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

TRANSFUSION-ASSOCIATED SEPSIS OR SEPTICEMIA REPORT

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

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

Transfusion-Associated Sepsis or Septicemia 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 transfusion-related sepsis or septicemia algorithm review.

B. SUMMARY OF FINDINGS

No studies were found that validated transfusion-associated sepsis specifically. Four studies were identified that validated sepsis definitions, and two were identified that examined the validity of codes for allogeneic red blood cell transfusions.

Because of the variability in algorithms and study populations, it is difficult to make a recommendation for one algorithm over another to identify sepsis. ICD-9-CM codes 038.x appear to have acceptable performance characteristics for identifying sepsis for most applications, with PPVs of 80% or greater found in non-Veteran's Administration (VA) settings. There is no clear evidence to indicate whether the additional codes utilized would improve or worsen the balance of performance characteristics. The study by Romano, et al.[10] in veterans showed slightly better performance characteristics with the addition of extra codes, though no significant difference in performance was described.

The code for transfusion was also found to have relatively good performance characteristics in a study conducted at one hospital. The specificity of ICD-9-CM procedure code 99.04 was excellent (100%), and sensitivity good (83%).[12] The performance of other transfusion codes, including that for autologous blood donation, was not studied. Another multi-center study found that ICD-9-CM code 99.04 was highly specific (100%) but had sensitivity of only 21%-31% depending on the number of procedure fields examined.[13]

No study described an algorithm specifically used to identify transfusion-associated sepsis or septicemia. Such an algorithm and validation study might consider the temporal relationship between transfusion and sepsis, as well as the probability that sepsis might have developed due to other exposures such as surgery or trauma, both of which are common in patients who receive blood transfusions.

In addition to the currently available codes, the FDA's Center for Biologics and Evaluation Research (CBER) has proposed new ICD-9-CM codes for identifying infections determined to be transmitted by blood transfusions.[16] Though it is uncertain whether adoption will take place, it will be important to consider these codes if they are adopted. Currently, blood product associated infections might receive an ICD-9-CM code 999.3 (complications of medical care, not elsewhere classified, other infection). The proposed code 999.32 would add more specificity to the definition (transfusion-transmitted infection). This code would be used in combination with an additional code to describe the type of infection.

C. RECOMMENDATION FOR ALGORITHMS AND SUGGESTIONS FOR FUTURE RESEARCH

Future research on sepsis code validation might focus on the performance of codes other than ICD-9 code 038.x, such that an optimal combination of codes could be determined. Overall, the number of studies on the validity of sepsis algorithms is relatively small with some inconsistent results. Further research on sepsis algorithms could be useful.

Transfusion codes other than ICD-9-CM procedure code 99.04 also have unknown performance characteristics, and even the performance of this code varied across studies. Given the relatively higher historical risk of bacterial contamination of platelets due in part to room temperature storage, it would be helpful to examine the performance characteristics of the code for platelet transfusion in order to study infections related to this exposure. It would also be helpful to examine concordance of transfusion procedure codes and "blood pints furnished" revenue codes, and the relationship of each of these codes to actual transfusion, to determine whether algorithms should be expanded beyond procedure codes when revenue codes are available. If a specific algorithm is designed to identify sepsis that is caused by a transfusion, special attention will need to be paid to the most likely source of the infection insofar as it can be determined. Patients who receive transfusions often have other risk factors for sepsis that would need to be considered. It may be useful to study specific infectious organisms or other specific criteria which might implicate the transfusion in the development of sepsis. It might also be useful to explore the addition of ICD-9-CM code 999.3, or the proposed code 999.32, to the algorithm to identify transfusion-related sepsis.

The newly formed U.S. Biovigilance Network will attempt to capture adverse events related to transfusion. This network may provide opportunities to examine the sensitivity of algorithms to identify transfusion-associated sepsis.

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 that were identified in a textbook chapter reviewing the validity of drug and diagnosis data used in pharmacoepidemiologic studies,[1] 2) a list of designated medical events developed from a proposed FDA rule on the safety reporting requirements for human drug and

biological products,[2] 3) the Observational Medical Outcomes Partnership (OMOP)'s[i] commissioned reports on algorithms used to identify the health outcome using administrative data.[3]

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.

Transfusion-related sepsis was one of the 20 HOIs selected for review. This report describes the review process and findings for the transfusion-related sepsis 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)[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 two sets of files, one containing the abstracts for review and the other for documenting abstract review results.

The search strategy and results for transfusion-related sepsis or septicemia are detailed in the Results section. The PubMed search was conducted on June 23, 2010, and the IDIS search on May 10, 2010. Because of the limited number of relevant articles identified, a number of Google Scholar searches were also explored and results scanned by one investigator to find additional relevant articles. The most useful search strategy is described in the results section.

[i] For more information, visit 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 was consulted to make the final decision.

2. Full-Text Exclusion Criteria

1. Poorly described HOI identification algorithm that would be difficult to operationalize.

2. No validation of outcome definition or reporting of validity statistics.

D. MINI-SENTINEL INVESTIGATOR SURVEY

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

E. EVIDENCE TABLE CREATION

A single investigator abstracted each study for the final evidence table. The data included in the table were confirmed by a second investigator for accuracy.

F. CLINICIAN OR TOPIC-EXPERT CONSULTATION

A clinician or topic-expert was consulted to review the results of the evidence table and discuss how they compare 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 and IDIS searches. The PubMed search identified 52 citations and the IDIS searches identified none.

Table 1. PubMed Search Strategy and Results (52): Performed on 06/23/10

Search	Query	Results
#1	("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 "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	373522
#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 2011/01/01	2603891
#3	Search #1 NOT #2 Limits: Humans, English, Publication Date from 1990/01/01 to 2011/01/01	253019
#4	("sepsis"[Mesh] OR "sepsis"[All Fields] OR "septicemia"[All Fields]) AND ("transfusion"[All Fields] OR "Blood Transfusion"[Mesh]) Limits: Humans, English, Publication Date from 1990/01/01 to 2011/01/01	1599
#5	Search #3 AND #4 Limits: Humans, English, Publication Date from 1990/01/01 to 2011/01/01	52

Table 2. IDIS Search Strategy and Results (0): Performed on 05/10/10

ADVANCED SEARCH

Disease:

038.* AND "TRANSFUSION BLOOD/COMPONENT 99.0"

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 **Abstract:**

((("sepsis" OR "septicemia") AND "transfusion") 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")

Records = 0

B. ABSTRACT REVIEWS

Of the 52 abstracts reviewed, 17 were selected for full-text review; 27 were excluded because they did not study the HOI, 7 were excluded because they were not administrative database studies, and 1 was 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 0.40.

C. FULL-TEXT REVIEWS

Of the 17 full-text articles reviewed, 1 was included in the final evidence tables (initially excluded for not studying the HOI, but later included since it validated sepsis with no transfusion requirement); 5 were excluded because they did not study the HOI; and 11 were excluded because they did not use an administrative database. Reviewers identified 1 citation for review from full-text article references, which was included in the final report since it validated transfusion codes though not sepsis codes.

