington from 1972 to 1986.[1]

G. SUMMARY OF EXCLUDED POPULATIONS AND DIAGNOSES

As indicated in section F above, of the 4 studies with validation estimates, 3 focused on cohorts extracted from the COMPASS Medicaid billing database, 2 of which are identical reports in different journals and 1 of which uses a slightly larger cohort.[3-5] The fourth study makes use of HMO claims data from the GHC of Puget Sound, Seattle, Washington.[1]

The 2 studies with algorithms but without validation estimates encompassed a more national breadth; 1 used Canadian hospital discharge data,[6] while the other analyzed data from the National Hospital Discharge Summary, National Ambulatory Care Survey, and the National Hospital Ambulatory Care Survey.[2]

H. EVIDENCE TABLES

Table 5. Positive Predictive Values by Algorithm

Citation	Study Population and Time Period	Description of Outcome Studied	Algorithm	Validation/Adjudication Procedure and Operational Definition	Validation Statistics
Chan , et al. 1990[1]	HMO claims data from Group Health Cooperative (GHC) of Puget Sound, Seattle, Washington with hospital discharge diagnosis of erythema multiforme (n=61), 1972–1986.	Incidence of EM, SJS, and TEN requiring hospitalization.	Diagnosis of ICDA-8: 695.1 (erythema multiforme). ICDA-8 695.1 should, in principle, include all hospitalized cases of EM, SJS, and TEN.	Review of discharge summaries, hospital records, and outpatient charts via criteria for diagnosis as described in paper.	PPV with SSSS = 65.6% (back-calculated via information provided in paper). PPV without SSSS = 59.6%.
Strom 2001[5]	Computerized On-Line Medicaid Pharmaceutical Analysis and Surveillance System (COMPASS), a computerized database consisting of Medicaid claims patients from the states of Michigan, Minnesota, Florida, Missouri, and Nebraska with an inpatient diagnosis of erythema multiforme and medical charts available for review (N=167), 1980–1985.	Assess the validity of the ICD-9-CM 695.1 code to ascertain SJS.	ICD-9-CM 695.1 for SJS and EM.	Medical record review.	PPV with SSSS = 61.2% (back-calculated via information provided in paper). PPV without SSSS = 54.0%.
Strom , et al. 1991[3, 4]	COMPASS, with an inpatient diagnosis of erythema multiforme and medical charts available for review (N=128),	Determine the incidence of SJS.	ICD-9-CM 695.1 for SJS and EM.	Medical record review.	PPV with SSSS = 60.9%. PPV without SSSS = 53.7%.

	1980–1984. Of the 273 potential cases from which the medical records were obtained, the majority were from Michigan (67%) and aged 0–19 years (60.4%); males comprised 39%, and 55% resided in urban areas.[3]				

Table 6. Non-validated Algorithms

Citation	Study Population and Time Period	Description of Outcome Studied	Algorithm
Mittmann, et al. 2004[6]	Patients admitted to burn treatment sites across Canada (n=250), patient cases reported to the Canadian Adverse Drug Reaction Monitoring Program (CADRMP) (N=25), and patient cases recorded by the Canadian Institute for Health Information (CIHI) with a hospital discharge summary containing a diagnosis of erythema multiforme (N=4349), 1995–2000.	TEN; all TEN cases	ICD-9-CM code 695.1. Hospital discharge summaries using the ICD-9-CM code 695.1 indicated that of the 4349 cases, 15.5% (n=674) were TEN.
Stern 2005[2]	The study analyzed data from the National Hospital Discharge Summary (1997–2001), National Ambulatory Care Survey (1995–2000), and National Hospital Ambulatory Care Survey (1995–2000) to determine the number of hospitalizations and visits with primary diagnoses of skin conditions that are often attributed to drugs. The study identified 22,656 hospitalizations with ICD-9 code 695.1. Of these, there were 10,875 males and 11,781 females. The mean age was 29±3.	The authors sought to quantify hospitalizations and visits to office-based physicians, hospital clinics, and emergency departments with primary diagnoses of skin conditions such as erythema multiforme, SJS, or TEN, which are often due to drug reaction.	SJS/TEN: 695.1 (erythema multiforme, Stevens-Johnson syndrome, toxic epidermal necrolysis). Drug eruption: 693.0. Drug allergy: 995.2. Urticaria/angioedema: 708.0, 708.9, 995.0, 995.1, 989.5. Erythroderma: 695.9, 695.89. Adverse effect of drug properly administered: E930–E949.

