

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

## ABO INCOMPATIBILITY REACTIONS 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.

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

## ABO Incompatibility Reactions Report

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## **I. EXECUTIVE SUMMARY**

### **A. OVERVIEW OF PROJECT**

The Food and Drug Administration (FDA) Mini-Sentinel contract is a pilot program that aims to conduct active surveillance to detect and refine safety signals that emerge for marketed medical products. To perform this active surveillance, it is necessary to develop and understand the validity of algorithms for identifying health outcomes of interest in administrative data. Thus, the goal of this project was 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 ABO incompatibility reaction algorithm review.

### **B. SUMMARY OF FINDINGS**

We were unable to identify any studies that validated algorithms for identifying ABO incompatibility reactions using administrative data. The one study that included ABO incompatibility in an algorithm and performed medical record review of the transfusion reactions identified from administrative data did not actually appear to identify any cases of ABO incompatibility reaction.<sup>6</sup> Another study that examined 2.23 million hospital discharge abstractions in which a transfusion was administered found no codes for any of the non-infectious complications of transfusion they studied.<sup>8</sup> Even though ABO incompatibility reactions are rare, this raises strong concern about the sensitivity of hospital discharge codes for identifying ABO incompatibility reactions. Also, the absence of validation studies does not allow verification of the predictive value of the codes. However, FDA staff noted that they have identified such codes in Medicare administrative data; this work is still ongoing (personal communication). Also, another study of pediatric hospital discharges identified ABO incompatibility reactions at a rate of about 1/10,000 transfusions.<sup>9</sup>

ICD-9-CM code 999.6 identifies ABO incompatibility reactions and was used for all studies identified that examined this outcome. An ICD-10-WHO code for this HOI is also available. Transfusions themselves were identified using ICD-9-CM procedure codes 99.0x or V58.2. One study examining the validity of the code typically representing transfusion of allogeneic red blood cells (99.04) found a sensitivity of 83% and specificity of 100% for this code at a single center.<sup>11</sup> Another multi-center study using hospital discharge abstracts from 1987 found sensitivities of 21% if three procedure codes were available and 31% if 25 procedure codes were available, and a specificity of 100%.<sup>12</sup> The transfusion code appears specific, but sensitivity is uncertain.

### **C. RECOMMENDATION FOR ALGORITHMS AND SUGGESTION FOR FUTURE RESEARCH**

Since no studies were identified that validated an algorithm for identifying ABO incompatibility reactions, the possibilities for research on algorithm validity are wide open. One might speculate that the positive predictive value of ICD-9-CM code 999.6 would be high, since there is likely little diagnostic ambiguity when a hemolytic reaction occurs after transfusion and it is determined that the wrong blood type was given. An exception might occur in the case of a transcription error in entering the code. Delayed reactions are also possible when antibody titers are low or the transfusion is a type with limited levels of antigen, thus leading to a lower risk of a severe hemolytic reaction, and these may be less likely

to be identified. Regardless of the type of reaction, medical record review is needed to establish validity of the ABO incompatibility codes recorded in administrative databases.

It is not clear that administrative data are sensitive in identifying such reactions. Research to determine the sensitivity of coding algorithms will be difficult because of the rarity of the event. Surveying hospitals and blood banks, including those participating in the Centers for Disease Control and Prevention's (CDC) Hemovigilance Network or the U.S. Biovigilance Network, to identify health plan members who have had ABO incompatibility reactions may be a feasible method for finding cases whose billing codes could then be examined to assess the sensitivity of the codes. Reviewing random charts of patients who received transfusions would be too inefficient, even if they were restricted to patients with an intensive care unit stay or some other criterion which might increase the prevalence of these reactions. Another route might be to identify fatal transfusion reactions that have been reported to FDA's Center for Biologics Evaluation and Research (CBER) since fatal reactions are reportable, and determine how these are coded in administrative data. It is likely, however, that the probabilities of submitting codes for fatal and non-fatal transfusion reactions may differ.

At FDA's request, new ICD-9-CM codes have been adopted that sub-classify the 999.6 code into more specific types of reactions.<sup>10</sup> It may be important to explore their performance characteristics now that they are available. However, they are still captured within the 999.6 code, so the importance of validating these more specific codes might depend on the specific purpose of the research utilizing these codes.

## **II. PROJECT OBJECTIVES**

The primary objective of this project was to identify studies that have validated algorithms used to identify various health outcomes of interest (HOIs) using administrative data from the United States or Canada, and to summarize the results of those validation studies. If fewer than five validation studies were identified, a secondary objective was to identify non-validated algorithms that have been 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 had been identified in a textbook chapter reviewing the validity of drug and diagnosis data used in pharmacoepidemiologic studies;<sup>1</sup> 2) a list of designated medical events had been created from a proposed FDA rule on the safety reporting requirements for human

drug and biological products;<sup>2</sup> 3) the Observational Medical Outcomes Partnership (OMOP)<sup>ii</sup> had commissioned reports on algorithms used to identify the health outcome using administrative data.<sup>3</sup>

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

ABO incompatibility reaction was one of the 20 HOIs selected for review. This report describes the review process and findings for the ABO incompatibility reaction definition algorithms.

## IV. METHODS

### A. SEARCH STRATEGY

The general search strategy was developed based on prior work by OMOP and its contractors, and modified slightly for these reports. Originally, OMOP contracted with two organizations to perform reviews of 10 HOIs. Because the search strategies used by each organization resulted in very different sets of articles, OMOP investigators reviewed the PubMed indexing of the articles deemed useful in final reports and developed a strategy that would identify the majority of these citations while maintaining efficiency in the number of abstracts that would need to be reviewed. Mini-Sentinel investigators made minor changes to this strategy that would result in the identification of more citations, and confirmed empirically that the majority of relevant articles from one set of OMOP reports (angioedema)<sup>4,5</sup> would be identified using this approach. The base search strategy was then combined with PubMed terms representing the HOIs. Medical subject heading (MeSH) terms were generally preferred as HOI search terms due to their likely specificity. Text word searches were sometimes used, particularly when the MeSH search resulted in a small number of citations for review. The workgroup also searched the database of the Iowa Drug Information Service (IDIS) using a similar search strategy to identify other relevant articles that were not found in the PubMed search. For a limited number of outcomes where very few citations were identified from PubMed and IDIS searches, Embase searches were conducted. Search results were restricted to articles published on or after January 1, 1990.