Cohen's kappa for agreement between reviewers on inclusion vs. exclusion of full-text articles reviewed was 0. Kappa was 0 because one reviewer excluded all 17 full-text articles reviewed. The other reviewer excluded 16 of the 17 articles. The one article on which they disagreed used a National Surgical Quality Improvement Program (NSQIP) database, which one reviewer initially thought was an administrative database. NSQIP data are collected and entered by research/quality improvement personnel, so this article was ultimately excluded after discussion between reviewers because it did not use an administrative database.

Because of the limited number of studies identified, Google Scholar searches were conducted to identify validation studies of sepsis or transfusion. Because of the large number of results obtained by certain searches, only the top results were reviewed for some searches. The searches included: 1. sensitivity sepsis ICD, 2. sensitivity sepsis "international classification of disease", 3. "predictive value" sepsis ICD, and 4. "predictive value" sepsis "international classification of disease". Various searches for transfusion validation studies were also conducted, and the above searches were combined with the term "transfusion" to find studies of sepsis related to transfusion. After many reviews of studies on infection related to transfusion, it was believed that only the two validation studies previously identified were available. However, three more validation studies of sepsis were identified through these additional searches.[6,7,9,10] One of the studies was identified serendipitously when searching for another article by that author.[10] While this process was less systematic compared to the original search result review process, and may have missed some validation studies of sepsis or transfusion, it seemed to be the most efficient method to find other relevant papers that might have been missed in the original search strategy. Given the number of articles reviewed that continually referenced the same validation studies, particularly the studies reported by Eaton, et al.[6] and Martin, et al.,[7] it seemed likely that the most relevant studies were identified.

D. MINI-SENTINEL INVESTIGATOR SURVEY

Mini-Sentinel investigators provided no validation studies for this HOI.

E. EVIDENCE INCLUDED IN TABLE

Of the 6 studies included in the tables, 1 was identified from the initial search strategy,[11] 1 was identified through references of articles that underwent full-text review,[12] and 3 were identified through the Google Scholar search process or serendipitously.[6,7,9,10] Another study was identified through references in a manuscript provided by FDA topic experts.[13]

F. SUMMARY AND DISCUSSION OF ALGORITHMS AND VALIDATION

Four studies were reviewed that determined the performance characteristics of codes for sepsis, and two were identified that did so for allogeneic red blood cell transfusion.

1. Validation Studies for Sepsis

The performance characteristics for sepsis varied by study. The ICD-9-CM codes 038.x were consistently used to identify sepsis, but a number of additional codes were included that varied by study.

Eaton, et al.[6] and Martin, et al.[7] reported on the same validation study at Emory University Hospital of the 038.x codes on discharge records for identifying sepsis. Eaton, et al.[6] reported it as an abstract, and

Martin, et al.[7] reported it as a part of a publication that included a separate study with no validation component. Medical record review was used to validate potential cases identified by 038.x codes, using a slight modification of a consensus conference definition as the reference standard. In 72 cases identified by the code during a six month period, the positive predictive value (PPV) was 89% for sepsis as defined by suspected or confirmed infection plus a systemic inflammatory response syndrome (SIRS). The PPV of the code in identifying SIRS was 99%. The PPV was 63% for identifying severe sepsis, defined as sepsis plus organ dysfunction. The negative predictive value (NPV) for codes 038.x among controls admitted immediately before or after the patient with a sepsis code was 80.0%. Finally, when what the authors described as the usual clinical definition of sepsis (SIRS plus organ dysfunction) was used, the PPV of the 038.x code was 97.7%. This difference would seem to relate largely to whether suspected infection was mentioned in the medical record, since the definitions are otherwise the same. Overall, the PPV of the 038.x code would be considered quite good, and NPV acceptable for most applications. The question becomes which patients with sepsis are less likely to receive a 038.x code, given that 20% is a substantial minority of the patients without a sepsis code who were septic. This study was limited in that it represents only a single institution's coding practices.

It is also notable that an epidemiologic study using the National Hospital Discharge Survey reported concurrently by Martin, et al.[7] included codes for septicemic (020.0), bacteremia (790.7), disseminated fungal infection (117.9), disseminated candida infection (112.5), and disseminated fungal endocarditis (112.81). This study also provided a set of codes utilized to ascertain acute organ dysfunction. No validation was conducted for this algorithm. Lastly, it should be noted that a number of the code definitions listed in the study, including those listed above for sepsis, did not match the ICD-9-CM codes found in an online code reference.[8] The details of the code mismatches are described in Appendix C.

Ollendorf, et al.[9] studied the sensitivity of a set of codes for identifying a group of 122 patients with severe sepsis presumed of infectious origin at 10 institutions. They were all participating in a clinical trial of a treatment for severe sepsis. In addition to various 038.x codes listed, this study utilized codes for anthrax septicemia (022.3), bacteremia not otherwise specified (NOS) (790.7), herpetic septicemia (054.5), meningococcemia (036.2), salmonella septicemia (003.1), and septicemic plague (020.2). The sensitivity of this set of codes was 75.4%. Of the 30 bills without a code for sepsis, 4 had major infection codes only, 9 had organ failure codes only, and 2 had no codes indicating sepsis. This study was unable to calculate PPV because it selected patients diagnosed clinically instead of selecting them based on billing codes. The multicenter nature of the study may improve generalizability, but it is unclear whether the fact that these patients were in a clinical trial for severe sepsis may have changed the way their cases were documented and thus the selection of codes.

The two remaining studies of sepsis looked at surgical populations. Romano, et al.[10] studied veterans by comparing administrative data to National Surgical Quality Improvement Program (NSQIP) data, which requires a chart diagnosis of sepsis to consider it present. This identified 75 patients with sepsis. The 038.x codes were first studied, and found to have a sensitivity of 32% and PPV of 44%. An alternative algorithm which added six codes (998.0, 998.1, 785.59, 785.50, 785.5, 785.52) had a sensitivity of 37% and PPV of 45%. The specificity was calculated as >99.1% considering all NSQIP patients as the source population. The alternative algorithm seems to be preferable in this patient population because of the higher sensitivity and PPV. Overall the performance of these codes was less impressive than in the previous studies. This may be due to the post-surgical population, as they might have had other codes which took precedence. This seems unlikely, however, since sepsis is a severe condition. Alternatively,

there may be different incentives to code sepsis properly in Department of Veterans Affairs (VA) facilities given their payment structure.

Scanlon, et al.[11] studied a set of codes among surgical patients aged 0-17 discharged from 76 pediatric hospitals, excluding neonates. Chart review was conducted for 279 patients with an ICD-9-CM code for sepsis. This study focused on new onset sepsis after surgery, as it was intended to assess pediatric hospital quality indicators. In addition to the 038.x ICD-9-CM codes, this study utilized codes for septic shock (785.52), shock without mention of trauma, other (785.59), postoperative shock (998.0), SIRS due to an infectious process without organ dysfunction (995.91), and SIRS due to an infectious process with organ dysfunction (995.92). The PPV was 79.93%.