I. CLINICIAN OR TOPIC-EXPERT CONSULTATION

The literature review identified only ICD code 695.1 as a coding algorithm used for EM major/minor/not otherwise specified, SJS, or TEN. Chan, et al.[1] used ICDA-8 code 695.1, and Strom[5] and Strom, et al.[3, 4] used ICD-9-CM code 695.1. These studies consistently found that nearly half of patients with this diagnostic code had EM, SJS, or TEN. The remaining half comprised SSSS, other skin diseases, and truly

misclassified diagnoses, contributing approximately 15%, 30%, and 5% to the total, respectively. These reviewed studies with validation estimates suggest that when a record is available for expert review, clinical experts frequently disagree with the discharge diagnosis of EM/SJS/TEN (ICD code 695.1).

Some recent changes to ICD-9-CM code 695.1, effective as of FY2009, should be noted. At the time of these studies, EM, SJS, and TEN were considered to be synonymous. This supported the rationale for inclusion of these diseases into a common ICD-9-CM code, which also included other closely related conditions such as SSSS.[13] More recently, this diagnostic terminology has changed based on the presence of epidermal detachment and the extent of the body surface area affected. Also, increased understanding of the diseases previously covered by ICD-9-CM code 695.1 has occurred. For example, TEN and SJS differ in etiology from SSSS; medications are commonly the cause for TEN/SJS, while staphylococcal infection is typically the causative agent for SSSS.[13] This increased knowledge has led to SSSS being coded as ICD-9-CM 695.81 and the inclusion of a fifth digit to ICD-9-CM code 695.1. This fifth digit provides specific codes to each of the individual diseases, excluding SSSS, previously contained in the 4-digit, multi-diagnostic ICD-9-CM code 695.1. The recent updates to this code are presented in Appendix E.

As a result of SSSS now being eliminated from ICD-9-CM code 695.1, we estimated the PPV of this code as if SSSS were not included, i.e., by reducing the denominator by approximately 15% (the percentage of SSSS cases). The result is that the PPVs are reduced to approximately between 54% and 60% (Appendix D). However, this likely underestimates the true PPV, as we assumed all other common misdiagnoses would remain within ICD-9-CM code 695.1, while in reality a proportion of these would most likely be transferred to the new code representing SSSS.

It is worth noting 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 section for L51 – erythema multiforme – refers to this HOI of interest.

VI. SUMMARY AND CONCLUSIONS

A. RECOMMENDATIONS FOR ALGORITHMS

We came across 6 studies that provided codes for erythema multiforme and related conditions. Of these 6 studies, 4 employed some method of validation strategy, while 2 studies only provided information on the codes employed. The studies identified in our search showed consistency in defining erythema multiforme and related conditions. One study used ICDA-8 code 695.1, while the remainder used ICD-9-CM code 695.1. We found that clinical experts frequently disagreed with the discharge diagnosis, with only approximately 50% of cases being consistent with EM, SJS, and TEN. At the time of these studies, EM, SJS, and TEN were defined by the 4-digit ICD-9-CM code 695.1, which also included SSSS. The PPV of ICD-9-CM code 695.1 with SSSS included a range between 61% and 66%. Effective as of FY2009, SSSS was eliminated from ICD-9-CM code 695.1, which may reduce the PPVs to approximately between 54% and 60%. This newly defined ICD-9-CM code 695.1 also includes a fifth digit, providing specific codes for the various conditions formerly under the umbrella of the 4-digit code. These more stringent diagnostic

coding definitions should aid future examination of coding algorithms for erythema multiforme and related conditions.

