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Predictive Ability of Positive Clinical Culture Results and *International Classification of Diseases, Ninth Revision,* to Identify and Classify Noninvasive *Staphylococcus aureus* Infections: A Validation Study

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Abstract

OBJECTIVE—To develop and validate an algorithm to identify and classify noninvasive infections due to *Staphylococcus aureus* by using positive clinical culture results and administrative data.

DESIGN—Retrospective cohort study.

SETTING—Veterans Affairs Maryland Health Care System.

METHODS—Data were collected retrospectively on all *S. aureus* clinical culture results from samples obtained from nonsterile body sites during October 1998 through September 2008 and associated administrative claims records. An algorithm was developed to identify noninvasive infections on the basis of a unique *S. aureus*–positive culture result from a nonsterile site sample with a matching *International Classification of Diseases, Ninth Revision* (*ICD-9-CM*), code for infection at time of sampling. Medical records of a subset of cases were reviewed to find the proportion of true noninvasive infections (cases that met the Centers for Disease Control and Prevention National Healthcare Safety Network [NHSN] definition of infection). Positive predictive value (PPV) and negative predictive value (NPV) were calculated for all infections and according to body site of infection.

RESULTS—We identified 4,621 unique *S. aureus*–positive culture results, of which 2,816 (60.9%) results met our algorithm definition of noninvasive *S. aureus* infection and 1,805 (39.1%) results lacked a matching *ICD-9-CM* code. Among 96 cases that met our algorithm criteria for noninvasive *S. aureus* infection, 76 also met the NHSN criteria (PPV, 79.2% [95% confidence interval, 70.0%–86.1%]). Among 98 cases that failed to meet the algorithm criteria, 80 did not meet the NHSN criteria (NPV, 81.6% [95% confidence interval, 72.8%–88.0%]). The PPV of all culture results was 55.4%. The algorithm was most predictive for skin and soft-tissue infections and bone and joint infections.

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CONCLUSION—When culture-based surveillance methods are used, the addition of administrative *ICD-9-CM* codes for infection can increase the PPV of true noninvasive *S. aureus* infection over the use of positive culture results alone.

During the past decade, there has been a dramatic increase in the incidence of infections due to community-associated methicillin-resistant *Staphylococcus aureus* (MRSA), many of which are skin and soft-tissue infections.[1–3] Although the incidence of *S. aureus* infection in specific populations, and according to certain infection types, has been reported, the overall burden of *S. aureus* infection remains unclear. To improve the public health response to the nationwide epidemic of community-associated MRSA infections, a better estimate of the overall burden and distribution of all *S. aureus* infections is necessary. This requires a validated approach to identifying and classifying *S. aureus* infections according to type and severity, which is relatively straightforward for invasive *S. aureus* infections, because the presence of *S. aureus* in a specimen obtained from a normally sterile body site is highly predictive of infection. However, invasive *S. aureus* infections comprise only a small proportion of *S. aureus* infections. The greater challenge is to identify and classify noninvasive *S. aureus* infections, largely because in a clinical culture, *S. aureus* that is isolated from a sample obtained from a nonsterile body site can represent either infection or colonization. Although data on culture results are often available from large clinical databases, many of these results represent colonization rather than infection, because *S. aureus* is an opportunistic pathogen.

Thus, a more predictive approach to identifying noninvasive *S. aureus* infections is needed, particularly because a substantial proportion of infections due to community-associated MRSA—specifically, skin and soft-tissue infections—are noninvasive.[1,4] In addition, there is a need for an automated approach to identifying *S. aureus* infections for use in large epidemiological research studies for which medical record review is impractical or when medical records are unavailable. To address these needs, we performed a retrospective study in a large population of patients who receive healthcare services through the Veterans Affairs Maryland Health Care System (VAMHCS). Our research objective was to develop and estimate the accuracy of a new algorithm to identify and classify noninvasive *S. aureus* infections.

METHODS

Design and Setting

This retrospective cohort study was conducted in the VAMHCS, which operates approximately 730 inpatient (mostly nonacute care) beds and provides comprehensive care to approximately 49,000 veterans annually. VAMHCS electronic medical records, administrative data (including *International Classification of Diseases, Ninth Revision, Clinical Modification* [*ICD-9-CM*], codes), and results of microbiological cultures served as the primary data sources for this study. The study took place during the period from October 1, 1998, through September 30, 2008. The VAMHCS Research and Development Committee and the institutional review board of the University of Maryland, Baltimore, approved this study.