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

The search strategy and results for ABO incompatibility reaction are detailed in the Results section. The PubMed search was conducted on June 22, 2010, and the IDIS search on September 2, 2010. Because of a small number of results from PubMed and IDIS searches, an Embase search was also conducted by Carol Mita, a Harvard librarian, on June 24, 2010. Because these search strategies were unsuccessful in identifying relevant manuscripts, a number of Google Scholar searches were explored as described in the results section of this document.

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<sup>ii</sup> For more information, go to the [OMOP website](#).

## **B. ABSTRACT REVIEW**

### **1. Abstract Review Methods**

Each abstract was reviewed independently by two 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 a 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 two investigators, with a goal of identifying validation studies described in the article itself or from the reference section of the article. Citations from the article's references were selected for full-text review if they were cited as a source for the HOI algorithm, or were otherwise deemed likely to be relevant. Full-text review exclusion criteria were applied sequentially, since 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 two reviewers attempted to reach consensus on inclusion by discussion. If the reviewers could not agree, a third investigator would be consulted to make the final the 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 and contrast 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 was included in the results.

## V. RESULTS

### A. SEARCH STRATEGY AND RESULTS

The following summarizes the search results obtained from PubMed, IDIS, and Embase searches. The PubMed search identified 63 citations, the IDIS searches 0 citations, and the Embase search 7 citations. The total number of unique citations from the combined searches was 69.

**Table 1. PubMed Search Strategy and Results (63)**

Search	Query	Results
#1	("Premier"[All] OR "Solucient"[All] OR "Cerner"[All] OR "Ingenix"[All] OR "LabRx"[All] OR "IHGIS"[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 "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 "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 "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 "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] OR (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]))) Limits: Humans, English, Publication Date from 1990/01/01 to 2011/01/01	373384
#2	("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]) Limits: Humans, English, Publication Date from 1990/01/01 to	2603134



	2011/01/01	
#3	"Blood Group Incompatibility"[Mesh] Limits: Humans, English, Publication Date from 1990/01/01 to 2011/01/01	3939
#4	abo incompatible Limits: Humans, English, Publication Date from 1990/01/01 to 2011/01/01	782
#5	abo incompatibility Limits: Humans, English, Publication Date from 1990/01/01 to 2011/01/01	1025
#6	Search #3 OR #4 OR #5 Limits: Humans, English, Publication Date from 1990/01/01 to 2011/01/01	4369
#7	Search #1 NOT #2 Limits: Humans, English, Publication Date from 1990/01/01 to 2011/01/01	252917
#8	Search #7 AND #6 Limits: Humans, English, Publication Date from 1990/01/01 to 2011/01/01	63

**Table 2. IDIS Search Strategy and Results**

<p><b>Disease:</b></p> <p>"MEDICAL CARE COMPL-ABO INCOM 999.6"</p> <p><b>NOT Author:</b></p> <p>( "(Editorial)" OR "Letter to Ed" )</p> <p><b>NOT Descriptor:</b></p> <p>("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")</p> <p><b>AND Abstract:</b></p> <p>((("ABO" AND "incompatibility") AND "transfusion") OR "Premier" OR "Solucient" OR "Cerner" OR "Ingenix" OR "LabRx" OR "IHCS" 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" )</p> <p>Records = 0</p>
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**Table 3. Embase Search Strategy and Results**