B. SUGGESTIONS FOR FUTURE RESEARCH BASED ON EVIDENCE GAPS

Our search revealed limited literature focusing on erythema multiforme and related conditions that provided validated algorithms and validation estimates. Furthermore, at the time of this current report, the most recent data identified in our search were 25 years old and therefore did not incorporate the changes to the diagnostic coding of these conditions that became effective as of FY2009. Updated research needs to be conducted on development and validation of coding algorithms for EM, SJS, and TEN to identify cases in administrative databases.

VII. REFERENCES

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2. Stern RS. Utilization of hospital and outpatient care for adverse cutaneous reactions to medications. *Pharmacoepidemiol Drug Saf*. Oct 2005; 14(10): 677-684.

3. Strom BL, Carson JL, Halpern AC, , et al. Using a claims database to investigate drug-induced Stevens-Johnson syndrome. *Stat Med*. Apr 1991; 10(4): 565-576.

4. Strom BL, Carson JL, Halpern AC, , et al. A population-based study of Stevens-Johnson syndrome. Incidence and antecedent drug exposures. *Arch Dermatol*. Jun 1991; 127(6): 831-838.

5. Strom BL. Data validity issues in using claims data. *Pharmacoepidemiol Drug Saf*. Aug-Sep 2001; 10(5): 389-392.

6. Mittmann N, Knowles SR, Gomez M, Fish JS, Cartotto R, Shear NH. Evaluation of the extent of under-reporting of serious adverse drug reactions: the case of toxic epidermal necrolysis. *Drug Saf*. 2004; 27(7): 477-487.

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11. Gau SS, Chao PF, Lin YJ, Chang CJ, Gau CS. The association between carbamazepine and valproate and adverse cutaneous drug reactions in patients with bipolar disorder: a nested matched case-control study. *J Clin Psychopharmacol*. Oct 2008; 28(5): 509-517.

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13. Kagan RJ, Kotoski GM. Successfully changing an ICD-9 diagnosis code: the ABA experience for Stevens-Johnson syndrome and toxic epidermal necrolysis. *J Burn Care Res*. Jan-Feb 2010; 31(1): 146-150.

VIII. APPENDICES

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

Chan HL, Stern RS, Arndt KA, Langlois J, Jick SS, Jick H, Walker AM. The incidence of erythema multiforme, Stevens-Johnson syndrome, and toxic epidermal necrolysis. A population-based study with particular reference to reactions caused by drugs among outpatients. *Archives of Dermatology*. 1990; 126(0003-987; 0003-987; 1): 43–47.

We carried out a study to estimate the incidence of erythema multiforme (EM), Stevens Johnson syndrome (SJS), and toxic epidermal necrolysis (TEN) requiring hospitalization and to determine which drug therapies were associated with these reactions. We reviewed the clinical records of all patients who were hospitalized with these discharge diagnoses at Group Health Cooperative (GHC) of Puget Sound, Seattle, Wash, from 1972 through 1986. During this 14-year period, an average of about 260,000 persons, with demographic characteristics similar to those of the general population, received their care from GHC, and there were about 25,000 admissions to hospitals per year at the GHC hospitals. Based on International Classification of Diseases-Adapted coding, a total of 61 suspect cases of EM, SJS, or TEN were identified from the computerized hospital discharge file. Based on record review and the application of a uniform set of diagnostic criteria, a total of 37 patients (61%) were classified as having EM, SJS, or TEN. Of these, 16 cases (43%) were attributed to drugs administered to these patients prior to hospitalization. The overall incidence of hospitalization for EM, SJS, or TEN due to all causes was 4.2 per 10(6) person-years. The incidence of TEN alone due to all causes was 0.5 per 10(6) person-years. The incidence of EM, SJS, or TEN associated with drug use were 7.0, 1.8, and 9.0 per 10(6) person-years, respectively, for persons younger than 20 years of age, 20 to 64 years of age, and 65 years of age and older. Drug therapies with reaction rates in excess of 1 per 100,000 exposed individuals include phenobarbital (20 per 100,000), nitrofurantoin (7 per 100,000), sulfamethoxazole and trimethoprim, and ampicillin (both 3 per 100,000), and amoxicillin (2 per 100,000). Overall, our data suggest that cases of EM, SJS, and TEN sufficiently severe to require hospitalization are infrequent among outpatients using well-established drug therapies. A continuing challenge is the evaluation of these severe cutaneous reactions that are associated with newly marketed or less frequently prescribed drug therapies.