Overall, the PPV of the various sets of codes was relatively high in every study except VA post-surgical patients.[6,7,9-11] As stated, this difference may have something to do with the patient population or the payment structure of the VA. Two studies took place after the year 2000 and thus reflect relatively recent coding practices,[10,11] while the specific dates of two other studies were unclear.[6,7,9]

2. Validation Studies for Transfusion

Segal, et al.[12] studied 358 patients with an ICD-9 procedure billing code 99.04 for transfusion and 358 controls without any billing code for a blood product from a single large academic medical center. The hospital's blood bank data was used to determine transfusion status, and electronic medical records were reviewed for patients without blood bank records. The sensitivity of the billing codes was 83%. Patients without commercial insurance were less likely to have a billing code for transfusion, perhaps reflecting an effect of reimbursement differences on the likelihood of receiving a code. A sensitivity analysis was conducted in which 9 patients who received a procedure code 99.04 but not a revenue code were considered either true negatives or false negatives. When they were considered true negatives, the specificity of code 99.04 was 100%. When they were considered false negatives, the specificity was 97.5%. At least at this single academic medical center, code 99.04 appears to be relatively sensitive and highly specific. Commercial insurance may improve the sensitivity of billing codes.

In another study of 2,579 California hospital discharge abstracts from 1988, Romano and Mark[13] found that the sensitivity of ICD-9 procedure code 99.04 was only 21% when 3 procedure codes were allowed (as were available in Medicare claims), and 31% when 25 procedure codes were allowed. The specificity was 100%. This study reduces the confidence that procedure code 99.04 is sensitive for capturing transfusions, but confirms a high specificity. The study included 30 hospitals randomly selected across type of hospital (e.g., e.g., university teaching, non-teaching, small rural, etc.). Though the results are somewhat dated, they might be considered more generalizable than the single-center study by Segal, et al.

G. SUMMARY OF EXCLUDED POPULATIONS AND DIAGNOSES

As described, two studies of sepsis looked at more general samples of patients with sepsis or severe sepsis,[6,7,9] while two examined post-surgical populations, one in pediatric patients[11] and one in veterans.[10] The performance was relatively good in most studies, with the exception of the study in veterans.[10] As previously stated, the reimbursement policies of the VA may have contributed to differences in coding practices and a lower sensitivity in this study.

While no specific exclusion criteria were described for the single center study validating transfusion codes, the generalizability may be limited since only one hospital's data were examined.[11] The multi-center study selected patients with the most common diagnosis related groups, but it does not seem likely that this would impact performance characteristics.[13] The large difference in sensitivity in these two studies may relate to unique coding practices at the single center, or changes in coding practice over time since the multi-center study is somewhat dated.

H. EVIDENCE TABLES

Table 3. Positive Predictive Values for Sepsis by Algorithm

Citation	Study Population and Time Period	Description of Outcome Studied	Algorithm	Validation/Adjudication Procedure, Operational Definition, and Validation Statistics
[6]Eaton, et al. 2002 [7]Martin, et al. 2003	Patients admitted to a large university hospital during a six-month period with a 038.x code in their discharge records were cases for the validation sample, and controls were those without a 038.x code in their discharge records matched by being admitted immediately before or after the case. Of the 72 patients with an ICD-9 code of 038.x, 51% were male, 57% were medical patients, 43% surgical patients, and 75% were in the ICU. The mean age was 58 (S.D. 14) years. Hospital mortality was 49%. Martin, et al reported on a separate study that included no validation, but used an expanded algorithm that is described here. This study used the National Hospital Discharge Survey, a random sample (stratified by region) of about 500 non-federal acute care hospitals in the United States.	Sepsis	Sepsis was identified by an ICD-9-CM code of 038.x (septicemia) *While 038.x, was the focus of the validation study, the following codes were also mentioned as used to identify sepsis in an epidemiologic portion of the Martin, et al study:* *This study described a number of codes differently than they were described on the look-up tables on www.ICD9data.com. These codes are marked with a* , and should not be used without examining details. Further details on the definitions can be found in Appendix C. This will not affect the performance characteristics as only 038.x was assessed in that regard.* Septicemic: 020.0* Bacteremia: 790.7 Disseminated fungal infection: 117.9* Disseminated candida infection: 112.5 Disseminated fungal endocarditis: 112.81* *Acute organ dysfunction associated with sepsis was identified by the following set of ICD-9-CM or CPT codes:* *Respiratory:*	Sepsis was confirmed in chart review by a consensus conference definition, though the literature cited used a slightly modified version of these criteria, which are detailed below. A confirmation of sepsis required the presence of known or suspected infection plus three or more signs of systemic inflammation. *Severe* sepsis also required at least one dysfunctional organ system, as described below.[14,15] A known or suspected infection was determined by one or more of the following: white cells in a normally sterile body fluid; perforated viscus; radiographic evidence of pneumonia in association with the production of purulent sputum; a syndrome associated with a high risk of infection. The determination of systemic inflammatory response syndrome required three of the following four criteria: a core temperature of $\geq$ 38 °C or $\leq$ 36 °C; a heart rate of $\geq$ 90 beats per minute, except in patients with a medical condition known to increase the heart rate or those receiving treatment that would prevent tachycardia; a respiratory rate of $\geq$ 20 breaths per minute or a $PaCO_2$ of $\leq$ 32 mm Hg or the use of mechanical ventilation for an acute respiratory process; a white-cell count of $\geq$ 12,000 / mm^3 or a differential count showing > 10 percent immature neutrophils. To be classified as having dysfunctional organs or systems, "patients had to meet at least one of the following five criteria: for cardiovascular system dysfunction, the arterial systolic blood pressure had to be $\leq$ 90 mm Hg or the mean arterial pressure $\leq$ 70 mm Hg for at

			Acute respiratory failure: 518.81 Acute respiratory distress syndrome: 518.82 Acute respiratory distress syndrome after shock or trauma: 518.5* (listed incorrectly as 518.85 in manuscript) Respiratory insufficiency: 786.09 Respiratory arrest: 799.1 Ventilator management: 96.7 *Cardiovascular:* Shock: 785.5 Shock, cardiogenic: 785.51 Shock, circulatory or septic: 785.59 Hypotension, postural: 458.0 Hypotension, specified type, not elsewhere classified: 458.8 Hypotension, arterial, constitutional: 458.9* Hypotension, transient: 796.3* *Renal:* Acute renal failure: 584 Acute glomerulonephritis: 580 Renal shutdown, unspecified: 585* Hemodialysis: 39.95 *Hepatic:* Acute hepatic failure or necrosis: 570* Hepatic encephalopathy: 572.2 Hepatitis, septic or unspecified: 573.3*	least 1 hour despite adequate fluid resuscitation, adequate intravascular volume status or the use of vasopressors in an attempt to maintain a systolic blood pressure of ≥ 90 mm Hg or a mean arterial pressure of ≥ 70 mm Hg; for kidney dysfunction, urine output had to be < 0.5 ml/kg of body weight/hr for 1 hour, despite adequate fluid resuscitation; for respiratory-system dysfunction, the ratio of PaO2 to FiO2 had to be ≤ 250 in the presence of other dysfunctional organs or systems or ≤ 200 if the lung was the only dysfunctional organ; for hematologic dysfunction, the platelet count had to be <80,000/mm^3 or to have decreased by 50 percent in the 3 days preceding enrollment; in the case of unexplained metabolic acidosis, the pH had to be ≤ 7.30 or the base deficit had to be ≥ 5.0 mmol/liter in association with a plasma lactate level that was >1.5 times the upper limit of the normal value for the reporting laboratory." Sepsis was confirmed in 64/72 patients with a discharge diagnosis code of 038.x, giving a **PPV** of **88.9%** (95% CI 81.6-96.2%). The negative predictive value (**NPV**) of code 038.x was **80.0%** (95% CI 67.8-93.2%). The **PPV** of a discharge diagnosis code 038.x in identifying *severe* sepsis only (sepsis + organ dysfunction) was **63%** (95% CI 52-74%). Another validation analysis defined sepsis as a systemic inflammatory response syndrome and acute organ dysfunction (the accepted clinical definition), without the requirement for infection. This increased the **PPV** of the 038.x code to **97.7%** (95% CI 93.9-100.0%). The **NPV** remained **80.0%**. In another analysis, the **PPV** for codes 038.x for identifying patients with a systemic inflammatory response syndrome was **99%** (95% CI 96-100%) The authors estimated the specificity and negative predictive value of the 038.x diagnosis code based on a

