HHS Public Access

Author manuscript

Infect Control Hosp Epidemiol. Author manuscript; available in PMC 2016 January 01.

Published in final edited form as:

Infect Control Hosp Epidemiol. 2015 January ; 36(1): 54–64. doi:10.1017/ice.2014.11.

Evaluating State-Specific Antibiotic Resistance Measures Derived from Central Line-Associated Bloodstream Infections, National Healthcare Safety Network, 2011

Minn M. Soe, MD, MPH, **Jonathan R. Edwards, MStat**, **Dawn M. Sievert, PhD**, **Philip M. Ricks, PhD**, **Shelley S. Magill, MD, PhD**, and **Scott K. Fridkin, MD**

Division of Healthcare Quality Promotion, Centers for Disease Control and Prevention, 1600 Clifton Road, NE, Atlanta, Georgia

Abstract

DISCLOSURE—The findings and conclusions in this report are those of the authors and do not necessarily represent the official position of the Centers for Disease Control and Prevention or the Agency for Toxic Substances and Diseases Registry.

OBJECTIVE—Describe the impact of standardizing state-specific summary measures of antibiotic resistance that inform regional interventions to reduce transmission of resistant pathogens in healthcare settings.

DESIGN—Analysis of public health surveillance data.

METHODS—Central line–associated bloodstream infection (CLABSI) data from intensive care units (ICUs) of facilities reporting to the National Healthcare Safety Network in 2011 were analyzed. For CLABSI due to methicillin-resistant *Staphylococcus aureus* (MRSA), extended-spectrum cephalosporin (ESC)-nonsusceptible *Klebsiella* species, and carbapenem-nonsusceptible *Klebsiella* species, we computed 3 state-level summary measures of nonsusceptibility: crude percent nonsusceptible, model-based adjusted percent nonsusceptible, and crude infection incidence rate.

RESULTS—Overall, 1,791 facilities reported CLABSIs from ICU patients. Of 1,618 *S. aureus* CLABSIs with methicillin-susceptibility test results, 791 (48.9%) were due to MRSA. Of 756 *Klebsiella* CLABSIs with ESC-susceptibility test results, 209 (27.7%) were due to ESC-nonsusceptible *Klebsiella*, and among 661 *Klebsiella* CLABSI with carbapenem susceptibility test results, 70 (10.6%) were due to carbapenem-nonsusceptible *Klebsiella*. All 3 state-specific measures demonstrated variability in magnitude by state. Adjusted measures, with few exceptions, were not appreciably different from crude values for any phenotypes. When linking values of crude and adjusted percent nonsusceptible by state, a state's absolute rank shifted slightly for MRSA in 5 instances and only once each for ESC-nonsusceptible and carbapenem-nonsusceptible *Klebsiella* species. Infection incidence measures correlated strongly with both percent nonsusceptibility measures.

Address correspondence to Minn M. Soe, MD, MPH, MS A-24, CDC, 1600 Clifton Road, NE Atlanta, GA 30333 (msoe@cdc.gov).

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

CONCLUSIONS—Crude state-level summary measures, based on existing NHSN CLABSI data, may suffice to assess geographic variability in antibiotic resistance. As additional variables related to antibiotic resistance become available, risk-adjusted summary measures are preferable.

Healthcare-associated infections (HAIs) caused by antibiotic-resistant bacteria are a serious public health threat; they are associated with poorer outcomes and increased cost of care compared to HAIs due to antibiotic-susceptible organisms.[1–4] The nature and extent of antibiotic resistance varies geographically, but the problem is widely prevalent.[5–14] Geographic variability may reflect differences in antibiotic use, infection control, and pathogen characteristics of prevalent strains. Complicating the interpretation of regional antibiotic resistance assessments is the fact that key metrics and methods of measuring antibiotic resistance often vary between regions.[5,10–12]

In the United States, the Centers for Disease Control and Prevention (CDC) has published guidelines for preventing the transmission of antibiotic-resistant pathogens in healthcare settings.[15] Individual healthcare facilities typically are responsible for implementing interventions designed to prevent transmission of HAIs including resistant organisms.[16] However, recent reports have underscored the importance of using regional data to inform regional collaborative efforts to reduce HAIs or antibiotic-resistant infections.[17–20] CDC has published risk-adjusted, state-level summary statistics regarding HAI prevention success.[21] These reports have helped local hospital administrators and state public health authorities understand HAI prevention successes and areas in need of improvement.[22,23]

Similar state-level summary data on antibiotic resistance may help state or regional efforts to reduce infections due to antibiotic-resistant bacteria,[24] and these data can be useful to aid antibiotic stewardship efforts.[1] Previous attempts to evaluate regional differences in antibiotic resistance among HAIs in the United States have varying results and relied on administrative data,[10] convenience samples of facilities,[9,13,14] or large geographic areas aggregating data across many states.[12] Surveillance through CDC's National Healthcare Safety Network (NHSN) began in 2006 as a voluntary, hospital-based reporting system to monitor HAIs and to inform local and national prevention efforts. When reporting of CLABSI from acute care hospital intensive care units (ICUs) was required for participation in the Centers for Medicare and Medicaid Services'(CMS) Hospital Inpatient Quality Reporting (IQR) program, enrollment expanded to 4,100 healthcare facilities at the beginning of 2011.[25] However, antibiotic susceptibility data are not reported publically as part of this program. As an initial step in developing state/regional summary measures of antibiotic resistance, we analyzed central line-associated bloodstream infection (CLABSI) data, and we have described an approach to risk-adjusting a state-level metric for direct comparison between states and the impact of this risk adjustment. Ultimately, these methods can be applied to more representative data to make accurate regional estimates of antibiotic resistance.