<p><b>1. Data source search</b></p> <p>'TennCare':ti,ab OR 'RAMQ':ti,ab OR 'Cigna':ti,ab OR ('british columbia':ti,ab AND ('health':ti,ab OR 'data':ti,ab OR 'database':ti,ab OR 'population':ti,ab)) OR 'CIHI' OR ('manitoba':ti,ab AND ('center for health policy' OR 'population':ti,ab OR 'health insurance':ti,ab)) OR ('ontario':ti,ab AND ('population':ti,ab OR 'OHIP':ti,ab OR 'registered persons database':ti,ab OR 'health insurance':ti,ab OR 'ICES' OR 'Institute for Clinical Evaluative Sciences')) OR ('Alberta':ti,ab AND ('health':ti,ab OR 'data':ti,ab OR 'database':ti,ab OR 'population':ti,ab)) OR 'Alberta Health and Wellness' OR 'Premier':ti,ab OR 'Solucient':ti,ab OR 'Cerner':ti,ab OR 'Ingenix':ti,ab OR 'LabRx':ti,ab OR 'IHGIS':ti,ab OR 'marketscan':ti,ab OR 'market scan':ti,ab OR 'Medstat':ti,ab OR 'Thomson':ti,ab OR 'pharmetrics':ti,ab OR 'healthcore':ti,ab OR 'united healthcare':ti,ab OR 'UnitedHealthcare':ti,ab OR 'UHC':ti,ab OR 'Research Database':ti,ab OR 'Group Health':ti,ab OR 'HCUP':ti,ab OR ('Healthcare Cost':ti,ab AND 'Utilization Project':ti,ab) OR ('Health Care Cost':ti,ab AND 'Utilization Project':ti,ab) OR 'MEPS':ti,ab OR 'Medical Expenditure Panel Survey':ti,ab OR 'NAMCS':ti,ab OR 'National Hospital Ambulatory Medical Care Survey':ti,ab OR 'National Ambulatory Medical Care Survey':ti,ab OR 'NHIS':ti,ab OR 'National Health Interview Survey':ti,ab OR 'Kaiser':ti,ab OR 'Health Maintenance Organization':ti,ab,de OR 'HMO':ti,ab OR 'Cleveland Clinic':ti,ab OR 'Lovelace':ti,ab OR 'Department of Defense':ti,ab OR 'Henry Ford':ti,ab OR 'i3':ti,ab OR 'Aetna':ti,ab OR 'Humana':ti,ab OR 'Wellpoint':ti,ab OR 'IMS':ti,ab OR 'Intercontinental Marketing Services':ti,ab OR 'Geisinger':ti,ab OR 'GE Healthcare':ti,ab OR 'MQIC':ti,ab OR 'PHARMO':ti,ab OR 'Pilgrim':ti,ab OR 'Puget Sound':ti,ab OR 'Regenstrief':ti,ab OR 'Saskatchewan':ti,ab OR 'Tayside':ti,ab OR 'MEMO':ti,ab OR 'Veterans Affairs':ti,ab OR 'Partners Healthcare':ti,ab OR 'Mayo Clinic':ti,ab OR 'Rochester Epidemiology':ti,ab OR 'Indiana Health':ti,ab OR 'Intermountain':ti,ab OR 'blue cross':ti,ab OR 'health partners':ti,ab OR 'health plan':ti,ab OR 'health services':ti,ab OR 'Nationwide Inpatient Sample':ti,ab OR 'National Inpatient Sample':ti,ab OR 'medicaid':ti,ab,de OR 'medicare':ti,ab,de OR 'MediPlus':ti,ab OR 'Outcome Assessment':ti,ab,de OR 'insurance database':ti,ab OR 'insurance databases':ti,ab OR 'Data Warehouse':ti,ab OR 'disease classification'/exp OR 'ICD-9':ti,ab OR 'international statistical classification':ti,ab OR 'international classification of diseases':ti,ab OR 'ICD-10':ti,ab OR 'CPT':ti,ab OR 'Current procedural terminology':ti,ab,de OR 'CPT':ti,ab OR 'medical information system'/de OR 'drug surveillance program'/de OR 'drug surveillance':ti,ab OR ('claims':ab AND 'administrative':ab) OR ('data':ab AND 'administrative':ab) OR 'factual database'/de OR 'data base'/de OR 'electronic medical record'/de OR 'diagnosis related group'/de</p> <p>- 402,908 results</p> <p><b>2. Prediction search</b></p> <p>'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</p> <p>AND [humans]/lim AND [english]/lim AND [1990-2010]/py</p> <p>- 456,998 results</p> <p><b>3. HOI Identifiers</b></p> <p>'blood group incompatibility'/de OR 'blood group ABO incompatibility'/de OR ('ABO' and ('incompatibility' OR 'incompatible')) AND [humans]/lim AND [english]/lim AND [1990-2010]/py</p> <p>- 1,972</p> <p><b>4. #1 and #2 and #3 = 7 results</b></p>
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## B. ABSTRACT REVIEWS

Of the 69 abstracts reviewed, 15 were selected for full-text review; 35 were excluded because they did not study the HOI, 17 were excluded because they were not administrative database studies, and 2 were excluded because the data source was not from the United States or Canada. Cohen's kappa for agreement between reviewers on inclusion vs exclusion of abstracts was 0.15. The primary reason for the low agreement was that one investigator was more liberal in including abstracts in hopes that something might be useful, since so few appeared relevant to the HOI.

### **C. FULL-TEXT REVIEWS**

Of the 15 full-text articles reviewed from the original 3 searches, none were included in the final evidence tables; 2 were excluded because they did not study the HOI, and 12 were excluded because they were not administrative database studies. One full-text article could not be obtained through interlibrary loan. However, this article had no abstract and appeared to be a news article as opposed to original research. Reviewers identified one citation for review in full-text article reviews for another HOI (infections related to blood products or tissue grafts).<sup>6</sup> Cohen's kappa for agreement between reviewers on inclusion vs exclusion of full-text articles reviewed was 1 (all studies from the original set were excluded).

Because the searches identified no articles that met the inclusion criteria, a number of exploratory Google Scholar searches were conducted. Searches were refined to try to restrict the number of results to a manageable number. Search results were scanned by one investigator who conducted full-text review when an article appeared potentially relevant. The search terms "ICD 999.6 transfusion" identified 20 results which captured the articles selected for inclusion in this report, with the exception of the article identified from the full-text reviews for the other HOI which was also included in this report (Scanlon 2008).<sup>6</sup> A number of studies were identified that used non-validated algorithms, all of which used ICD-9-CM code 999.6 to identify ABO incompatibility, usually as a part of studying a broader list of complications of medical care. Because of this, only two studies from this search that provided some uniquely useful information were included in this report. A technical report on methodology for quality indicators was also included since it provided ICD-10 codes that can be used to identify ABO incompatibility. Another study was included because it reported identifying a few cases of ABO incompatibility reaction using pediatric hospital discharge data.

### **D. MINI-SENTINEL INVESTIGATOR SURVEY**

Mini-Sentinel investigators provided no reports of validation studies that had been completed by their teams.

### **E. EVIDENCE INCLUDED IN TABLE**

Of the 4 studies included in the table, 0 were identified from the initial search strategy, 0 were identified through references of articles from this search that underwent full-text review, and 0 were provided by Mini-Sentinel Investigators. One was identified through the full-text reviews for another HOI. Three non-validated algorithms were identified through Google Scholar searches as previously described.

### **F. SUMMARY AND DISCUSSION OF ALGORITHMS AND VALIDATION**

We found little information that was useful for determining the validity of algorithms to identify ABO incompatibility reaction from administrative data. This is likely due in part to the rarity of the event.

Scanlon, et al.<sup>6</sup> examined the positive predictive value of patient safety indicators in 28 pediatric hospitals using administrative data from 2003-2005 (Table 4). They found only 7 patients with any one of three codes indicating a transfusion reaction had occurred, one of which was ICD-9-CM code 999.6 (ABO incompatibility reaction). The codes were accurate in all cases, for a positive predictive value of 100%. Two transfusion reactions were present on admission. They noted that it was unlikely that the

other five were preventable since they were reactions to antibodies or antigens that cannot be typed, which infers that none of the reactions they validated was actually an ABO incompatibility reaction.