			Hematologic: Disseminated intravascular coagulation: 286.2 Purpura fulminans: 286.6 Coagulopathy: 286.9 Thrombocytopenia, primary, secondary, or unspecified: 287.3-287.5 *Metabolic:* Acidosis, metabolic or lactic: 276.2 *Neurologic:* Transient organic psychosis: 293* Anoxic brain injury: 348.1 Encephalopathy, acute: 348.3 Coma: 780.01 Altered consciousness, unspecified: 780.09 Electro-encephalography: 89.14	conservative estimate of 2% for the prevalence of sepsis in hospitalized patients, and apparently based on the calculated PPV of 88.9%. This involved calculations that used the National Hospital Discharge Survey from 1979-2000. The estimated specificity was calculated as 98.8%, and NPV 98.6%. It is unclear from the manuscript how to resolve this with the 80% NPV that was found in the validation study, particularly since they described few exclusion criteria for the hospitalized control group other than not being diagnosed with sepsis on the discharge abstract. It would seem that the 80.0% NPV is more trustworthy given that it is derived from an actual validation study instead of an estimate of how many hospitalized patients 'should' have sepsis. It is possible that the difference is because they utilized a broader set of ICD-9-CM codes in the overall study than in the validation study (including 020.0, 790.7, 117.9, 112.5, and 112.81 in addition to 038.x).
[9]Ollendorf, et al. 2002	The study sample included 122 hospitalized patients from 10 medical centers participating in a clinical trial for severe sepsis of presumed infectious origin. The demographics of the sample and time frame of the hospitalizations were not reported.	Severe sepsis was present in all patients. Diagnostic codes were reviewed to determine their sensitivity in identifying these patients.	*The following ICD-9 CM codes on hospital bills (UB-92 forms) were considered sepsis:* Anaerobic septicemia: 038.3 Anthrax septicemia: 022.3 Bacteremia not otherwise specified (NOS): 790.7 *E. Coli* septicemia: 038.42 Gram-negative septicemia not elsewhere classified (NEC): 038.49 Gram-negative septicemia NOS: 038.40 *H. Influenzae*	"Severe sepsis was defined by the simultaneous presence of five clinical criteria, as follows: 1. isolated organism(s) from one or more positive cultures within 72 hours of study entry or clinical diagnosis of an organ abscess or suppurative inflammation; 2. hyperthermia (core temperature ≥38.0°C) or hypothermia (≤35.6°C); 3. tachycardia (≥90 beats/min) in the absence of beta blockade or cardiac pacemaker; 4. tachypnea (≥20 breaths/min) or mechanical ventilation; 5. hypotension (systolic blood pressure ≤90 mmHg, decrease in systolic blood pressure of ≥40 mmHg, or use of vasopressors), evidence of systemic toxicity, or poor end organ perfusion."

			septicemia: 038.41 Herpetic septicemia: 054.5 Meningococcemia: 036.2 Pneumococcal septicemia: 038.2 Pseudomonas septicemia: 038.43 Salmonella septicemia: 003.1 Septicemia NEC: 038.8 Septicemia NOS: 038.9 Septicemic plague: 020.2 Serratia septicemia: 038.44 Staphylococcal septicemia: 038.1 Streptococcal septicemia: 038.0	92 of 122 hospital bills for these septic patients included a code for sepsis, for a **sensitivity of 75.4%** 15 of the remaining 30 bills included codes for both major systemic infection and organ failure. Of the 15 without codes for systemic infection and organ failure, 4 had major infection codes only, 9 had organ failure codes only, and 2 had no codes that might indicate the presence of sepsis.
[10]Romano, et al. 2008	The study sample included 55,752 hospitalizations for 59,838 surgeries in 110 Veterans Affairs (VA) hospitals in fiscal year 2001. All subjects were veterans and all hospitalizations were required to be linked with VA National Surgical Quality Improvement Program (NSQIP) data. Males comprised 95.4% of the sample, the mean age was 63 years, and 47% of the sample was over age 65. The final sample included 12,011 patients who qualified to be assessed for the	The outcome of interest to this report was postoperative sepsis. Other postoperative outcomes were also studied, but are not reported here.	The original patient safety indicator algorithm for sepsis used ICD-9-CM codes of 038.x in any discharge diagnosis field to identify sepsis. An alternative algorithm tested in this study used the following ICD-9-CM codes in any secondary discharge diagnosis to identify sepsis: 038.xx, 998.0, 998.1, 785.59, 785.50, 785.5, 785.52.	For systemic sepsis to be coded in the NSQIP data (the gold standard), the primary physician or chart must have stated that the patient had systemic sepsis within 30 days after the operation. This diagnosis typically requires definitive evidence of infection, plus evidence of a systemic response manifested by two or more of the following conditions: 1. Temp > 38 °C or < 36 °C 2. Septic shock with hypotension 3. Heart rate > 90 bpm 4. RR > 20 breaths/min or $PaCO_2$ < 32 mmHg 5. WBC > 12,000 cells/mm^3, < 4,000 cells/mm^3, or > 10% immature forms Using NSQIP data as the gold standard, the following performance characteristics were determined for the original patient safety indicator algorithm (ICD-9-CM codes 038.x): **Sensitivity: 32%** (95% CI 23-43%) **PPV: 44%** (95% CI 31-47%)