Mittmann N, Knowles SR, Gomez M, Fish JS, Cartotto R, Shear NH. Evaluation of the extent of under-reporting of serious adverse drug reactions: the case of toxic epidermal necrolysis. *Drug Safety: An International Journal of Medical Toxicology and Drug Experience.* 2004; 27(7): 477–487.

INTRODUCTION: Toxic epidermal necrolysis (TEN) is a life-threatening adverse drug reaction (ADR) that is primarily the result of drug exposure (incidence 0.4-1.3 per million person-years). Life-threatening ADRs such as TEN should be reported to ADR monitoring programmes, which collect reports for suspected ADRs and alert the public and medical practitioners to new drug hazards. In Canada, reports are made to the Canadian Adverse Drug Reaction Monitoring Program (CADRMP). OBJECTIVE: To examine the extent of under-reporting for TEN in Canada. DESIGN: A retrospective case series design was used to collect all TEN cases for the period January 1995 to December 2000. METHODS: The CADRMP and 22 burn centres across Canada were contacted for all TEN patients treated during the specified time period. PATIENT GROUPS STUDIED: The study population consisted of patients admitted to burn treatment sites across Canada, patient cases reported to the CADRMP and patient cases recorded by the Canadian Institute for Health Information (CIHI) hospital discharge summaries as the International Classification of Diseases Version 9 Clinical Modification (ICD-9-CM) code 695.1. RESULTS: Twenty-five TEN cases (six fatal) were reported to CADRMP from

January 1995 to December 2000. During this period, 14 (63.6%) burn treatment sites reported admission of 250 TEN cases. Hospital discharge summaries using the ICD-9-CM code 695.1 indicated that 4349 cases were admitted to hospital during this time period and it was estimated that 15.5% (n = 674) of these cases were TEN. Using the burn facility data as the denominator, 10% (25 of 250) of TEN cases were reported to CADRMP. Using CIHI data as a denominator, only 4% (25 of 674) of TEN cases were reported to CADRMP. CONCLUSIONS: There is serious under-reporting of TEN. Lack of reporting of life-threatening ADRs can compromise population safety. There is a need to increase awareness of ADR reporting programmes.

Stern RS. Utilization of hospital and outpatient care for adverse cutaneous reactions to medications. *Pharmacoepidemiology and Drug Safety*. 2005; 14(10): 677–684.

Purpose: To quantify hospitalizations, visits to office based physicians, hospital clinics and emergency departments with primary diagnoses of skin conditions that are often due to drug reaction. Methods: I analyzed data from the National Hospital Discharge Summary (1997-2001), National Ambulatory Care Survey (1995-2000) and National Hospital Ambulatory Care Survey (1995-2000) to determine the number of hospitalizations and visits with primary diagnoses of skin conditions that are often attributed to drugs. Using statistical methods for surveys, I determined the demographic characteristics of patients with these diagnoses and compared them with patients seeking care for other reasons. Results: In the United States, there are about 5000 hospitalizations each year with a primary diagnosis of erythema multiform, Stevens-Johnson Syndrome or Toxic Epidermal Necrolysis, of which 35% are specifically ascribed to drugs. Annually, there are more than 100 000 outpatient visits for these diagnoses and about two million visits for immediate hypersensitivity reactions that may be due to drugs. Outpatient visits for drug eruptions and drug allergies that include a skin component exceed 500 000 annually. Conclusions: Skin conditions often attributed to drugs are frequent reasons for hospitalization and physician visits. Optimal care of the individual patients with these conditions requires careful attention to drugs as a possible cause.

Strom BL. Data validity issues in using claims data. *Pharmacoepidemiology and Drug Safety*. 2001; 10(5): 389–392.

