Title

Variation in Empiric Coverage Versus Detection of Methicillin-Resistant Staphylococcus aureus and Pseudomonas aeruginosa in Hospitalizations for Community-Onset Pneumonia Across 128 US Veterans Affairs Medical Centers

Journal

Infection Control and Hospital Epidemiology, 38(8)

ISSN

0899-823X

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Publication Date

2017-08-01

DOI

10.1017/ice.2017.98

Peer reviewed

TITLE: "Variation in Empiric Coverage Versus Detection of MRSA and *Pseudomonas aeruginosa* in Hospitalizations for Community-Onset Pneumonia across 128 U.S. VA Medical Centers."

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ABBREVIATED TITLE:
MRSA and *Pseudomonas aeruginosa* in Community-onset Pneumonia.

ABSTRACT WORD COUNT: 248
MANUSCRIPT WORD COUNT: 2,458

ABSTRACT

Objective: To examine variation in antibiotic coverage and detection of resistant pathogens in community-onset pneumonia.

Design: Cross-sectional.

Setting: 128 VA hospitals.

Participants: Hospitalizations with a principal diagnosis of pneumonia from 2009 through 2010.

Methods: We examined proportions of hospitalizations with empiric antibiotic coverage for methicillin-resistant *Staphylococcus aureus* (MRSA) and *Pseudomonas aeruginosa* (PAER) and those with initial detection in blood or respiratory cultures, compared lowest- versus highest-decile hospitals, and estimated adjusted probabilities (AP) for patient and hospital-level factors predicting coverage and detection using hierarchical regression modeling.

Results: Among 38,473 hospitalizations, empiric coverage varied widely across hospitals (MRSA: 8.2% versus 42.0%, lowest vs highest; PAER: 13.9% versus 44.4%). Detection also varied (MRSA 0.5% versus 3.6%; PAER 0.6% versus 3.7%). While coverage was greatest in patients with recent hospitalizations (AP for anti-MRSA 54%, anti-PAER 59%) and long-term care (anti-MRSA 60%, anti-PAER 66%), detection was greatest in patients with a previous history of a positive culture (MRSA 7.9%, PAER 11.9%*)* and in hospitals with high prevalence of the organism in pneumonia (AP for MRSA 3.9%, PAER 3.2%). Low complexity and rurality were strong negative predictors of coverage but not detection.

Conclusions: Hospitals demonstrated widespread variation in both coverage and detection of MRSA and PAER, but probability of coverage correlated poorly with probability of detection. Factors associated with empiric coverage (healthcare exposure) were different from those associated with detection (microbiology history). Providing microbiology data during empiric antibiotic decision-making could better align coverage to risk for resistant pathogens and promote more judicious use of broad-spectrum antibiotics.

BACKGROUND

Pneumonia is the leading infectious cause of death in the United States[1 2] and is the target of numerous quality improvement efforts, including the dissemination and implementation of practice guidelines[3 4] and performance measures.[5] Starting in 2005, the Infectious Disease Society of America (IDSA) and American Thoracic Society (ATS) recommended empiric coverage for organisms resistant to standard antibiotics, predominantly methicillin-resistant *Staphylococcus aureus (*MRSA*)* and *Pseudomonas aeruginosa* (PAER), for patients with community-onset pneumonia but recent healthcare exposure (such as previous hospitalizations, residence at nursing facilities, parenteral therapy, wound care, and hemodialysis). [3 4] The substantial increase in the use of broad-spectrum antibiotics for pneumonia that followed[6 7] has raised concerns that this recommendation may have encouraged overuse.[8] Widespread variation in antibiotic prescribing for pneumonia has been reported,[79] as has a wide range in prevalence of resistant organisms.[10 11 12] It is unclear whether variation in antimicrobial coverage is related to variation in pathogen detection. The aims of our study were to examine variation in 1) detection of MRSA and PAER in initial cultures and 2) empiric antibiotic coverage for MRSA and PAER among patients hospitalized for community-onset pneumonia, and to identify patient and hospital factors driving variation.