	postoperative sepsis patient safety indicator (operating room procedure for elective surgery plus hospitalization ≥ 4 days). Sepsis was present in 75 patients according to NSQIP data, the gold standard.			The following performance characteristics were determined for the alternative algorithm with additional ICD-9-CM codes: **Sensitivity: 37%** (95% CI 27-49%) **PPV: 45%** (95% CI 33-57%) **Specificity** of all algorithms studied for various outcomes was reported to be **>99.1%**
[11]Scanlon, et al. 2008	The overall study objective was to evaluate pediatric quality of care indicators. The study population included 1,794,675 pediatric hospital discharges from 2003 to 2005 from 76 hospitals. All surgery patients aged 0-17 years (excluding neonates) with a hospital stay >4 days, without sepsis or infection on admission and without a principal diagnosis of infection, were eligible. These criteria were met by 174,038 patients, and 4,367 patients met criteria for post-operative sepsis. Chart review was conducted for 279 cases.	New onset sepsis after surgery	A secondary diagnosis code for sepsis during a post-surgical hospitalization as described. Sepsis was identified by the presence of at least 1 of 20 ICD-9-CM codes that indicated sepsis. Patients were excluded if they had infection or sepsis on admission, or a primary diagnosis of infection. *The sepsis ICD-9 CM codes included:* Streptococcal septicemia: 038.0 Staphylococcal septicemia: 038.1 Staphylococcal septicemia, unspecified: 038.10 Methicillin susceptible staphylococcus aureus septicemia (Oct 08 and forward): 038.11 Methicillin resistant staphylococcus aureus septicemia (Oct 08 and forward): 038.12 Other staphylococcal septicemia: 038.19 Pneumococcal septicemia (streptococcus pneumonia septicemia): 038.2 Septicemia due to anaerobes: 038.3	Chart reviewers were physicians or nurses with clinical experience from participating hospitals. They confirmed the presence or absence and preventability of outcomes, as well as whether an outcome was present on admission if it was not a new-onset outcome during the hospital stay. The methods stated that a number of outcome-specific questions were developed by pediatric experts, but did not state specific validation criteria. Postoperative sepsis was confirmed in 223/279 cases in which chart review was conducted, giving a **PPV** of **79.93%**

			Septic shock: 785.52 Shock without mention of trauma, other (not valid for discharges after Oct 1, 2004): 785.59 Postoperative shock: 998.0 Septicemia due to gram negative organism, unspecified: 038.40 Septicemia due to hemophilus influenzae: 038.41 Septicemia due to escherichia coli: 038.42 Septicemia due to pseudomonas: 038.43 Septicemia due to serratia: 038.44 Septicemia due to other gram-negative organisms: 038.49 Other specified septicemias: 038.8 Unspecified septicemia: 038.9 Systemic inflammatory response syndrome due to infectious process without organ dysfunction: 995.91 Systemic inflammatory response syndrome due to infectious process with organ dysfunction: 995.92 Infection and surgery codes are available from the AHRQ Pediatric Quality Indicators Technical Specifications Appendices.[16]	

Table 4. Positive Predictive Values for Transfusion by Algorithm

Citation	Study Population and Time Period	Description of Outcome Studied	Algorithm	Validation/Adjudication Procedure, Operational Definition, and Validation Statistics
[12]Segal, et al. 2001	The study sample included 716 hospital admissions, 358 with a billing code for red blood cell transfusion (ICD-9 procedure code 99.04) and 358 controls with no code for a blood component (ICD-9 procedure codes 99.0-99.09). Each group was randomly selected among eligible hospital patients that met the criteria at a large academic medical center (Johns Hopkins). Controls were stratified by diagnosis related group (DRG) to get approximately the same number from each DRG. The two one-month time periods utilized were August 1998 and March 1999.	Blood transfusion	Blood transfusion was identified by ICD-9 procedure code 99.04. This is meant to capture allogeneic red blood cell transfusions, since there is a separate code for autologous blood transfusion. Controls did not have any blood component procedure code (99.0-99.09), including the code for autologous blood donation (99.02).	The hospital's blood bank database was reviewed using medical record numbers to determine whether there was a record of transfusion. For patients who were not included in the blood bank database, the electronic medical record was reviewed. In 48 psychiatric hospitalizations for which the details were not available in the medical record, the authors assumed that no transfusion had occurred. Another 17 patients were not in the blood bank database but had medical records in which the discharge summaries did not suggest transfusion, so they were classified as non-transfused. Nine patients were identified by ICD-9 procedure code 99.04, but their records did not have a revenue code indicating they'd been billed for transfusion. As a sensitivity analysis, these patients were categorized as true negative then false negative then sensitivity and specificity were again calculated. Of 358 admissions in which red blood cells were transfused, 61 were not billed. Thus, the **sensitivity** of billing codes was **83%** (95% CI 79-87%). When the 9 patients who were given procedure code 99.04 but had no revenue code were considered true negatives, the **specificity** was **100%**. When these patients were considered false-negatives, the **specificity** was **97.5%** (95% CI 96-99%) and the sensitivity was unchanged. Patients who were not billed for transfusion were less likely to have commercial insurance, suggesting that the likelihood of reimbursement may have played a role in the choice to bill for transfusion or not.
[13]Romano and Mark, 1994	This study examined 2,579 California hospital discharge abstracts from July to December 1987. Thirty hospitals	Blood transfusion	Blood transfusion was identified by ICD-9 procedure code 99.04 (allogeneic blood transfusions). The authors	A total of 87/2,579 patients received transfusions, as determined by a re-abstraction of the hospital records in which specific comorbidities and procedures were purposefully identified. The **sensitivity** of procedure codes from original discharge abstracts truncated at 3

	were randomly selected for participation, stratified across different types of hospitals. Patients from the 10 most common diagnosis related groups (DRGs), or 9 related DRGs, were selected. The sample was 53.6% female with a mean age of 50.9 years; 66% were white, 13% black, 15% Hispanic, 5% Asian, and 1% other race.		examined both the sensitivity and specificity of abstracts that allowed for either 3 procedure codes(i.e., truncated at 3) or 25 procedure codes.	fields was **21%.** When this was expanded to allow 25 fields in the original discharge abstract, the **sensitivity** increased to **31%.** The **specificity** was **100%** regardless of the number of fields considered.

I. CLINICIAN OR TOPIC-EXPERT CONSULTATION

Given the limited available information on the identification of sepsis specifically related to transfusion in administrative data, it is difficult to assess the potential to identify this outcome. Populations that receive transfusions are often at high risk of infection and sepsis due to other reasons (e.g., trauma or surgery). The most definitive diagnosis might take place if a specific organism is identified late in cultures of platelet samples, for example, taken prior to the transfusion, as all platelets are now screened for bacterial contamination.[17] Platelets may be contaminated with low levels of microorganisms from the outset, but growth during storage at room temperature may lead to higher levels when the transfusion is actually given. Various changes in blood collection and screening have decreased the risk, but none of these added measures have resulted in perfect safety.[17] Other infections might be deemed related to transfusion if no other potential source of the specific infectious organism is known, but true confirmation of the source of the infection can be difficult.

Since platelets have historically had a higher rate of contamination with infectious organisms than other transfusion types due to room temperature storage, particularly prior to routine screening of platelets for contamination, it would be useful to examine the performance characteristics of codes for platelet transfusion for surveillance of platelet-related infections.