Case Definition

Data on all *S. aureus*–positive results from nonsurveillance specimens obtained during the period from October 1, 1998, through September 30, 2008, were identified. Only *S. aureus*–positive clinical culture results from samples that were obtained from a nonsterile body site were included in the study. Clinical culture results from samples obtained from a normally sterile body site (blood, cerebrospinal fluid, pleural fluid, pericardial fluid, peritoneal fluid,

joint or synovial fluid, bone, internal body site, muscle, or other normally sterile site, including deep tissue that is sampled during surgery), as defined by the US Centers for Disease Control and Prevention (CDC) Active Bacterial Core surveillance systems criteria, were omitted.[5] A unique culture was defined as the first *S. aureus*–positive clinical culture result from a sample of a nonsterile site obtained from the same patient during a 6-month period without a concurrent *S. aureus*–positive culture result from a sterile site specimen.

We collected data on all *ICD-9-CM* administrative claim codes and corresponding *ICD-9-CM* terms associated with either the outpatient visit or the inpatient assessment during which each unique *S. aureus*–positive culture result from a nonsterile site specimen was obtained. For a *S. aureus*–positive culture result from a nonsterile site specimen obtained during an outpatient visit for which the patient was not subsequently hospitalized within a 72-hour period after culture sampling, we obtained all *ICD-9-CM* codes associated with all of the patient's outpatient visits on the day of culture sampling. For a *S. aureus*–positive culture result from a non-sterile site specimen obtained during an outpatient visit for which the patient was subsequently hospitalized within a 72-hour period after culture sampling, we obtained the outpatient visit *ICD-9-CM* codes along with the hospital discharge *ICD-9-CM* codes. Last, we collected the *ICD-9-CM* hospital discharge codes for all *S. aureus*–positive culture results from nonsterile site specimens obtained during a hospitalization, rehabilitation, or long-term care stay.

We developed an algorithm (Figure 1) to identify noninvasive *S. aureus* infections on the basis of a confirmed *S. aureus*–positive culture result from a nonsterile site specimen without a concurrent *S. aureus*–positive culture result from a sterile site during the same 6-month period, and at least 1 *ICD-9-CM* code for *S. aureus*–related infection from the visit or hospitalization associated with the positive culture result. A comprehensive list of *ICD-9-CM* codes for *S. aureus*–related infections was developed on the basis of *ICD-9-CM* codes used in previous studies that described *S. aureus* infections (refer to Appendix, Table A1, for the complete list of codes). *ICD-9-CM* codes were categorized according to the site of infection most consistent with the associated code (eg, septic arthritis was classified as a bone and joint infection). Once cultures were linked with respective *ICD-9-CM* codes, each code was categorized according to type of infection. Bone and joint infections were ranked as the most important and most likely associated with *S. aureus*, followed in order by infections of skin and soft tissue, endovascular site, respiratory tract, intra-abdominal or pelvic site, central nervous system, urinary tract, nonspecific site, and other or site not specified. For culture results with more than 1 matching *ICD-9-CM* code, the primary code was defined as the code that corresponded to the most likely infection type.

Statistical Analysis

Among all unique *S. aureus*–positive culture results obtained from samples of nonsterile body sites, we calculated the proportions with and without a matching *ICD-9-CM* code for infection and described the site of infection for the ones with a matching code. To validate this approach, we randomly selected a sample of cases that met the definition of noninvasive infection (ie, positive culture result with matching *ICD-9-CM* code) and a sample of cases that did not meet the definition (ie, positive culture result without matching *ICD-9-CM* code). Focusing on the clinical and laboratory information pertaining to the date(s) of hospitalization or outpatient visit associated with the date of the positive *S. aureus* culture result, the first author (L.A.T.) performed a detailed review of the medical records of all cases to identify and confirm the presence or absence of infection. A "true infection" was determined by using the CDC National Healthcare Safety Network (NHSN) definitions (reference standard), which were adapted for our study by sorting according to body site of infection (defined as bone and joints, skin and soft tissue, endovascular site, respiratory tract, intra-abdominal or pelvic site, central nervous system, or urinary tract) and removing

the requirement that the infection be healthcare associated.[6] The positive predictive value (PPV) was calculated as the probability that an infection identified with use of our algorithm was confirmed as an infection according to the reference standard criteria. Analogously, the negative predictive value (NPV) was calculated as the probability that a case that did not meet the definition of noninvasive *S. aureus* infection (positive culture result that lacked a matching *ICD-9-CM* code for infection) on the basis of our algorithm also did not meet the reference standard criteria. A 20% subset of the medical records was randomly selected and independently reviewed by the senior author (M.-C.R.). The Cohen κ was calculated to assess the level of interreviewer agreement.[7]

The validation study sample size was based on the minimum number of cases required to achieve 95% confidence that the true (population) PPV was within 10% of the observed (sample) PPV value.[8,9] Similar calculations were performed to determine the appropriate sample size required to estimate the NPV in the validation study.