METHODS

Study Population

The study used data from all VA Medical Centers (VAMCs) with ≥ 10 acute care beds and complete electronic medication records. We included hospitalizations between January 1, 2006 through December 31, 2010, of patients ≥ 18 years old at acute medical, surgical, or neurological wards and intensive care units with a principal *International Classification of Disease, 9th*

Revision (ICD-9) code consistent with pneumonia (481-486), similar to other studies.[13 14] Data were accessed using Veterans Informatics, and Computing Infrastructure (VINCI).[15]

Patient and hospital factors

We assessed 4 patient-level risk factors: age, history of a positive culture from any body site for MRSA or PAER in the past 2 years, the number of days a patient spent in a VA hospital in the previous 90 days according to previous definitions of hospital exposure and rounded to whole weeks (<2, 2-14, or ≥ 15 days), and the number of days a patient spent in a long-term care facility in the previous 90 days rounded to months (zero, 1-28, or ≥29 days). We assessed 4 hospital-level risk factors: historical prevalence of MRSA and PAER-positive respiratory or blood cultures in previous pneumonia cases (based on a 3-year retrospective window using data from 2006-2008), rural or urban status, region (Northeast, South, Midwest, or West), and hospital complexity score (a 5-point ordinal scale that incorporates levels of hospital services, patient volume, intensive care and surgical services, patient risk, and resident or research involvement.[16] To adjust for regression to the mean, the observed prevalence was shrunken towards the grand-mean of MRSA and PAER using a hierarchical logistic model with random intercepts corresponding to each facility. [17]

Detection and coverage

We accessed microbiology data on cultures drawn during each hospitalization, standardized into Systemized Nomenclature of Medicine format.[18] Since we were interested in identifying cultures that were clinically relevant to pneumonia and were present upon hospital admission rather than acquired during a hospitalization, we defined a positive culture as the detection of MRSA and PAER from blood or respiratory sources (sputum, endotracheal aspirate, bronchiolar lavage, wash, biopsy, or pleural fluid) obtained during the first 2 calendar days of the hospitalization.

Antibiotic coverage was measured using bar code medication administration, which records all medications administered to patients hospitalized on acute care wards.[19] To identify antibiotic use prior to culture results, we identified the systemic administration of at least one dose within the first 2 calendar days of hospitalization. We identified antibiotics with activity against MRSA pneumonia (vancomycin and linezolid) and specific activity against PAER (piperacillin-tazobactam, ticarcillin-clavulanate, ceftazidime, cefepime, meropenem, doripenem, imipenem, aztreonam and aminoglycosides).

To examine variation in thresholds of treatment with broad-spectrum agents, we measured coverage-to-culture ratios for MRSA and PAER, defined as the ratio of the proportion of patients administered anti-MRSA or anti-PAER coverage to the proportion of patients with MRSA or PAER. We calculated coverage-to-culture ratios for the entire 2009-2010 population, each hospital, and for quantiles of each patient-and facility-level risk factor.

Statistical Analysis

Because the facility-level prevalence variable required 3 years of prior data, we conducted all analyses on hospitalizations from 2009 and 2010 only. We compared rates of detection and coverage for the lowest (p10) versus the highest (p90) deciles by calculating inter-decile relative ratios (IDRs). We examined relationships between all factors and each of the 4 outcomes (detection and coverage, for MRSA and PAER) using bivariate and multivariable hierarchical logistic regression models with facility-level random intercepts. Individual and facility-level MRSA culture histories were used in models of MRSA detection and coverage, while PAER histories were used in models of PAER detection and coverage. For bivariate models, each patient-level and facility-level predictor was entered separately. For multivariable models, adjusted probabilities (APs) were estimated using logistic regression models by calculating marginal probabilities.[20] Inverse variance weighted linear regression on proportions was used to plot the graphs in Figure 1. Hospital-level cluster bootstrapping was used to calculate

confidence intervals.[21] All statistical analyses were performed using R (http://cran.r-project.org). The study was approved by the University of Utah Institutional Review Board and Salt Lake City VA Human Research Protection Program.

RESULTS

We identified 95,511 hospitalizations for pneumonia at 128 facilities, of which 38,473 occurred during 2009-2010. Among those hospitalizations, 2.1% had positive cultures for MRSA and 2.1% had positive cultures for PAER. Detection of positive cultures for MRSA varied across hospitals (Figure 1), ranging from 0.5% among the lowest decile (p10) to 3.6% among the highest decile (p90), for an IDR 95% confidence interval (IDRCI) of 6.1-16.1-fold. Detection of PAER also varied (Figure 1), ranging from 0.6% (p10) to 3.7% (p90) with an IDRCI of 4.1-10.0-fold.