A technical report by Drösler<sup>7</sup> was included because it provided some additional codes beyond ICD-9-CM code 999.6 for identifying transfusion reactions. An external cause of injury code, E8760 (mismatched blood in transfusion), was added to the ICD-9-CM code algorithm. Though this is not specific to ABO incompatibility reactions, it may be relevant for studying this HOI. This report also provided corresponding ICD-10-WHO codes for transfusion reactions, which are provided in Table 5.

Morton, et al.<sup>8</sup> examined all discharges in the Healthcare Cost and Utilization Project Nationwide Inpatient Sample database from 2004, including 2.23 million in which the patient received a transfusion (Table 5). Transfusions were identified by ICD-9-CM procedure codes 99.0x or V58.2. It is notable that the 99.0x procedure codes represent transfusion with a number of different types of blood products. They examined a range of transfusion-related outcomes. ABO incompatibility reaction was one of a number of non-infectious transfusion-related complications. Despite the large number of discharges studied, the authors reported that they did not identify a single code for a non-infectious transfusion-related complication, including ABO incompatibility reactions. This is in contrast to the rate of 0.01 transfusion reactions per 1,000 hospitalizations identified in pediatric patients.<sup>6</sup> This finding raises doubt about the sensitivity of discharge abstract data in identifying ABO incompatibility reactions, as it seems unlikely that not a single transfusion reaction would occur among 2.23 million transfusion recipients. In contrast to this finding, FDA staff report that they have identified ABO incompatibility reaction codes in Medicare data, though they remain rare (personal communication).

In another study of all consecutive discharges from 35 independent academic pediatric hospitals from 2001-2003, Slonim, et al.<sup>9</sup> used the ICD-9-CM code 999.6 to identify ABO incompatibility reactions. The hospitals represented a wide range of geographic areas and varied in size. Demographics were not reported, but the authors noted the proportion of different races and ethnicities who received transfusions, which suggested that a range was included. Of 1,085,259 patients, 51,720 received 74,123 transfusions and 492 patients experienced 793 transfusion complications. ABO incompatibility reactions were identified in recipients of only two types of blood products, red blood cells (ICD-9-CM procedure code 99.04) and platelets (ICD-9-CM procedure code 99.05). ABO incompatibility reactions were identified in 3/44,632 patients with ICD-9-CM procedure code 99.04 and 2/14,274 patients with ICD-9-CM procedure code 99.05.

## **G. SUMMARY OF EXCLUDED POPULATIONS AND DIAGNOSES**

Since there were no studies identified that validated ABO incompatibility reaction algorithms, it is of limited use to review the exclusion criteria in detail.

Scanlon, et al.<sup>6</sup> studied pediatric patients. As stated previously, their description suggested that they identified no ABO incompatibility reactions in their validation study. In contrast, Slonim, et al.<sup>9</sup> studied pediatric patients and identified several ABO incompatibility reactions, though the rate was extremely low.

The technical report by Drösler<sup>7</sup> did not use a study sample. It simply described coding algorithms.

Morton, et al.<sup>8</sup> examined all discharges in the Healthcare Cost and Utilization Project Nationwide Inpatient Sample database from 2004, including 2.23 million in which the patient received a transfusion. The average age of the transfusion recipients was 66.9 years and 41.1% were male.

## H. EVIDENCE TABLES

**Table 4. Positive Predictive Values by Algorithm**

Citation	Study Population and Time Period	Description of Outcome Studied	Algorithm	Validation/Adjudication Procedure, Operational Definition, and Validation Statistics
<sup>6</sup> Scanlon, et al. 2008	<p>The validation study included pediatric (age &lt;18) hospital discharges from 28 children's hospitals in the Health Care Utilization Project state inpatient databases.</p> <p>Only 7 patients in the validation study had a code for a transfusion reaction.</p>	Transfusion reaction	<p>ICD-9-CM codes:</p> <p>999.6: ABO incompatibility reaction</p> <p>999.7: Rh incompatibility reaction</p> <p>E8760: Mismatched blood in transfusion</p>	<p>Medical records were reviewed by clinicians at each of the 28 participating hospitals. They assessed whether the outcome was present on admission, and whether it was preventable, using a set of general and outcome-specific questions developed by experts.</p> <p>A transfusion reaction was present in 7/7 of the patients with a code from the algorithm. <b>PPV =100%</b></p> <p>The outcome was present on admission in 2/7 patients.</p> <p>4/5 of the reactions that occurred after admission were considered non-preventable, and one had uncertain preventability.</p> <p>The specific transfusion reaction codes identified in administrative data were not described. The discussion noted that all 7 reactions were reactions to correctly typed blood known to occur even when the best typing available was used, because of antibodies or antigens that could not be typed. Thus, <u>one could infer that none of the reactions was an ABO incompatibility reaction.</u></p> <p>It should also be noted that this was an extremely rare outcome, with a rate of 0.01 events per 1,000 hospitalizations.</p>

**Table 5. Non-Validated Algorithms**

Citation	Study Population and Time Period	Description of Outcome Studied	Algorithm
<sup>7</sup> Drösler. 2008	No study population. Technical report on cross-national comparisons of patient safety outcomes.	Transfusion reaction	<p><u>ICD-9-CM codes:</u></p> <p>999.6 (ABO incompatibility reaction)</p> <p>999.7 (Rh incompatibility reaction)</p> <p>E8760 (mismatched blood in transfusion)</p> <p><u>ICD-10-WHO codes:</u></p> <p>T80.3 (ABO incompatibility reaction)</p>