This paper overviews the use of claims data in pharmacoepidemiology, examines problems related to claims data use, and focuses on the uncertain validity of diagnosis data. Two contrasting studies are provided of drug-induced neutropenia and Stevens-Johnson Syndrome; both studies were launched at the same time with similar designs. Neutropenia is a laboratory-driven diagnosis, easy to make and confirm. The neutropenia study yielded many useful results, ranging from incidence rates to results with specific drug classes and individual drugs. However, the medical records revealed major unexpected issues from chronic and cyclic neutropenia. In contrast, Stevens-Johnson Syndrome is harder to diagnose, and is represented poorly in the ICD-9-CM coding system. The result was a study productive of much less clinical information. These studies show the important implications of variable data validity to study interpretation. Uniquely problematic situations exist: the illness does not reliably come to medical attention; inpatient drug exposures; an outcome is poorly defined by the diagnostic coding system; descriptive studies; drug effects are delayed and patients lose eligibility; and there are important unknown confounders such as cigarette smoking, occupation, menarche, menopause, etc., about which information cannot be obtained without accessing the patient.

Strom BL, Carson JL, Halpern AC, Schinnar R, Snyder ES, Shaw M, Tilson HH, Joseph M, Dai WS, Chen D. A population-based study of Stevens-Johnson syndrome. Incidence and antecedent drug exposures. *Archives of Dermatology*. 1991; 127(0003-987; 0003-987; 6): 831–838.

To determine the incidence of Stevens-Johnson syndrome, a descriptive epidemiology study was performed using computerized Medicaid billing data from 1980 to 1984 from the states of Michigan, Minnesota, and Florida. The ratio of persons hospitalized with a discharge diagnosis of erythema multiforme (ICD-9-CM code 695.1) to persons with any claim for medical service was first used as an estimate of the incidence rate of the disease. Then, since the ICD-9-CM code for erythema multiforme includes other illnesses in addition to Stevens-Johnson syndrome and because these illnesses are frequently misdiagnosed, the information provided by a review of medical records for a subset of cases of erythema multiforme was used to determine the proportion of patients with true Stevens-Johnson syndrome. The incidence rates of Stevens-Johnson syndrome were 7.1 (6.1 to 8.2), 2.6 (1.6 to 4.0), and 6.8 (4.3 to 10.3) per million per year in each state, respectively. Penicillins, especially aminopenicillins, were frequently used in the 19 patients judged to be true cases of Stevens-Johnson syndrome. In conclusion, Stevens-Johnson syndrome is a uncommon condition. The excess risk of Stevens-Johnson syndrome due to any drug must, therefore, be very low.

Strom BL, Carson JL, Halpern AC, Schinnar R, Snyder ES, Stolley PD, Shaw M, Tilson HH, Joseph M, Dai WS. Using a claims database to investigate drug-induced Stevens-Johnson syndrome. *Statistics in Medicine*. 1991; 10(4): 565–576.

In order to explore a priori hypotheses about drug-induced Stevens-Johnson Syndrome (SJS), a case-control study was initiated using data from COMPASS, a computerized data base consisting of Medicaid claims data. The records of 3.8 million patients in five U.S. states were searched to identify patients with an inpatient diagnosis of ICD-9-CM code 695.1 (erythema multiforme-EM). Out of the total of 367 cases that were identified, primary medical records for 249 were sought and 128 (51.4 per cent) of these were obtained. The remainder could not be obtained because: in 36 (29.8 per cent) the hospital refused to provide medical records; in 33 (27.3 per cent) there were transcription errors; in 20 (16.5 per cent) the state could not translate the identification number, primarily because the patients lost Medicaid eligibility too long before our request; in 27 (22.3 per cent) the hospital could not locate the patient's record; and in 5 (4.1 per cent) there were other reasons. Of those with a medical record, 121 (94.5 per cent) had a skin diagnosis and 109 (85.2 per cent) had a diagnosis compatible with ICD-9-CM code 695.1 specified on their discharge summary. However, in 35 (27.3 per cent) an expert reviewer felt that the discharge diagnosis was incorrect. In 50 (39 per cent) the computer diagnosis was incorrect. Only 19 (14.8 per cent) were judged by the expert reviewer to truly have Stevens-Johnson Syndrome, and an additional 37 (28.9 per cent) were judged to have erythema multiforme minor. Thus, the computerized diagnosis agreed very well with the diagnoses specified on the discharge summary. However, EM is frequently misdiagnosed, ICD-9-CM code 695.1 contains multiple other diagnoses which are not EM, and much of hospitalized EM is EM minor. Thus, studies of SJS cannot be performed except in patients whose medical records are available.