Anti-MRSA coverage was included in the initial treatment regimen for 30.2% hospitalizations while anti-pseudomonal coverage was used for 34.3%. Coverage varied significantly across hospitals (Figure 1) for both anti-MRSA (p10=8.2%, p90=42.0%, IDRCI=5.1 3.9-6.4) and anti-pseudomonal coverage (p10=13.9%, p90=44.4%, IDRCI=2.5-4.0).

The overall coverage:culture ratio, or the number of hospitalizations receiving coverage per hospitalization with a positive culture, was 14.4 for MRSA and 16.3 for PAER. We found substantial hospital-level variation in coverage:culture ratios, which was greater for MRSA (p10=4.7, p90=51.4, IDRCI=7.0-21.8) than for PAER (p10=7.5, p90=39.5, IDRCI=4.1-8.7).

Patient-level factors were predictive of detection (Tables 1, 2 and Figures 1 & 2; bivariate models in Appendix). The strongest predictor of MRSA and PAER was a history of a positive culture (AP=7.9% versus 1.6% for MRSA; 11.9% versus 1.4% for PAER). This factor was substantially more predictive than acute care stay of >14 days in the past 90 days and long-term care exposure of greater than 28 days (Tables 1 & 2).

Patient-level factors were also predictive of coverage, but in different ways (Tables 1, 2, Figures 1 & 2). In contrast to detection, the individual factors that were predictive of coverage were long-term care exposure in the past 90 days for both MRSA (59.4% versus 28.8%) and PAER (65.8% versus 31.7%), recent history of hospitalization in the past 90 days, and to a lesser degree, individual positive culture history (Tables 1 and 2). As individual risk of detection increased, actual detection increased proportionately (Figure 2, A & B); however coverage increased to a disproportionately high degree for the lower deciles of risk, and not to the same degree for the highest decile of risk. (Figure 2, C and D)

Hospital factors were also predictive of both detection and coverage in different ways (Tables 1, 2). Prevalence of MRSA and PAER was associated with detection, but not treatment decisions. Hospitals with the highest group of prevalence demonstrated higher detection for MRSA (Tables 1: 4.7% versus 1.6%) and to a smaller degree PAER (Table 2: 2.7% versus 1.7%), but they demonstrated no significant increase in coverage. Similarly, hospital-level predicted risk of detection was associated with detection but not coverage (Figure 1). Hospitalizations at rural and low complexity facilities had low probability of coverage for both MRSA and PAER, despite detection rates that were similar to urban or high-complexity hospitals. As a result of this mismatch between prevalence of resistance and prescribing, facilities with the highest MRSA and PAER prevalence had lower coverage-to-culture ratios than facilities with low prevalence (Table 1 and 2).

DISCUSSION

We compared variation in antibiotic coverage to variation in MRSA and *P. aeruginosa* detection among patients admitted to VA hospitals with a principal diagnosis of pneumonia. The factors most predictive of detection were the patient's microbiological history and the hospital's past prevalence of these organisms among pneumonia cases. In their choice of antibiotics, we found

that clinicians overestimated the importance of prior nursing home or hospital exposure, underestimated the significance of individual microbiologic history, and neglected population prevalence of MRSA and Pseudomonas. Our analysis, which included detailed electronic health record data from 128 acute inpatient facilities, significantly extends the findings of previously published studies and points the way toward using tailored patient and population data to improve clinical decision-making.

Our findings suggest that incorporating microbiology data into the empiric antibiotic selection decision could improve patient care and curb inappropriate use of broad-spectrum antibiotics. The two most common risk factors from the previous "healthcare-associated pneumonia" (HCAP) criteria – previous exposure to acute care and long-term care facilities – were only weakly associated with MRSA and PAER detection, a finding that is consistent with other studies,[22 23] some of which also found patient history of colonization or infection to be a more important factor.[24 25] We found data tailored to a specific organism to be far more informative than generic exposure to nosocomial pathogens through healthcare exposure. We found differences between MRSA and PAER: population prevalence demonstrated a stronger correlation with risk of MRSA infection than risk of PAER infection, while individual microbiological history was a comparatively stronger predictor of PAER infection than of MRSA infection. These findings are consistent with the hypothesis that exposure to organisms due to person-to-person transmission is a more important risk factor for MRSA infection,[26] while *P. aeruginosa* may depend more upon host susceptibility.[27 28]