			T80.4 (Rh incompatibility reaction) Y65.0 (mismatched blood in transfusion)
<sup>8</sup> Morton, et al. 2010	All discharges in the Healthcare Cost and Utilization Project 2004 Nationwide Inpatient Sample database.	<p>Transfusion-related complications. Transfusion codes and non-infectious complication codes are reported here.</p> <p>Notably, the authors reported that <u>no discharges with an ICD-9-CM code for a non-infectious complication of transfusion were identified</u>, despite studying 2.23 million patients who received transfusions. Even though the outcomes are rare, their complete absence raises questions about the sensitivity of administrative data for identifying patients that experienced these outcomes.</p>	<p>Transfusion was identified by ICD-9-CM procedure codes 99.0X or V58.2.</p> <p>Non-infectious transfusion-related complications were identified by the following ICD-9-CM codes:</p> <p>518.7 (transfusion-related acute lung injury);</p> <p>999.4 (anaphylactic shock caused by serum);</p> <p>999.5 (other serum reaction);</p> <p>999.6 (ABO incompatibility reaction);</p> <p>999.7 (Rh incompatibility reaction).</p> <p>Other complications described as possibly related to transfusion were identified by the following ICD-9-CM codes:</p> <p>999.1 (air embolism);</p> <p>999.2 (other vascular complications);</p> <p>999.3 (other infection);</p> <p>999.8 (transfusion reaction not otherwise specified).</p>
<sup>9</sup> Slonim, et al. 2008	All consecutive pediatric discharges (age ≤ 18 years) from 2001 to 2003 included in the Pediatric Health Information System data set. This data comes from 35 independent academic pediatric hospitals in the United States that vary by geographic location, bed size, and mean daily census. Data include up to 15 diagnostic and procedure codes. The demographics of the population were not described, though it was reported that subjects with a wide range of racial and ethnic characteristics were included. Of 1,085,259 patients, 51,720 received 74,123 transfusions and 492 patients experienced 793 transfusion complications.	<p>Transfusion complications. ABO incompatibility was reported as a separate entity.</p> <p>It is notable that ABO incompatibility reactions were identified in recipients of only two types of blood products, red blood cells (ICD-9-CM procedure code 99.04) and platelets (ICD-9-CM procedure code 99.05). ABO incompatibility reactions were identified in 3/44,632 patients with ICD-9-CM procedure code 99.04 and 2/14,274 patients with ICD-9-CM procedure code 99.05.</p>	<p>999.4 (anaphylactic shock caused by serum);</p> <p>999.5 (other serum reaction);</p> <p>999.6 (ABO incompatibility reaction);</p> <p>999.7 (Rh incompatibility reaction);</p> <p>999.8 (transfusion reaction not otherwise specified).</p>

## I. CLINICIAN OR TOPIC-EXPERT CONSULTATION

It is difficult to assess the usefulness of the code for ABO incompatibility reactions given the lack of validation studies. Clinically, these reactions can be nearly immediate and severe, but are sometimes delayed (> 24 hours after transfusion) in the event that the titer of antigens or antibodies in a transfused product is low, the antibody titer in the patient is low, or perhaps in the case of immunosuppression. The diagnosis might be less obvious in these delayed cases, though confirming a blood mismatch or observing free hemoglobin in the serum due to a hemolytic reaction can lead to high specificity of the diagnosis.<sup>10</sup> One might suspect that the specificity of the ABO incompatibility code would be quite high since blood mismatches often become clearly apparent after the fact when the blood types of the patient and transfusion are checked. Nearly all such mismatches are due to human error of one kind or another (e.g., transfusing the wrong patient). Given the fact that the reactions are often quite severe and may require high-intensity treatments to prevent patient mortality, one might suspect that they would be coded. There can be diagnostic ambiguity, however, if the reaction is delayed, less severe, has symptoms that overlap with other health conditions, or it is not recognized that the patient was not properly matched to the blood. It is also possible that not all cases are recorded in administrative data, as evidenced by the lack of any such codes in the study by Morton, et al.<sup>8</sup> Regardless of the type of reaction, medical record review is needed to establish validity of the ABO incompatibility codes recorded in administrative databases.

ABO incompatibility reactions can also occur in organ transplant, or when a mother develops antibodies to the fetus blood type. No studies were identified to examine these codes. Historically, the ABO-barrier has rarely been crossed in transplantation. This is typically done only in emergency cases of liver transplant, and success rates are low. In most cases such transplants are failures, though some ABO incompatible heart transplants in small children have been successful.<sup>11</sup> Another exception is that there has been an increase in ABO incompatible renal transplantation, in which success is achieved by desensitization protocols involving plasma exchange.

## VI. SUMMARY AND CONCLUSIONS

### A. RECOMMENDATIONS FOR ALGORITHMS

We were unable to identify any studies that validated algorithms for identifying ABO incompatibility reactions using administrative data. The one study that included ABO incompatibility in an algorithm and performed medical record review of the transfusion reactions identified from administrative data did not actually appear to identify any cases of ABO incompatibility reaction.<sup>6</sup> Another study that examined 2.23 million hospital discharge abstractions in which a transfusion was administered found no codes for any of the non-infectious complications of transfusion they studied.<sup>8</sup> Even though ABO incompatibility reactions are rare, this raises strong concern about the sensitivity of hospital discharge codes for identifying ABO incompatibility reactions. In contrast, FDA staff noted that they have found cases in their ongoing investigation of Medicare administrative data (personal communication), and another study in pediatric hospital discharges identified several such reactions at a rate of about 1/10,000 transfusions.

ICD-9-CM code 999.6 identifies ABO incompatibility reactions and was used for all studies identified that examined this outcome. An ICD-10-WHO code for this HOI is also available. A number of other codes that are less specific to this HOI but used to study transfusion reactions are provided in Tables 4 and 5.



Transfusions themselves were identified using ICD-9-CM procedure codes 99.0x or V58.2. One study examining the validity of the code typically representing transfusion of allogeneic red blood cells (99.04) found a sensitivity of 83% and specificity of 100% for this code at a single center.<sup>12</sup> Another multi-center study using data from 1987 found a sensitivity of 21% if only three procedure codes were available (as in Medicare data) and 31% when up to 25 procedure codes were available.<sup>13</sup> Thus, it may be difficult to identify transfusions, despite good specificity of the code. Revenue codes are another potential source of transfusion data that might be used to augment procedure codes, though the validity of these codes is unknown.<sup>14</sup> It is also important to establish the validity of codes for other types of transfusions, such as platelets, since ABO incompatibility reactions can occur with blood products other than red blood cells.