There have also been some cases of emerging infectious diseases contracted from transfusion. The blood supply is not necessarily screened for these diseases previously more confined to endemic areas outside the U.S., but increasing incidence of infection with these diseases related to transfusion would support expansion of screening efforts to include them.[18]

One study of transfusion that used both ICD-9-CM procedure code 99.03 (transfusion of whole blood) and 99.04 (transfusion of red blood cells, in addition to the "blood pints furnished" variable from Medicare Provider Analysis and Review (MedPAR) data sets, provides some useful information about the codes, despite a lack of validation studies on the "blood pints furnished" variable. Anderson, et al.[19] examined blood use in elderly Medicare beneficiaries with an inpatient hospital stay during 2001. Using either procedure codes or non-zero entry for blood pints furnished as the criteria for transfusion, only

77% of transfusion recipients had a procedure code for transfusion. A total of 36% of transfusion recipients had a nonzero blood pints furnished value, and only 13% had both a nonzero blood pints furnished variable and a procedure code for transfusion. Most blood centers charge for the transfusion preparation and procedure but not for the blood itself, and there is evidence of confusion in how to bill for blood transfusions that likely led to under-coding of transfusions in recent history. Thus, it is likely that transfusions are under-identified in administrative data, despite the fact that transfusions are highly likely to have taken place when transfusion codes are present in these data.

VI. SUMMARY AND CONCLUSIONS

A. RECOMMENDATIONS FOR ALGORITHMS

Because of the variability in algorithms and study populations, it is difficult to make a recommendation for one algorithm over another to identify sepsis. Codes 038.x appear to have acceptable performance characteristics for identifying sepsis for most applications, with PPVs of about 80% or greater found in non-VA settings. There is no clear evidence to indicate whether the additional codes utilized would improve or worsen the balance of performance characteristics. The study by Romano, et al.[10] in veterans showed slightly better performance characteristics with the addition of extra codes, though no significant difference in performance was described.

The code for transfusion was also found to have relatively good performance characteristics in a study conducted at one hospital.[12] The specificity of code 99.04 was 100%, and sensitivity 83%. The performance of other transfusion codes, including those for autologous blood donation or platelet transfusion, was not studied. Another study, however, found that the codes were highly specific (100%) but had a sensitivity of only 21-31%,[13] and other evidence suggests that transfusion procedures are under-coded in administrative data.[19] Thus it is likely that the codes are specific but not necessarily sensitive.

No study described an algorithm specifically used to identify transfusion-associated sepsis or septicemia. Such an algorithm and validation study might consider the temporal relationship between transfusion and sepsis, as well as the probability that sepsis might have developed due to other exposures such as surgery or trauma, both of which are common in patients who receive blood transfusions.

In addition to the currently available codes, the FDA's Center for Biologics and Evaluation Research (CBER) has proposed new ICD-9-CM codes for identifying infections determined to be transmitted by blood transfusions.[20] Though it is uncertain whether adoption will take place, it will be important to consider these codes if they are adopted. Currently blood product associated infections might receive an ICD-9-CM code 999.3 (complications of medical care, not elsewhere classified, other infection). The proposed code 999.32 would add more specificity to the definition (transfusion-transmitted infection). This code would be used in combination with an additional code to describe the type of infection.

B. SUGGESTIONS FOR FUTURE RESEARCH BASED ON EVIDENCE GAPS

Future research on sepsis code validation might focus on the performance of codes other than ICD-9 code 038.x, such that an optimal combination of codes could be determined. Overall, the number of studies on the validity of sepsis algorithms is relatively small with some inconsistent results. Further research on sepsis algorithms could be useful.

Transfusion codes other than ICD-9-CM procedure code 99.04 also have unknown performance characteristics, and even the performance of this code varied across studies. Given the relatively higher historical risk of bacterial contamination of platelets due in part to room temperature storage, it would be helpful to examine the performance characteristics of the code for platelet transfusion in order to study infections related to this exposure. It would also be helpful to examine concordance of transfusion procedure codes and "blood pints furnished" revenue codes, and the relationship of each of these codes to actual transfusion, to determine whether algorithms should be expanded beyond procedure codes when revenue codes are available.

If a specific algorithm is designed to identify sepsis that is caused by a transfusion, special attention will need to be paid to the most likely source of the infection insofar as it can be determined. Patients who receive transfusions often have other risk factors for sepsis that would need to be considered. It may be useful to study specific infectious organisms or other specific criteria which might implicate the transfusion in the development of sepsis. It might also be useful to explore the addition of ICD-9-CM code 999.3, or the proposed code 999.32, to the algorithm to identify transfusion-related sepsis.

The newly formed U.S. Biovigilance Network will attempt to capture adverse events related to transfusion. This network may provide opportunities to examine the sensitivity of algorithms to identify transfusion-associated sepsis.

In future HOI evidence reviews, it is generally recommended that the search for validation studies of an outcome not be limited to studies in which the HOI is associated with a particular exposure. Separate searches to find validation studies of algorithms to identify the exposure and algorithms to identify the outcome seem more likely to yield informative studies. There may be scenarios where this is not the case, but the experience from this review process suggests that using such a limited search may create difficulty in achieving the overall goals. It is likely that a broader search for algorithms to identify an outcome that is not restricted to an exposure would also identify those studies where the exposure was relevant. On the other hand, the framing of such reports may be more appropriate in the context of the specific HOI as it relates to an exposure.

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VIII. APPENDICES

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

1. Studies of Sepsis

Eaton S, Burnham E, Martin GS, Moss M. The ICD-9 code for septicemia maintains a high positive predictive value for clinical sepsis. *Am J Respir Crit Care Med*. 2002; 165: A471.

[Abstract only, so not reproduced here due to potential copyright issues.]

Martin GS, Mannino DM, Eaton S, Moss M. The epidemiology of sepsis in the United States from 1979 through 2000. *N Engl J Med*. 2003; 348: 1546-54.

BACKGROUND: Sepsis represents a substantial health care burden, and there is limited epidemiologic information about the demography of sepsis or about the temporal changes in its incidence and outcome. We investigated the epidemiology of sepsis in the United States, with specific examination of race and sex, causative organisms, the disposition of patients, and the incidence and outcome. METHODS: We analyzed the occurrence of sepsis from 1979 through 2000 using a nationally representative sample of all nonfederal acute care hospitals in the United States. Data on new cases were obtained from hospital discharge records coded according to the International Classification of Diseases, Ninth Revision, Clinical Modification. RESULTS: Review of discharge data on approximately 750 million hospitalizations in the United States over the 22-year period identified 10,319,418 cases of sepsis. Sepsis was more common among men than among women (mean annual relative risk, 1.28 [95 percent confidence interval, 1.24 to 1.32]) and among nonwhite persons than among white persons (mean annual relative risk, 1.90 [95 percent confidence interval, 1.81 to 2.00]). Between 1979 and 2000, there was an annualized increase in the incidence of sepsis of 8.7 percent, from about 164,000 cases (82.7 per 100,000 population) to nearly 660,000 cases (240.4 per 100,000 population). The rate of sepsis due to fungal organisms increased by 207 percent, with gram-positive bacteria becoming the predominant pathogens after 1987. The total in-hospital mortality rate fell from 27.8 percent during the period from 1979 through 1984 to 17.9 percent during the period from 1995 through 2000, yet the total number of deaths continued to increase. Mortality was highest among black men. Organ failure contributed cumulatively to mortality, with temporal improvements in survival among patients with fewer than three failing organs. The average length of the hospital stay decreased, and the rate of discharge to nonacute care medical facilities increased. CONCLUSIONS: The incidence of sepsis and the number of sepsis-related deaths are increasing, although the overall mortality rate among patients with sepsis is declining. There are also disparities among races and between men and women in the incidence of sepsis. Gram-positive bacteria and fungal organisms are increasingly common causes of sepsis.