Incorporating microbiology information into decision-making for pneumonia will require greater recognition and availability of this data as well as guidance in its interpretation. Some – but not all – of the newly proposed predictive models intended to replace HCAP incorporate MRSA colonization or infection histories;[29 30] only one includes history of gram-negative organism infection as an important factor.[31] Although the use of local prevalence and susceptibility data was recommended to enhance antibiotic decision-making for community-acquired pneumonia[3]

and has been recently emphasized by the IDSA updated guidelines for hospital-acquired pneumonia,[32] no clear guidance has been provided on how to access or interpret this information, and few clinicians are aware of local prevalence. Because of the varied performance of the newer prediction models, experts have called for healthcare systems to examine the microbiology of their own populations rather than rely upon data from other sites to determine appropriate treatment thresholds.[33 34] However, none of the currently proposed risk prediction models uses local prevalence, and most clinicians lack this information about their settings. Standardized,[35] setting-[36] and population-specific[37] antibiograms may improve use. Providing clinicians with patient- and setting-specific microbiology information at the point of care is well within the capabilities of an electronic health record and is an important step to helping clinicians better align their antimicrobial coverage decisions with actual risk.

Our metric, the coverage-to-culture ratio, helped us to identify differences in antibiotic decision-making across hospitals and patient groups, and could be useful for both research and policy to examine variation or track the impact of interventions. Differences in coverage-to-culture ratio reflect differences in either estimated risk of organisms or the threshold of risk at which providers decide to cover those organisms. We found substantially lower coverage-to-culture ratios in lower-complexity, rural hospitals compared to higher-complexity, urban hospitals. Whether this reflects differences in uptake of guidelines, concern for resistant organisms, or patient illness severity or complexity, and whether it represents overtreatment by urban providers or under-treatment by rural providers, requires further study. We did not examine the relationship between coverage and clinical outcomes, so the question remains: at which threshold of risk for resistant pneumonia *should* clinicians administer broad-spectrum antibiotics, and which factors should change this threshold? Future study is warranted to address this question.

Our study has limitations. We identified our population retrospectively using principal diagnosis codes that did not include clinical data such as radiographic findings or symptoms. Incomplete culturing practices and imperfect performance of microbiologic tests may have underestimated

the true prevalence of MRSA and PAER or contributed to some of the variation observed; additionally, since no gold standard exists for the diagnosis of pneumonia, misdiagnosed patients with positive cultures could represent colonization rather than infection. We did not examine MRSA surveillance swab data, a potentially useful factor for decision-making in MRSA pneumonia,[38] as the data were incomplete during the study period. As the intent of our study was to compare coverage to detection rather than to provide a comprehensive model for clinical use, we did not examine all of the previously proposed predictors of resistant organisms or empiric coverage, including antibiotic use, non-VA care history of hemodialysis, outpatient parenteral therapy, or antibiotic use.[11 10 30] Our study also did not address the reasons why MRSA and Pseudomonas prevalence were heterogeneous across facilities. Further investigation is needed to identify the drivers of inter-hospital differences in prevalence, which may include variation in antibiotic selection pressure or environmental factors. Evaluating models that incorporate all relevant factors is the subject of future work. However, our examination of accurate, granular clinical microbiology and coverage data from a national system revealed a larger number of positive cases across more settings than other studies, which increased our ability to measure variation and relationships between factors and independent pathogens.

The discordance between the factors associated with detection and those associated with coverage represents an important opportunity to improve practice. The substantial variation in antibiotic decision-making that we observed has implications for guideline recommendations, clinical prediction models, and antibiotic stewardship efforts. As we continue to develop ways to improve pneumonia care in the future, exploring the mechanisms of this variation and determining optimal risk thresholds at which to treat with broad-spectrum antibiotics will be crucial.

ACKNOWLEDGMENTS

Financial support. This work was supported by IDEAS Center 2.0 at VA Salt Lake City Health Care System (#150HX001240), a U.S. Department of Veterans Affairs, Health Services Research and Development (VA HSR&D) funded Center of Innovation. Drs. B. Jones and M. Jones are supported by Career Development Awards (#CDA 10-030 and () from the US VA HSR&D Service. The contents do not represent the views of the U.S. Department of Veterans Affairs or the U.S. Government.

Potential conflicts of interest. All authors report no conflicts of interest relevant to this article.

The authors thank Pat Nechodom PhD for administrative support and Kevin Nechodom PhD for guidance with data management.

Table 1. Predictors of MRSA detection and coverage.

Multivariable model is shown using 38,473 hospitalizations at 128 hospitals during the years 2009-2010. Bivariate models are available in the Appendix.