RESULTS

We identified 4,621 unique *S. aureus*–positive clinical culture results from samples obtained during the period October 1, 1998, through September 30, 2008, of which 2,816 positive results (60.9%; 2,511 unique patients) met the definition of noninvasive *S. aureus* infection and 1,805 positive results (39.1%; 1,666 unique patients) did not meet the definition because they lacked a matching *ICD-9-CM* infection code. Among all noninvasive *S. aureus* infections, 1,807 (64%) of 2,816 were methicillin resistant. Skin and soft tissue were the most common sites of infection, accounting for 1,704 (60.5%) of the 2,816 noninvasive *S. aureus* infections, according to the highest priority (most likely noninvasive infection) matching *ICD-9-CM* code. The second most common site was the respiratory tract, accounting for 345 (12.3%) infections, followed by the urinary tract (322 infections [11.4%]), non-specified site of infection (184 infections [6.5%]), bone and joints (173 infections [6.1%]), endovascular site (40 infections [1.4%]), intra-abdominal or pelvic site (23 infections [0.8%]), other or infection not specified (21 infections [0.7%]), and central nervous system (4 infections [0.1%]). The site from which the culture sample was obtained matched the site of infection, as determined according to *ICD-9-CM* code, for 163 (94%) of 173 bone and joint infections, for 1,620 (95%) of 1,704 skin and soft-tissue infections, for 289 (84%) of 345 respiratory tract infections, and for 180 (56%) of 322 urinary tract infections.

Validation of Algorithm to Identify and Classify Noninvasive *S. aureus* Infections

Among a sample of 96 cases that met our algorithm criteria for noninvasive *S. aureus* infection, 76 (79.2% [95% confidence interval {CI}, 70.0%–86.1%]) cases also met the criteria for a clinical infection on the basis of the NHSN surveillance definitions (Table 1). On the basis of CIs, these results suggest that the probability that an infection identified with use of our case definition is also an infection on the basis of accepted clinical definitions is in the range 70.0%–86.1%. Among the 2,816 unique *S. aureus*–positive clinical culture results with matching *ICD-9-CM* codes, we could expect that approximately 2,225 were true noninvasive *S. aureus* infections on the basis of estimated PPV. There was substantial agreement (κ = 0.60–0.70) between reviewer findings in the mutually reviewed subset of records. The estimated PPV varied widely according to infection site: 95% for skin and soft tissue, 78% for bone and joints, 67% for endovascular sites, 55% for respiratory tract, 71% for nonspecific sites, and 22% for urinary tract (Table 2).

Among 98 randomly selected cases that failed to meet the algorithm criteria for noninvasive *S. aureus* infection, 80 (81.6% [95% CI, 72.8%–88.0%]) cases did not meet the NHSN clinical criteria for infection on the basis of medical record review (Table 1). These results

suggest a case definition NPV (the absence of an infection determined on the basis of the clinical definition although a positive culture result was present) of approximately 72.8%–88.0%. Among the 1,805 unique *S. aureus*–positive clinical culture results that lacked a matching *ICD-9-CM* code for infection, approximately 332 could represent a clinical infection on the basis of estimated NPV.

Increase in PPV with Matching *ICD-9-CM* Code

To estimate the increase in PPV with the additional requirement of a matching *ICD-9-CM* code for infection, we also estimated the PPV of any *S. aureus*–positive clinical culture result. On the basis of 79.2% PPV, we calculated that among the noninvasive *S. aureus* infections (n = 2,816), 2,230 (2,816 × 0.792) cases would represent clinical infection on the basis of the *minimum* requirement of *S. aureus*–positive clinical culture; and on the basis of 81.6% NPV, we calculated that among the cases that did not meet the definition for infection (n = 1,805), 332 ([1,805 × 0.184], where 0.184 is 1 – NPV) would represent clinical infection on the basis of the *minimum* requirement of *S. aureus*–positive clinical culture, for a total of 2,562 (55.4%) of 4,621 cases (Table 3). Thus, the additional requirement of a matching *ICD-9-CM* code for infection with *S. aureus*–positive clinical culture result increases the PPV for a true noninvasive *S. aureus* infection over that of a positive clinical culture result from 55.4% to 79.2%, a 23.8% increase.