Ollendorf DA, Fendrick AM, Massey K, Williams GR, Oster G. Is sepsis accurately coded on hospital bills? *Value Health*. 2002; 5(2): 79-81.

OBJECTIVE: To examine whether sepsis is accurately coded on hospital bills. METHODS: Hospital inpatient uniform bills (UB-92) for 122 patients with clinically documented severe sepsis of presumed infectious origin were retrospectively examined. Final UB-92 hospital bills were obtained for all study subjects. ICD-9-CM diagnosis codes from these bills were then reviewed to ascertain the number of subjects for whom one or more diagnostic codes for septicemia and/or bacteremia were present. RESULTS: A total of 92 hospital bills (75.4%) contained one or more ICD-9-CM diagnostic codes for septicemia and/or bacteremia. Of the 30 that did not, 15 (12.3%) had codes for major

systemic infection and organ failure. No diagnoses indicative of sepsis (i.e., organ failure and major infection) were present on the remaining 15 (12.3%) bills. CONCLUSIONS: Our findings suggest that use of ICD-9-CM codes for identifying patients with sepsis using hospital bills is only moderately sensitive. Strict reliance on administrative data sources for sepsis surveillance or research planning may therefore be prone to substantial error.

Romano PS, Mull HJ, Rivard PE, et al. Validity of selected AHRQ indicators based on VA National Surgical Quality Improvement Program data. *Health Serv Res*. 2009; 44(1): 182-204.

OBJECTIVES: To examine the criterion validity of the Agency for Health Care Research and Quality (AHRQ) Patient Safety Indicators (PSIs) using clinical data from the Veterans Health Administration (VA) National Surgical Quality Improvement Program (NSQIP).
DATA SOURCES: Fifty five thousand seven hundred and fifty two matched hospitalizations from 2001 VA inpatient surgical discharge data and NSQIP chart-abstracted data.
STUDY DESIGN: We examined the sensitivities, specificities, positive predictive values (PPVs), and positive likelihood ratios of five surgical PSIs that corresponded to NSQIP adverse events. We created and tested alternative definitions of each PSI.
DATA COLLECTION: FY01 inpatient discharge data were merged with 2001 NSQIP data abstracted from medical records for major noncardiac surgeries.
PRINCIPAL FINDINGS: Sensitivities were 19-56 percent for original PSI definitions; and 37-63 percent using alternative PSI definitions. PPVs were 22-74 percent and did not improve with modifications. Positive likelihood ratios were 65-524 using original definitions, and 64-744 using alternative definitions. "Postoperative respiratory failure" and "postoperative wound dehiscence" exhibited significant increases in sensitivity after modifications.
CONCLUSIONS: PSI sensitivities and PPVs were moderate. For three of the five PSIs, AHRQ has incorporated our alternative, higher sensitivity definitions into current PSI algorithms. Further validation should be considered before most of the PSIs evaluated herein are used to publicly compare or reward hospital performance.

Scanlon MC, Harris JM 2nd, 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.

2. Studies of Transfusion

Segal JB, Ness PM, Powe NR. Validating billing data for RBC transfusions: a brief report. *Transfusion*. 2001; 41(4): 530-3.

BACKGROUND: Administrative data are used often for research, but without validation of their accuracy. The validity of the billing for blood transfusion was assessed in one tertiary-care hospital. MATERIALS AND METHODS: Patient discharge data were retrieved from a database containing demographics, diagnoses, and charges. There was random selection of 358 patients who were billed for RBC transfusion and 358 who were not, within a 2-month period. The blood bank's transfusion records were reviewed. Sensitivity was defined as the proportion of transfused patients who were billed, and specificity as the proportion of nontransfused patients who were not billed. Patient characteristics were compared by using Wilcoxon's rank sum test and the chi-square test. RESULTS: Sixty-one transfused patients were not billed for the transfusion. No patient was billed without transfusion. Thus, the sensitivity and specificity were 83 percent (95% CI, 79-87%) and 100 percent, respectively. Nine patients who were not issued RBCs were appropriately not billed for RBCs, although the billing record suggests they had a procedure involving transfusion. These patients were called true-negative. The patients not billed were older (58 years vs. 55 years; p = 0.046) and less likely to have commercial insurance (5% vs. 15%; p = 0.035) than billed patients. CONCLUSIONS: The

billing for RBC transfusion in one large institution is reassuringly valid. The specificity is excellent, and the sensitivity is higher than that seen in other studies of coding validity.

Romano PS, Mark DH. Bias in coding of hospital discharge data and its implications for quality assessment. *Medical Care*. 1994; 32(1): 81-90.

No abstract.

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

Alshekhlee A, Hussain Z, Sultan B, Katirji B. Immunotherapy for guillain-barre syndrome in the US hospitals. *J Clin Neuromuscul Dis*. 2008; 10(1): 4-10.

Dasta J, Mody SH, McLaughlin T, et al. Current management of anemia in critically ill patients: Analysis of a database of 139 hospitals. *Am J Ther*. 2008; 15(5): 423-430.

Haber GP, Campbell SC, Colombo JR Jr, et al. Perioperative outcomes with laparoscopic radical cystectomy: "pure laparoscopic" and "open-assisted laparoscopic" approaches. *Urology*. 2007; 70(5): 910-915.

Rogers MA, Blumberg N, Saint S, Langa KM, Nallamothu BK. Hospital variation in transfusion and infection after cardiac surgery: A cohort study. *BMC Med*. 2009; 7: 37.

Villers MS, Jamison MG, De Castro LM, James AH. Morbidity associated with sickle cell disease in pregnancy. *Am J Obstet Gynecol*. 2008; 199(2): 125.e1-125.e5.

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

Banbury MK, Brizzio ME, Rajeswaran J, Lytle BW, Blackstone EH. Transfusion increases the risk of postoperative infection after cardiovascular surgery. *J Am Coll Surg*. 2006; 202(1): 131-138.

Campos-Lobato LF, Wells B, Wick E, et al. Predicting organ space surgical site infection with a nomogram. *J Gastrointest Surg*. 2009; 13(11): 1986-1992.

Cheung RC. Epidemiology of hepatitis C virus infection in American veterans. *Am J Gastroenterol*. 2000; 95(3): 740-747.

Dohner ML, Wiedmeier SE, Stoddard RA, et al. Very high users of platelet transfusions in the neonatal intensive care unit. *Transfusion*. 2009; 49(5): 869-872.

Heuer M, Taeger G, Kaiser GM, et al. Prognostic factors of liver injury in polytraumatic patients. Results from 895 severe abdominal trauma cases. *J Gastrointestin Liver Dis*. 2009; 18(2): 197-203.

Koch CG, Li L, Sessler DI, et al. Duration of red-cell storage and complications after cardiac surgery. *N Engl J Med*. 2008; 358(12): 1229-1239.

Mamoun NF, Xu M, Sessler DI, Sabik JF, Bashour CA. Propensity matched comparison of outcomes in older and younger patients after coronary artery bypass graft surgery. *Ann Thorac Surg*. 2008; 85(6): 1974-1979.