	Adjusted Probability of Detection (%)	Adjusted Probability of Coverage(%)	Coverage:Culture Ratio
Patient-level factors			
Age			
Less than 60	2.16 (1.84-2.51)	31.02 (30.05-32.08)	14.37 (12.35-16.92)
60 to 69	1.97 (1.71, 2.22)	31.44 (30.63-32.23)	15.93 (14.12-18.34)
70 to 79	1.84 (1.55-2.12)	29.35 (28.43-30.32)	15.95 (13.88-18.96)
80 or more	2.22 (1.95-2.51)	29.01 (28.28-29.79)	13.05 (11.61-14.88)
History of MRSA-positive Cultures			
No	1.56 (1.44-1.69)	29.39 (28.92-29.86)	18.25 (16.17-20.79)
Yes	7.91 (6.87-9.12)	42.17 (40.13-44.08)	5.33 (4.65-6.17)
Acute Care Exposures in last 90 days			
0-1 days	1.62 (1.46-1.78)	22.53 (22.01-23.01)	13.93 (12.66-15.47)
2 to 14 days	2.59 (2.28-2.94)	47.33 (46.37-48.40)	18.25 (16.17-20.79)
15 or more days	3.78 (3.05-4.49)	54.09 (52.07-55.94)	14.32 (12.06-17.78)
Long-term care Exposures in last 90 days			
None	2.00 (1.55-2.96)	28.80 (28.35-29.28)	14.44 (13.41-15.70)
1 to 28 days	2.20 (1.55-2.96)	43.49 (40.37-48.40)	19.74 (14.60-28.65)
29 or more days	2.85 (2.13-3.62)	59.40 (56.74-61.90)	20.83 (16.43-27.75)
Facility-level factors			
Rural			
No (105 facilities)	2.10 (1.94-2.27)	30.87 (30.38-31.36)	14.69 (13.60-15.90)
Yes (23 facilities)	1.68 (1.26-2.05)	23.40 (21.58-25.18)	13.91 (11.37-18.65)
Census Regions			
Northeast (25 facilities)	2.05 (1.72-2.45)	30.43 (29.26-31.68)	14.69 (13.60-15.90)
Midwest (36 facilities)	2.00 (1.68-2.20)	30.24 (29.26-31.68)	13.91 (11.37-18.65)
South (40 facilities)	1.98 (1.74-2.24)	30.17 (29.30-31.04)	15.08 (13.66-18.07)
West (27 facilities	2.27 (1.90-2.75)	29.91 (28.51-31.30)	13.17 (10.92-15.59)
Complexity Score			
1a (38 facilities)	2.06 (1.88-2.35)	34.66 (33.93-35.55)	16.83 (14.74-18.49)
1b (16 facilities)	2.15 (1.80-2.66)	34.57 (33.31-36.04)	16.09 (13.03-19.25)
1c (17 facilities)	2.06 (1.63-2.41)	32.04 (30.78-33.16)	15.58 (13.38-19.71)
2 (34 facilities)	1.94 (1.54-2.13)	25.14 (23.97-26.19)	12.92 (11.72-16.36)
3 (23 facilities)	2.08 (1.55-2.76)	10.62 (9.28-11.68)	5.11 (3.78-6.94)
Hospital prevalence of MRSA-positive cultures in pneumonia cases (%)			
0 to 1.4	1.57 (1.49-2.36)	31.35 (29.86-32.98)	19.96 (13.27-21.21)
1.5 to 2.4	1.72 (1.51-1.89)	30.30 (29.43-31.34)	17.62 (16.14-20.13)
2.5 to 3.4	2.29 (1.74-2.47)	30.33 (28.47-31.86)	13.27 (12.16-17.40)
3.5 to 4.4	3.50 (2.71-4.32)	28.37 (25.69-30.96)	8.10 (6.44-10.68)
4.5 or more	4.68 (3.11-5.65)	26.10 (21.71-29.81)	5.57 (4.40-8.29)

Table 2. Predictors of *P. aeruginosa* detection and coverage.

Multivariable model is shown using 38,473 hospitalizations at 128 hospitals during the years 2009-2010. Bivariate models are available in the Appendix.