DISCUSSION

In this study, we measured the validity of an algorithm consisting of clinical culture plus *ICD-9-CM* coding for identification of noninvasive *S. aureus* infection. On the basis of medical record documentation of clinical infection for a representative sample of cases that meet the algorithm criteria and cases that do not meet the criteria, we calculated a PPV of 79.2% (95% CI, 70.0%–86.1%) and an NPV of 81.6% (95% CI, 72.8%–88.0%). Furthermore, we estimated that coding in addition to culture may increase the probability of identifying true infection by approximately 23.8% over positive clinical culture result alone. The sites of infection with the highest PPVs were skin and soft tissue and bone and joints. We found some discordance between the body site from which the specimen was collected and the *ICD-9-CM* code for infection, specifically for cultures of urine and sputum samples, which coincides with findings that the algorithm was less predictive of true infection for respiratory tract and urinary tract sites. Although our calculated PPV for pneumonia was only 54.5% (95% CI, 28.0%–78.7%), it is consistent with other reported estimates in the literature.[10,11] We attribute this low PPV to the difficulty in the clinical diagnosis of these infections, particularly of pneumonia, as a result of ambiguity in clinical symptoms and radiographic results as determined during the review of medical records. Requiring a match between the culture site and the *ICD-9-CM*–based site of infection would have been technically difficult, because the culture sampling site is not always consistent with the diagnosis. In addition, multiple culture samples are often obtained from a patient during a single infection period, which would complicate any matching approach.

A study by Sherman et al[12] assessed the sensitivity, PPVs, and NPVs of identifying healthcare-associated infections on the basis of infection-specific *ICD-9-CM* codes assigned at hospital discharge. True infections were those that met the definitions of the CDC National Nosocomial Infections Surveillance system (the predecessor to the CDC NHSN) on the basis of medical record review. They reported a sensitivity of 61% and a PPV of only 20% for identification of healthcare-associated infections on the basis of *ICD-9-CM* coding. They concluded that review of administrative records did not provide accurate data and often led to misclassification of the 4 most common types of healthcare-associated infection (central line–associated bloodstream infection, surgical-site infection, catheter-associated urinary tract infection, and ventilator-associated pneumonia). Such infections are commonly

caused by *S. aureus;* therefore, these findings are relevant to concerns about the limitations of *ICD-9-CM* coding alone to identify *S. aureus* infection. Although a few studies have examined the validity of *ICD-9-CM* coding and other healthcare administrative data, such as antimicrobial use data in predicting infections, they assessed only surgical-site infections or did not focus specifically on *S. aureus* infections.[13,14] A few studies have attempted to estimate the national burden of *S. aureus* infection but used administrative coding only and not clinical culture results and coding.[15–17]

There are some limitations to our study. First, our use of clinical culture results to define infection leads to an underestimation of the true number of infections, which leads to a decrease in sensitivity, because for some *S. aureus* infections it is not often feasible to culture (eg, cellulitis) and others are not always cultured (eg, furuncles). However, because many of these infections can be due to bacteria other than *S. aureus*, the requirement of a positive culture result increases the specificity of our definition. Second, we cannot exclude the possibility that there was a change in microbiologic culturing practices during the 10-year study period. However, the annual number of *S. aureus*–positive culture results was similar from year to year and there was no significant change in the size of our veteran population (data not shown). Third, the coding practices at the VAMHCS may differ from those used at other centers; for example, inpatient hospitalizations may have fewer codes assigned than in other types of hospitals. However, with the requirement of a positive culture result and *ICD-9-CM* code, we would expect differences in coding practices to have a small effect on our results.

Our study has several important implications. It is the first study to assess the validity of the use of clinical culture results plus *ICD-9-CM* codes for identifying noninvasive *S. aureus* infections. In addition, this study revealed that surveillance with use of positive culture results alone can lead to low predictability of true infection. Our algorithm was highly predictive of noninvasive *S. aureus* infections, specifically for skin and soft-tissue infections. However, it is also important to recognize that a single automated algorithm is unlikely to accurately identify all infections, particularly those with complex clinical presentations. These results offer a starting point from which future epidemiological studies, using large clinical databases, can be focused to identify and quantify noninvasive *S. aureus* infections, which will provide a better estimate of the public health burden of *S. aureus* infections.