O'Connell NM, Perry DJ, Hodgson AJ, O'Shaughnessy DF, Laffan MA, Smith OP. Recombinant FVIIa in the management of uncontrolled hemorrhage. *Transfusion*. 2003; 43(12): 1711-1716.

O'Keeffe SD, Davenport DL, Minion DJ, Sorial EE, Endean ED, Xenos ES. Blood transfusion is associated with increased morbidity and mortality after lower extremity revascularization. *J Vasc Surg*. 2010; 51(3): 616-21, 621.e1-3.

Ryan T, Mc Carthy JF, Rady MY, et al. Early bloodstream infection after cardiopulmonary bypass: Frequency rate, risk factors, and implications. *Crit Care Med*. 1997; 25(12): 2009-2014.

Yilmaz M, Keegan MT, Iscimen R, et al. Toward the prevention of acute lung injury: Protocol-guided limitation of large tidal volume ventilation and inappropriate transfusion. *Crit Care Med*. 2007; 35(7): 1660-6.

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

Type of Code	Code	Description
Codes used to identify Sepsis or Septicemia		
ICD-9-CM	003.1	Salmonella septicemia
ICD-9-CM	020.0	Described as "septicemic" in the Martin, et al 2003 manuscript, but look-up of code identified it as "bubonic plague." A more appropriate code would be 020.2, which is "septicemic plague" (www.icd9data.com)
ICD-9-CM	020.2	Septicemic plague
ICD-9-CM	022.3	Anthrax septicemia
ICD-9-CM	036.2	Meningococcemia
ICD-9-CM	038.0	Streptococcal septicemia
ICD-9-CM	038.1	Staphylococcal septicemia
ICD-9-CM	038.10	Staphylococcal septicemia unspecified
ICD-9-CM	038.11	Methicillin susceptible staphylococcus aureus septicemia
ICD-9-CM	038.12	Methicillin resistant staphylococcus aureus septicemia
ICD-9-CM	038.19	Other staphylococcal septicemia
ICD-9-CM	038.2	Pneumococcal septicemia
ICD-9-CM	038.3	Septicemia due to anaerobes
ICD-9-CM	038.4	Septicemia due to other gram-negative organisms
ICD-9-CM	038.41	Septicemia due to hemophilus influenzae [h. influenzae]
ICD-9-CM	038.42	Septicemia due to escherichia coli [e. coli]
ICD-9-CM	038.43	Septicemia due to pseudomonas
ICD-9-CM	038.44	Septicemia due to serratia
ICD-9-CM	038.49	Other septicemia due to gram-negative organisms
ICD-9-CM	038.8	Other specified septicemias
ICD-9-CM	038.9	Unspecified septicemia
ICD-9-CM	038.x	Septicemia
ICD-9-CM	054.5	Herpetic septicemia
ICD-9-CM	112.5	Disseminated candida infection

ICD-9-CM	112.81	Described as "disseminated fungal endocarditis" in Martin, et al 2003 manuscript, while look-up of code identified it as "candidal endocarditis." (www.ICD9data.com)
ICD-9-CM	117.9	Described as "disseminated fungal infection" in the Martin, et al 2003 manuscript, while look-up of code identified it as "other and unspecified mycoses." (www.ICD9data.com)
ICD-9-CM	785.50	Shock unspecified
ICD-9-CM	785.52	Septic shock
ICD-9-CM	790.7	Bacteremia
ICD-9-CM	995.91	Systemic inflammatory response syndrome due to infectious process without organ dysfunction
ICD-9-CM	995.92	Systemic inflammatory response syndrome due to infectious process with organ dysfunction
ICD-9-CM	998.0	Post-operative shock not elsewhere classified
ICD-9-CM	998.1	Hemorrhage or hematoma complicating a procedure not elsewhere classified (seems inappropriate for sepsis)
Codes used to identify Acute Respiratory Dysfunction		
ICD-9-CM	518.5	Described as "acute respiratory distress syndrome after shock or trauma" in Martin, et al 2003 manuscript, but look up of code identified it as "pulmonary insufficiency following trauma and surgery" (www.ICD9data.com)
ICD-9-CM	518.81	Acute respiratory failure
ICD-9-CM	518.82	Described as "acute respiratory distress syndrome" in Martin, et al 2003 manuscript, but look-up of code identified it as "other pulmonary deficiency not elsewhere classified", which includes acute respiratory distress, acute respiratory insufficiency, and adult respiratory distress syndrome not elsewhere classified.
ICD-9-CM	786.09	Other respiratory distress or insufficiency
ICD-9-CM	799.1	Respiratory arrest
ICD-9-CM Procedure	96.7	Ventilator management / other continuous mechanical ventilation
Codes used to identify Acute Cardiovascular Dysfunction		
ICD-9-CM	458.0	Hypotension, postural
ICD-9-CM	458.8	Hypotension, specified type, not elsewhere classified
ICD-9-CM	458.9	Described as "Hypotension, arterial, constitutional" in the Martin, et al 2003 manuscript, while look-up of code identified it as "hypotension unspecified" (www.ICD9data.com)
ICD-9-CM	785.5	Shock without mention of trauma
ICD-9-CM	785.51	Cardiogenic shock

ICD-9-CM	785.59	Other shock without trauma
ICD-9-CM	796.3	Described as "hypotension, transient" in the Martin, et al 2003 manuscript, while look-up of code identified it as "Nonspecific low blood pressure reading"
Codes used to identify Acute Renal Dysfunction		
ICD-9-CM Procedure	39.95	Hemodialysis
ICD-9-CM	580.x	Acute glomerulonephritis
ICD-9-CM	584.x	Acute kidney failure
ICD-9-CM	585.x	Described as "renal shutdown unspecified" in the Martin, et al 2003 paper, while look-up of code identified it as "chronic kidney disease" with subtypes specified by 585.1-585.6, or unspecified by 585.9
Codes used to identify Acute Hepatic Dysfunction		
ICD-9-CM	570	Described as "acute hepatic failure or necrosis" in the Martin, et al 2003 paper, while a look-up of code described it as "acute and subacute necrosis of liver" (www.ICD9data.com)
ICD-9-CM	572.2	Hepatic encephalopathy
ICD-9-CM	573.3	Described as "hepatitis, septic or unspecified" in Martin, et al 2003 paper, while look-up of code identified it as "hepatitis unspecified." Note that other specified categories include "hepatitis in viral diseases classified elsewhere" (573.1) and "hepatitis in other infectious diseases classified elsewhere" (573.2).
Codes to identify Acute Metabolic Dysfunction		
ICD-9-CM	276.2	Acidosis
Codes to identify Acute Neurologic Dysfunction		
ICD-9-CM	293	Described as "transient organic psychosis" by Martin, et al 2003 paper, while look-up of code identified it as "transient mental disorders due to conditions classified elsewhere." A number of subclassifications are available.
ICD-9-CM	348.1	Anoxic brain injury
ICD-9-CM	348.3	Encephalopathy, not elsewhere classified. Also includes subclassifications.
ICD-9-CM	780.01	Coma
ICD-9-CM	780.09	Alteration of consciousness, other
ICD-9-CM Procedure	89.14	Electroencephalogram
Codes to identify Transfusions		
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 (code not in this report but identified for another report so included here for completeness)