	Adjusted Probability of Detection, % (CI)	Adjusted Probability of Coverage, %(CI)	Coverage:Culture Ratio (CI)
Patient-level factors			
Age			
Less than 60	1.98 (1.65-2.27)	33.01 (32.01-34.09)	16.71 (14.48-19.98)
60 to 69	2.27 (1.99-2.53)	34.21 (33.35-34.99)	15.02 (13.47-17.11)
70 to 79	2.57 (2.25-2.92)	32.66 (31.69-33.66)	12.71 (11.04-14.53)
80 or more	1.60 (1.39-1.85)	32.65 (31.90-33.44)	20.45 (17.71-23.53)
History of *PAER*-positive Cultures in past 2 years			
No	1.38 (1.26-1.51)	32.27 (31.79-32.76)	23.31 (21.30-25.62)
Yes	11.85 (10.46-13.30)	47.29 (45.29-49.32)	3.99 (3.57-4.53)
Acute Care Exposures in last 90 days			
0-1 days	1.83 (1.64-1.99)	24.88 (24.35-25.39)	13.62 (12.45-15.14)
2 to 14 days	2.48 (2.17-2.78)	52.14 (51.18-53.29)	21.04 (18.79-24.01)
15 or more days	2.72 (2.28-3.35)	59.17 (57.22-61.14)	21.72 (17.63-26.09)
Long-term care Exposures in last 90 days			
None	2.13 (1.99-2.29)	31.69 (31.22-32.17)	14.86 (13.81-15.97)
1 to 28 days	2.17 (1.49-2.93)	47.65 (44.35-50.84)	22.00 (16.14-31.98)
29 or more days	1.40 (0.95-1.94)	65.74 (62.81-68.49)	46.83 (33.89-69.17)
Facility-level factors			
Rural			
No (105 facilities)	2.12 (1.96-2.28)	33.62 (33.13-34.15)	15.87 (14.71-17.14)
Yes (23 facilities)	1.89 (1.46-2.35)	29.55 (27.73-31.49)	15.60 (12.48-20.51)
Census Regions			
Northeast (25 facilities)	2.36 (1.90-2.59)	30.87 (29.62-32.03)	13.10 (11.86-16.05)
Midwest (36 facilities)	1.96 (1.75-2.26)	34.74 (33.76-35.78)	17.73 (15.44-19.94)
South (40 facilities)	1.99 (1.76-2.28)	33.06 (32.12-33.99)	16.63 (14.51-18.71)
West (27 facilities)	2.27 (1.88-2.63)	33.25 (32.01-34.48)	14.62 (12.63-17.74)
Complexity Score			
1a (38 facilities)	2.12 (1.94-2.40)	36.05 (35.29-36.86)	16.98 (15.10-18.67)
1b (16 facilities)	2.03 (1.63-2.42)	37.61 (36.28-39.07)	18.57 (15.53-23.01)
1c (17 facilities)	2.12 (1.94-2.40)	33.79 (32.48-35.04)	15.97 (13.37-19.13)
2 (34 facilities)	2.07 (1.65-2.33)	30.84 (29.71-31.90)	14.93 (13.16-18.48)
3 (23 facilities)	2.04 (1.57-2.57)	18.39 (16.87-19.74)	9.04 (6.98-11.71)
Hospital prevalence of *PAER*-positive cultures in pneumonia cases (%)			
0 to 1.4	1.71 (1.60-2.32)	33.79 (32.49-35.46)	19.78 (14.52-21.21)
1.5 to 2.4	1.95 (1.57-2.57)	32.95 (32.07-33.77)	16.86 (15.21-18.70)
2.5 to 3.4	2.92 (2.19-3.05)	32.79 (30.88-34.49)	11.24 (10.65-15.07)
3.5 or more	2.70 (0.78-2.88)	36.25 (30.18-41.73)	13.45 (12.06-46.60)

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FIGURE LEGENDS.

Figure 1. Hospital variation in detection and coverage of MRSA and PAER.

Data are presented using 38,473 hospitalizations that occurred during 2009-2010.

Predicted risks of MRSA (A, B) and PAER (C, D) were estimated for each hospital from

the model represented in Table 1. Lines represent best-fit regression lines.

Figure 2. Relationship between individual predicted risk, detection, and coverage. Data are

presented using 38,473 hospitalizations that occurred during 2009-2010. X-axis represents

patients categorized by decile of predicted risk of positive cultures for MRSA (A, C) and

PAER (B, D) estimated from the model represented in Tables 1 & 2. Confidence intervals are

shown. Y-axis represents percent of those hospitalizations with detection of positive cultures

(A, B) and antibiotic coverage (C, D).

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