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APPENDIX

TABLE A1

International Classification of Diseases, Ninth Revision, Codes for *Staphylococcus aureus*–Related Infections

Site of infection	*ICD-9-CM* code
Bone and joints	
Septic arthritis[18]	711.00–711.09, 996.66, 996.67

Site of infection	*ICD-9-CM* code
Joint effusions and/or pain	719.06–.08 (.42, .49)
Osteomyelitis[18]	730.00–730.09, 730.10–730.19 (.9, .20–.29, .81, .88, .96–.97)
Skin and soft tissue	
Oral soft-tissue disease, not elsewhere classified	528.9 (.3)
Anal rectal abscess	566
Inflammatory disease of breast[19]	611.0
Infective mastitis or nonpurulent mastitis[19]	675.2, 771.50
Breast abscess	675.1
Carbuncle or furuncle[2,19]	680 (.0–.9)
Felon[2,19]	681.01
Cellulitis and abscess of finger and toe[2,19]	681.00, 681.9, 681.10
Other cellulitis and abscess[2,19]	682 (.0–.9)
Acute lymphadenitis	683
Impetigo[2,19]	684
Pilonidal cyst with abscess	685.0
Pyoderma	686.0
Unspecified local infection[19]	686.9
Other specified diseases of hair and hair follicles[2,19]	704.8
Hydradenitis[2,19]	705.83
Myositis[19]	728.0
Gangrene	785.4
Posttraumatic wound infection, not elsewhere classified	958.3
Amputation stump infection, chronic	997.62
Surgical-site infection[18]	998.3 (.31–.32), 998.5 (.51, .59)
Endovascular system	
Tricuspid valve disease	397.0
Endocarditis[18]	421.0 (.9), 996.61
Aortic valve disorder	424.1
Endocarditis, not otherwise specified	424.90–.91, .99
Phlebitis and thrombophlebitis of superficial veins of upper extremities	451.82
Thrombophlebitis, not otherwise specified	451.9
Due to vascular device, implant, and graft	996.62
Respiratory tract	
Bacterial pneumonia, not otherwise specified	482.9
Pneumonia, organism, not otherwise specified	486
Bacterial pleural effusion, not tuberculosis	511.1
S. aureus pneumonia[15,16,18]	482.41
Pneumonia due to *Staphylococcus*	482.4
Empyema without fistula	510.9
Intra-abdominal or pelvic	

Site of infection	*ICD-9-CM* code
Staphylococcal enterocolitis[8]	008.41
Suppurative peritonitis, not elsewhere classified	567.2
Peritonitis, not otherwise specified	567.9
Acute pancreatitis	577.0
Cystitis, not otherwise specified	595.9
Acute cholecystitis	575.0
Central nervous system	
Meningitis, not otherwise specified	322.9
Central nervous system abscess, not otherwise specified	324.9
Intraspinal abscess	324.1
Urinary tract	
Chronic pyelonephritis, not otherwise specified	590
Acute pyelonephritis, not otherwise specified	590.10
Urinary tract infection, not otherwise specified	599.0
Bacteremia without focus	
Bacteremia[18]	038.1, 790.7
Bacterial diseases, not elsewhere classified	040.89
Bacterial infection, not otherwise specified	041.9
S. aureus, nonspecific[a]	
S. aureus septicemia[15,16,18]	038.11 (.1, .8, .9)
S. aureus infection in conditions classified elsewhere or of unspecified site[15,16,18]	041.11
Methicillin-resistant *S. aureus*[18]	V09.0
Vancomycin-resistant *S. aureus*[18]	V09.8
Other or not specified[a]	
Infection with microbial resistance, cephalosporin and other	V09.1
Infection with microbial resistance, other specified antimicrobial	V09.70
Infection with microbial resistance, other specified drugs	V09.80, .81
Infection complicating medical care, not elsewhere classified	999.3

NOTE. Values in parentheses are additional subcodes added subsequent to review of study *ICD-9-CM* codes.

[a]These *ICD-9-CM* codes are generally used with an infection code; V codes are designed to modify other codes.