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

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

Gau SS-F, Chao PF, Lin YJ, Chang CJ, Gau CS. The association between carbamazepine and valproate and adverse cutaneous drug reactions in patients with bipolar disorder: a nested matched case-control study. *Journal of Clinical Psychopharmacology*. 2008; 28(1533-712; 5): 509–517.

Mittmann N, Knowles SR, Gomez M, Fish JS, Cartotto R, Shear NH. Evaluation of the extent of under-reporting of serious adverse drug reactions: the case of toxic epidermal necrolysis. *Drug Safety*. 2004; 27(7): 477–487.

Mockenhaupt M, Kelly JP, Kaufman D, Stern RS. The risk of Stevens-Johnson syndrome and toxic epidermal necrolysis associated with nonsteroidal antiinflammatory drugs: a multinational perspective. *Journal of Rheumatology*. 2003; 30(10): 2234–2240.

Stern RS. Utilization of hospital and outpatient care for adverse cutaneous reactions to medications. *Pharmacoepidemiology and Drug Safety*. 2005; 14(10): 677–684.

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

Type of Code	Code	Description
ICDA-8	695.1	Erythema multiforme
ICD-9-CM	695.1	Erythema multiforme

D. APPENDIX D: ERYTHEMA MULTIFORME CODING ALGORITHMS AND PPV OF CITATIONS WITH VALIDATION

	Chan, et al.[1]	Strom[5]	Strom, et al.[3, 4]
Outcome	Incidence of EM, SJS, and TEN requiring hospitalization	Assess the validity of the ICD-9-CM 695.1 code to ascertain SJS	Incidence of SJS
Population	Group Health Cooperative (GHC) of Puget Sound, Seattle	COMPASS (Medicaid claims) patients from 5 states	COMPASS (Medicaid claims) patients from 3 states
Number with chart review	61	167	128
Proportion of ICD code 695.1 corresponding to:			
EM, SJS, or TEN	50.8	45.6***	45.3
EM	27.9	43.8	43.8
SJS	19.7		
TEN	3.3		1.6
SJS or EM Major		14.8	14.8
EM Minor or EM NOS			28.9
Common misdiagnosis (%)			
SSSS*	14.8	15.6	15.6
Other skin diseases	29.5	33.8	33.6
Truly misclassified	4.9	5.0**	5.5
PPV of ICD code 695.1 with SSSS	65.6***	61.2***	60.9
PPV of ICD code 695.1 without SSSS	59.6	54.0	53.7

EM = erythema multiforme; SJS = Stevens-Johnson syndrome; TEN = toxic epidermal necrolysis; SSSS = staphylococcus scalded-skin syndrome

* At the time of these studies, staphylococcus scalded-skin syndrome was part of ICD-9 695.1; it is now coded as ICD-9 695.81

** Based on 95% with a skin diagnosis from article

*** Not directly reported; calculated based on information provided in paper

E. APPENDIX E: ICD-9-CM CODE 695.1, ERYTHEMA MULTIFORME, AS OF FY2009

ICD-9-CM code	Definition
695.1	Erythema multiforme
695.10	Erythema multiforme, unspecified
695.11	Erythema multiforme, minor
695.12	Erythema multiforme, major
695.13	Stevens-Johnson syndrome
695.14	Stevens-Johnson syndrome – toxic epidermal necrolysis overlap syndrome
695.15	Toxic epidermal necrolysis
695.19	Other erythema multiforme