It should also be noted that ABO incompatibility reactions can occur not only with transfused blood products, but when mismatched organs are transplanted or when a mother develops antibodies to the fetus blood type. No administrative database studies were identified that studied these types of ABO incompatibility reactions using any alternative algorithms.

New ICD-9-CM codes have also been adopted as of October 1<sup>st</sup>, 2010, which should increase the specificity of the information provided by code 999.6 and other transfusion reaction codes.<sup>15</sup> The new codes for ABO incompatibility reactions include 999.62 (ABO incompatibility with acute hemolytic transfusion reaction, i.e., < 24 hours post-transfusion) and 999.63 (ABO incompatibility with delayed hemolytic transfusion reaction, i.e., ≥ 24 hours post-transfusion). These codes should be utilized in future research.

## **B. SUGGESTIONS FOR FUTURE RESEARCH BASED ON EVIDENCE GAPS**

Since no studies were identified that validated an algorithm for identifying ABO incompatibility reactions, the possibilities for research on algorithm validity are wide open. One might speculate that the positive predictive value of this code would be high, since there is likely little diagnostic ambiguity when a hemolytic reaction occurs after transfusion and it is determined that the wrong blood type was given. An exception might occur in the case of a transcription error in entering codes. Further validation studies, utilizing large population-based administrative databases and medical record review, are needed to establish positive predictive value of the ABO incompatibility codes.

It is not clear that administrative data are sensitive in identifying ABO incompatibility reactions. Research to determine the sensitivity of coding algorithms will be difficult because of the rarity of the event. Surveying hospitals and blood banks to identify health plan members who have had ABO incompatibility reactions may be a feasible method for finding cases whose billing codes could then be examined. Identifying cases through CDC's Hemovigilance Network or the U.S. Biovigilance Network may offer a good starting point for the process of establishing sensitivity of the codes. Reviewing random charts of patients who received transfusions would be too inefficient, even if they were restricted to patients with an intensive care unit stay or some other criterion which might increase the prevalence of these reactions. Another route might be to identify fatal transfusion reactions that have been reported to FDA's Center for Biologics Evaluation and Research, since fatal reactions are reportable, and determine how these are coded in administrative data. It is likely, however, that the probabilities of submitting codes for fatal and non-fatal transfusion reactions may differ. The U.S. Biovigilance Network intends to capture both fatal and non-fatal transfusion reactions, so it may be more useful in this regard.



The performance of new ICD-9-CM codes for ABO incompatibility reactions might also be explored now that these more specific codes are available. However, they are still captured within the 999.6 code, so the importance of validating these more specific codes might depend on the specific purpose of the research utilizing these codes.

Finally, the sensitivity of codes for allogeneic red blood cell transplant is suspect, and the validity of codes for other types of blood product transfusion is unknown. Future research on the validity of these codes would help to augment research on ABO incompatibility reactions.

## VII. REFERENCES

1. West SL, Strom BL, Poole C. Validity of pharmacoepidemiologic drug and diagnosis data. In: Strom BL, ed. *Pharmacoepidemiology*. Chichester: John Wiley, 2005; 709-766.
2. FDA Designated Medical Events (DME). Listing of DMEs is adapted from “Safety Reporting Requirements for Human Drug and Biological Products; Proposed Rule”. Available at: <http://www.fda.gov/OHRMS/DOCKETS/98fr/03-5204.pdf>. Accessed 6/4/2010.
3. The Observational Medical Outcomes Partnership (OMOP). Health Outcomes of Interest. Available at: <http://omop.fnih.org/HOI>. Accessed 6/4/2010.
4. Jarrett N, Lux L, West S. Systematic evaluation of health outcome of interest definitions in observational studies and clinical definitions for the Observational Medical Outcomes Partnership: angioedema: report. Available at: <http://omop.fnih.org/sites/default/files/RTI%20Angioedema%20Final%20Report%20110509.pdf>. Accessed 6/7/2010.
5. Kachroo S, Jones N, Reynolds MW. Systematic literature review for evaluation of angioedema. Final report prepared for the Foundation of the National Institutes of Health via the Observational Medical Outcomes Partnership. Available at: <http://omop.fnih.org/sites/default/files/UBC-OMOP%20Systematic%20Lit%20Review%20Angioedema%20Final%20Report%209-11-2009.pdf>. Accessed 6/7/2010.
6. Scanlon MC, Harris JM, Levy F, Sedman A. Evaluation of the Agency for Healthcare Research and Quality pediatric quality indicators. *Pediatrics*. 2008; 121: e1723-31.
7. Drösler S. Facilitating Cross-National Comparisons of Indicators for Patient Safety at the Health-System Level in the OECD Countries. OECD Health Technical Papers No. 19. Available at: <http://www.oecd.org/dataoecd/24/48/40401929.pdf>. Accessed 8/30/2010.
8. Morton J, Anastassopoulos KP, Patel T, et al. Frequency and outcomes of blood products transfusion across procedures and clinical conditions warranting inpatient care: an analysis of the 2004 Healthcare Cost and Utilization Project Nationwide Inpatient Sample database. *Am J Med Qual*. 2010; 25(4): 289-96.
9. Slonim AD, Joseph JG, Turenne WM, Sharangpani A, Luban NLC. Blood transfusions in children: a multi-institutional analysis of practices and complications. *Transfusion*. 2008; 48: 73-80.
10. Bakdash S, Yazer MH. What every physician should know about transfusion reactions. *CMAJ*. 2007; 177(2): 141-7.
11. Rydberg L. ABO-incompatibility in solid organ transplantation. *Transfusion Medicine*. 2001; 11: 325-42.