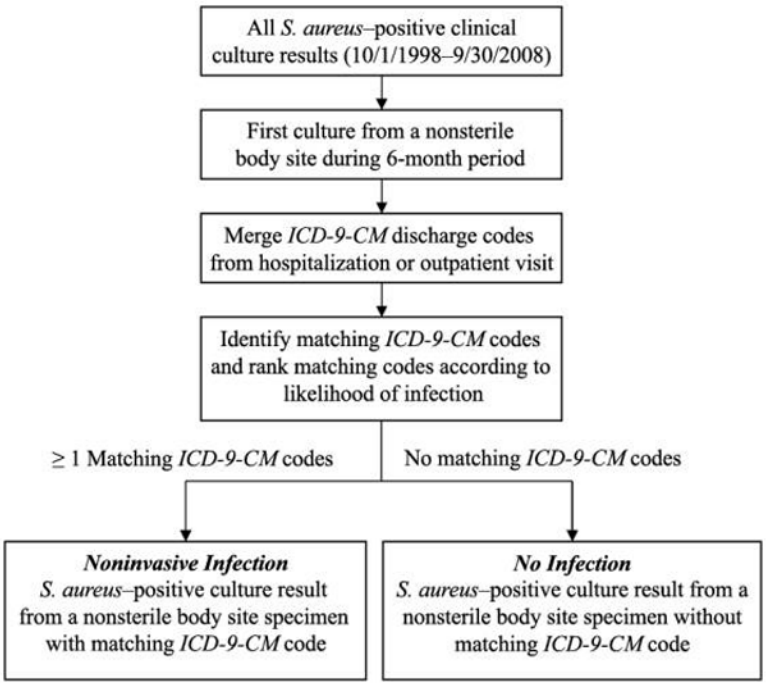

FIGURE 1.

Algorithm to identify noninvasive infections due to *Staphylococcus aureus* on the basis of a confirmed *S. aureus*–positive culture result from a specimen obtained from a nonsterile body site (all cultures *not* classified as coming from a normally sterile body site according to the US Centers for Disease Control and Prevention Active Bacterial Core surveillance systems criteria) and at least 1 *International Classification of Diseases, Ninth Revision* (*ICD-9-CM*), code for *S. aureus*–related infection (*ICD-9-CM* code from outpatient visit or hospitalization during which culture sample was obtained or hospitalization within 72 hours of culture sampling).

TABLE 1

Positive Predictive Value (PPV) and Negative Predictive Value (NPV) of Case Definition of Noninvasive Infection due to *Staphylococcus aureus* from a Random Sample of Patients with *S. aureus*–Positive Culture Results from a Sample Obtained from a Nonsterile Body Site

	Noninvasive infection due to *S. aureus* present according to reference standard		
Variable	**Yes**	**No**	**Predictive value (% [95% CI])**
Positive culture result and matching *ICD-9-CM* code	76	20	PPV, 76/96 (79.2 [70.0–86.1])
Positive culture result alone	18	80	NPV, 80/98 (81.6 [72.8–88.0])

NOTE. Reference standard as determined by means of medical chart review and application of the CDC/NHSN surveillance definitions for specific type of infection. Cases of noninvasive infection due to *S. aureus* that meet the criteria are those with a positive clinical culture result and a matching *International Classification of Diseases, Ninth Revision* (*ICD-9-CM*), code for infection (refer to Appendix 1 for list of codes) from a same-day outpatient encounter or associated hospitalization. Cases that do not meet the criteria are those with positive clinical culture result without *ICD-9-CM* code for infection. CI, confidence interval.

TABLE 2

Positive Predictive Value (PPV) According to Site of Infection for Noninvasive Infections due to *Staphylococcus aureus*

Site of infection	True infections[a] (*n* = 76)	False-positive results[b] (*n* = 20)	PPV, % (95% CI)[c]
Skin and soft tissue	54	3	95 (86–98)
Bone and joints	7	2	78 (45–94)
Endovascular site	2	1	67 (21–94)
Respiratory tract	6	5	55 (28–79)
Nonspecific site	5	2	71 (36–92)
Urinary tract	2	7	22 (8–64)

NOTE. Site of infection based on matching *ICD-9-CM* code for infection. CI, confidence interval.

[a] Cases that were identified with use of algorithm and also meet reference standard criteria.

[b] Cases that were identified with use of algorithm but do not meet reference standard criteria.

[c] According to site of infection based on random sample of validation cohort.

TABLE 3

Estimated Positive Predictive Value (PPV) of Any *Staphylococcus aureus*–Positive Culture Result from a Sample Obtained from a Nonsterile Body Site

Variable	Estimated no.		Total infections, no.	Estimated PPV, %
	Infection present	Infection absent		
Positive culture result with matching *ICD-9-CM* code	2,230	586	2,816	79.2
Positive culture result without matching *ICD-9-CM* code	332	1,473	1,805	18.4
All positive culture results	2,562	2,059	4,621	55.4

NOTE. ICD-9-CM, International Classification of Diseases, Ninth Revision.