12. Segal JB, Ness PM, Powe NR. Validating billing data for RBC transfusions: a brief report. *Transfusion*. 2001; 41: 530-33.
13. Romano PS, Mark DH. Bias in coding of hospital discharge data and its implications for quality assessment. *Medical Care*. 1994; 32(1): 81-90.
14. Anderson S, Menis M, O'Connell K, Burwen DR. Blood use by inpatient elderly population in the United States. *Transfusion*. 2007; 47: 582-92.
15. Menis M. Proposed changes to ICD-9-CM: transfusion associated adverse events. Presented at the ICD-9-CM Coordination and Maintenance Committee Meeting, September 17, 2009. Available at: [http://www.cdc.gov/nchs/ppt/icd9/att1\\_Menis\\_Sep09.pdf](http://www.cdc.gov/nchs/ppt/icd9/att1_Menis_Sep09.pdf). Accessed 9/1/2010.

## VIII. APPENDICES

### A. APPENDIX A: ABSTRACTS OF STUDIES INCLUDED IN EVIDENCE TABLES

Scanlon MC, Harris JM, Levy F, Sedman A. Evaluation of the Agency for Healthcare Research and Quality pediatric quality indicators. *Pediatrics*. 2008; 121: e1723-31.

**OBJECTIVES:** Pediatric quality indicators were developed in 2006 by the Agency for Healthcare Research and Quality to identify potentially preventable complications in hospitalized children. Our objectives for this study were to (1) apply these algorithms to an aggregate children's hospital's discharge abstract database, (2) establish rates for each of the pediatric quality indicator events in the children's hospitals, (3) use direct chart review to investigate the accuracy of the pediatric quality indicators, (4) calculate the number of complications that were already present on admission and, therefore, not attributable to the specific hospitalization, and (5) evaluate preventability and calculate positive predictive value for each of the indicators. In addition, we wanted to use the data to set priorities for ongoing clinical investigation.

**METHODS:** The Agency for Healthcare Research and Quality pediatric quality indicator algorithms were applied to 76 children's hospital's discharge abstract data (1794675 discharges) from 2003 to 2005. Rates were calculated for 11 of the pediatric quality indicators from all 3 years of discharge data: accidental puncture or laceration, decubitus ulcer, foreign body left in during a procedure, iatrogenic pneumothorax in neonates at risk, iatrogenic pneumothorax in nonneonates, postoperative hemorrhage or hematoma, postoperative respiratory failure, postoperative sepsis, postoperative wound dehiscence, selected infections caused by medical care, and transfusion reaction. Subsequently, clinicians from 28 children's hospitals reviewed 1703 charts in which complications had been identified. They answered questions as to correctness of secondary diagnoses that were associated with the indicator, whether a complication was already present on admission, and whether that complication was preventable, nonpreventable, or uncertain.

**RESULTS:** Across 3 years of data the rates of pediatric quality indicators ranged from a low of 0.01/1000 discharges for transfusion reaction to a high of 35/1000 for postoperative respiratory failure, with a median value of 1.85/1000 for the 11 pediatric quality indicators. Indicators were often already present on admission and ranged from 43% for infection caused by medical care to 0% for iatrogenic pneumothorax in neonates, with a median value of 16.9%. Positive predictive value for the subset of pediatric quality indicators occurring after admission was highest for decubitus ulcer (51%) and infection caused by medical care (40%). Because of the very large numbers of cases identified and its low preventability, the indicator postoperative respiratory failure is particularly problematic. The initial definition includes all children on ventilators postoperatively for >4 days with few exclusions. Being on a ventilator for 4 days would be a normal occurrence for many children with extensive surgery; therefore, the majority of the time does not indicate a complication and makes the indicator inappropriate.

**CONCLUSIONS:** A subset of pediatric quality indicators derived from administrative data are reasonable screening tools to help hospitals prioritize chart review and subsequent improvement projects. However, in their present form, true preventability of these complications is relatively low; therefore, the indicators are not useful for public hospital comparison. Identifying which complications are present on admission versus those that occur within the hospitalization will be essential, along with adequate risk adjustment, for any valid comparison between institutions. Infection caused by medical care and decubitus ulcers are clinically important indicators once the present-on-admission status is determined. These complications cause significant morbidity in hospitalized children, and research has shown a high level of preventability. The pediatric quality

indicator software can help children's hospitals objectively review their cases and target improvement activities appropriately. The postoperative-respiratory-failure indicator does not represent a complication in the majority of cases and, therefore, should not be included for hospital screening or public comparison. Chart review should become part of the development process for quality indicators to avoid inappropriate conclusions that misdirect quality-improvement resources.

Drösler S. Facilitating Cross-National Comparisons of Indicators for Patient Safety at the Health-System Level in the OECD Countries. OECD Health Technical Papers No. 19. Available at: <http://www.oecd.org/dataoecd/24/48/40401929.pdf>. Accessed 8/30/2010.

Technical report. No abstract.

Morton J, Anastassopoulos KP, Patel T, et al. Frequency and outcomes of blood products transfusion across procedures and clinical conditions warranting inpatient care: an analysis of the 2004 Healthcare Cost and Utilization Project Nationwide Inpatient Sample database. *Am J Med Qual.* 2010; 25(4): 289-96.

The objective of this retrospective cohort study was to assess frequency and outcomes associated with blood products transfusion. Data from the 2004 Nationwide Inpatient Sample database were used. Length of stay (LOS), postoperative infections, noninfectious transfusion-related complications, in-hospital mortality, and total charges were evaluated for transfused and nontransfused cohorts. Of the estimated 38.66 million discharges in the United States in 2004, 5.8% (2.33 million) were associated with blood products transfusion. Average LOS was 2.5 days longer, and charges were \$17 194 higher for the transfused cohort ( $P < .0001$ ). Odds of death were 1.7 times higher ( $P < .0001$ ) and odds of infection 1.9 times higher ( $P < .0001$ ) for the transfused cohort. Increased provider awareness and recognition of the frequency and potential negative outcomes of blood products transfusion may encourage the adoption of novel approaches to minimize intraoperative and early postoperative bleeding, reduce transfusion requirements, and most important, improve patient-level postoperative outcomes and health-related quality of life.

Slonim AD, Joseph JG, Turenne WM, Sharangpani A, Luban NLC. Blood transfusions in children: a multi-institutional analysis of practices and complications. *Transfusion.* 2008; 48: 73-80.

**BACKGROUND:** Blood product transfusions are a valuable health-care resource. Guidelines for transfusion exist, but variability in their application, particularly in children, remains. The risk factors that threaten transfusion safety are well established, but because their occurrence in children is rare, single-institution studies have limited utility in determining the rates of occurrence. An epidemiologic approach that investigates blood transfusions in hospitalized children may help improve our understanding of transfused blood products in this vulnerable population.

**STUDY DESIGN AND METHODS:** This was a nonconcurrent cohort study of pediatric patients not more than 18 years of age hospitalized from 2001 to 2003 at 35 academic children's hospitals that are members of the Pediatric Health Information System (PHIS).

**RESULTS:** A total of 51,720 (4.8%) pediatric patients received blood product transfusions during the study period. Red blood cells ( $n = 44,632$ ) and platelets ( $n = 14,274$ ) were the two most frequently transfused products. The rate of transfusions was highest among children with neutropenia, agranulocytosis, and sickle cell crisis. Asian and American Indian patients had important differences in the rate of blood transfusions and their complications. Resource use in terms of length of stay and costs were higher in patients who received transfusion. Of those patients who received transfusions, 492 (0.95%) experienced a complication from the administered blood product. This accounted for a rate of complications of 10.7 per 1,000 units transfused.

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CONCLUSIONS: The administration of blood products to children is a common practice in academic children's hospitals. Complications associated with these transfused products are rare.

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

### **1. Studies Excluded Because They Did Not Study the HOI**

Arndt PA. 2008 Immunohematology Reference Laboratory Conference: Summary of presentations. *Immunohematology*. 2008; 24: 61-72.

### **2. Studies Excluded Because They Did Not Use an Administrative Database**

Callum JL, Merkley LL, Coovadia AS, Lima AP, Kaplan HS. Experience with the medical event reporting system for transfusion medicine (MERS-TM) at three hospitals. *Transfus Apher Sci*. 2004; 31: 133-143.

Domen RE, Hoeltge GA. Allergic transfusion reactions: An evaluation of 273 consecutive reactions. *Arch Pathol Lab Med*. 2003; 127: 316-320.

Figueroa PI, Ziman A, Wheeler C, Gornbein J, Monson M, Calhoun L. Nearly two decades using the check-type to prevent ABO incompatible transfusions: One institution's experience. *Am J Clin Pathol*. 2006; 126: 422-426.

Lee KW, Cameron AM, Maley WR, Segev DL, Montgomery RA. Factors affecting graft survival after adult/child split-liver transplantation: Analysis of the UNOS/OPTN data base. *Am J Transplant*. 2008; 8: 1186-1196.

Maclvor D, Triulzi DJ, Yazer MH. Enhanced detection of blood bank sample collection errors with a centralized patient database. *Transfusion*. 2009; 49: 40-43.

Mayne S, Parker JH, Harden TA, Dodds SD, Beale JA. Rate of RhD sensitisation before and after implementation of a community based antenatal prophylaxis programme. *BMJ*. 1997; 315: 1588.

Pagliari P, Turdo R, Capuzzo E. Patients' positive identification systems. *Blood Transfus*. 2009; 7: 313-318.

Robillard P, Nawej KI, Jochem K. The Quebec hemovigilance system: Description and results from the first two years. *Transfus Apher Sci*. 2004; 31: 111-122.

Sanchez-Urdazpal L, Sterioff S, Janes C, Schwerman L, Rosen C, Krom RA. Increased bile duct complications in ABO incompatible liver transplant recipients. *Transplant Proc*. 1991; 23: 1440-1441.

Schwartz J, Stegall MD, Kremers WK, Gloor J. Complications, resource utilization, and cost of ABO-incompatible living donor kidney transplantation. *Transplantation*. 2006; 82: 155-163.

Vamvakas EC, Pineda AA, Reisner R, Santrach PJ, Moore SB. The differentiation of delayed hemolytic and delayed serologic transfusion reactions: Incidence and predictors of hemolysis. *Transfusion*. 1995; 35: 26-32.

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

Type of Code	Code	Description
<i>Codes for identifying transfusion reactions</i>		
ICD-9-CM	518.7	Transfusion-related acute lung injury
ICD-9-CM	999.1	Air embolism
ICD-9-CM	999.2	Other vascular complications
ICD-9-CM	999.3	Other infection
ICD-9-CM	999.4	Anaphylactic shock caused by serum
ICD-9-CM	999.5	Other serum reaction
<b>ICD-9-CM</b>	<b>999.6</b>	<b>ABO incompatibility reaction</b>
ICD-9-CM	999.7	Rh incompatibility reaction
ICD-9-CM	999.8	Transfusion reaction not otherwise specified
<b>ICD-9-CM</b>	<b>E8760</b>	<b>Mismatched blood in transfusion</b>
<b>ICD-10</b>	<b>T80.3</b>	<b>ABO incompatibility reaction</b>
ICD-10	T80.4	Rh incompatibility reaction
<b>ICD-10</b>	<b>Y65.0</b>	<b>Mismatched blood in transfusion</b>
<i>Codes for identifying transfusions</i>		
ICD-9-CM procedure	99.0	Transfusion of blood and blood components
ICD-9-CM procedure	99.00	Perioperative autologous transfusion of whole blood or blood components
ICD-9-CM procedure	99.01	Exchange transfusion
ICD-9-CM procedure	99.02	Transfusion of previously collected autologous blood
ICD-9-CM procedure	99.03	Other transfusion of whole blood
ICD-9-CM procedure	99.04	Transfusion of packed cells
ICD-9-CM procedure	99.05	Transfusion of platelets
ICD-9-CM procedure	99.06	Transfusion of coagulation factors
ICD-9-CM procedure	99.07	Transfusion of other serum
ICD-9-CM procedure	99.08	Transfusion of blood expander
ICD-9-CM procedure	99.09	Transfusion of other substance (such as a blood surrogate or granulocytes; excludes transfusion of bone marrow—ICD-9-CM procedure code 41.0)
ICD-9-CM	V58.2	Blood transfusion without reported diagnosis