METHODS

Surveillance Infrastructure

NHSN surveillance processes on CLABSI are described in detail on the CDC website (http://www.cdc.gov/nhsn/about.html). Pathogen and antimicrobial susceptibility data reported to NHSN are provided by the facility's designated clinical microbiology laboratory. Susceptibility test results must have been reported for a select group of pathogens and antimicrobials if testing was performed. Laboratories are expected to use current Clinical and Laboratory Standards Institute (CLSI) standards for antimicrobial susceptibility testing. Results for each of the selected pathogens were reported to NHSN as the category interpretation of "susceptible" (S), "intermediate" (I), "resistant" (R), or "not tested." We limited the analysis to ICUs reporting CLABSIs in 2011 because reporting from these locations was nearly complete in 2011 due to the CMS IQR program requirement.[25]

Selection of Antibiotic-Resistant Infections

For this analysis, 3 distinct antibiotic-resistant phenotypes were identified among ICU CLABSI reported to the NHSN: (1) methicillin-resistant *Staphylococcus aureus* (MRSA), defined as *S. aureus* reported as resistant to oxacillin, methicillin, or cefoxitin; (2) extended-spectrum cephalosporin (ESC)-nonsusceptible *Klebsiella* species, defined as *K. pneumoniae* or *K. oxytoca* reported as I or R to cefotaxime, ceftazidime, ceftriaxone, or cefepime; and (3) carbapenem-nonsusceptible *Klebsiella* species, defined as *K. pneumoniae* or *K. oxytoca* reported as I or R to imipenem, meropenem, or doripenem.

Statistical Analyses

Statistical analyses were conducted using SAS version 9.3 (SAS Institute, NC) and SAS callable SUDAAN version 11.0 (Research Triangle Institute, NC). Frequency distributions of selected healthcare facility characteristics were determined for ICU CLABSIs according to study isolates or not. To determine factors influencing variability in resistance metrics, associations between patient- or facility-level characteristics among ICU CLABSIs due to an antibiotic-resistant phenotype were compared to those without resistance using χ^2 or Fisher's exact tests as appropriate. A separate analysis was performed for each resistant phenotype.

Factors associated with an ICU CLABSI being attributed to an antibiotic-resistant phenotype were explored in multivariable regression models including patient-level characteristics (age, gender) because these might be plausible indicators of a biological association with antibiotic-resistant infections and facility-level percentage of isolates tested for antibiotic resistance. Other facility-level characteristics such as facility type, facility bed size, and medical school affiliation were evaluated in bivariate analyses but were not considered for multivariable modeling. These characteristics may be proxies for factors such as infection control practices, for which adjustment may not be appropriate in this setting, and therefore we did not include hospital bed size or teaching status into the modeling process. Specifically, adjustment would not be appropriate, as doing so would "discount" resistance metrics based on poor cross-transmission prevention efforts (if bed size or teaching status were proxy measures for such poor efforts) when trying to compare resistance metrics by

region, state, or facility. To develop models for each of the 3 phenotypes, multivariable logistic regression by the backward elimination method was employed. Because patient age was a continuous variable, different parameter categorizations were examined when obtaining the best fit model with the smallest AIC and −2 log likelihood value. Statistical significance was assessed at the 0.05 level, and all tests were 2-sided.

Calculation of State-Specific Summary Measures of Nonsusceptibility

The infection rate was calculated by dividing the total number of ICU CLABSIs for each antibiotic-resistant phenotype in each state by the pooled number of ICU central line days for each state. The crude percent nonsusceptible was calculated by dividing the total number of ICU CLABSIs for each antibiotic-resistant phenotype in each state by the total number of ICU CLABSI isolates of *S. aureus* or *Klebsiella* species tested for susceptibility to at least 1 of the antibiotics within the antibiotic-resistant phenotype definition.[26] For MRSA, the percent nonsusceptible is equivalent to the percent resistant because, by definition, there are no breakpoints for *S. aureus* for testing intermediate (I) to oxacillin or cefoxitin.

A third state summary metric, the adjusted percent non-susceptible, was calculated for direct comparison between states. Adjusted percent nonsusceptible for each phenotype was computed for states reporting antibiotic susceptibility test results from a minimum of 20 ICU CLABSI isolates of *S. aureus* or *Klebsiella* species to impose statistical precision. Among these states, state-specific point estimates of adjusted percent nonsusceptible were obtained as functions of predicted marginals by multivariable logistic regression using SAS-callable SUDAAN. Marginal prediction takes a model-based approach to computing standardized estimates and allows comparisons of predicted outcomes (percent nonsusceptible) between groups after controlling for differences in covariate distributions.[27] Therefore, standardized results from fitted logistic regression models can be compared like percentages (percent non-susceptible) across these states. To compute 95% confidence intervals of the metrics, variance estimates of unadjusted and adjusted percent nonsusceptible were obtained using the Taylor linearization method,[28] and variances of infection rates were estimated using the mid-*P* method.[26]

RESULTS

Reporting Facilities

During 2011, 22,561 CLABSIs were reported from 2,212 facilities (58.0% of the total facilities participating in NHSN CLABSI reporting); 1,145 facilities (51.8%) reported at least 1 *S. aureus* CLABSI, and 732 (33.1%) reported at least 1 *Klebsiella* CLABSI (Table 1).

Crude Distributions of Nonsusceptible Isolates by Facility and Patient Characteristics

Of 1,750 *S. aureus* CLABSIs reported from ICUs, methicillin susceptibility test results were available in 1,618 isolates, among which 791 (48.9%) were due to MRSA. Of 889 *Klebsiella* CLABSIs reported from ICUs, ESC susceptibility test results were available in 756 isolates, among which 209 (27.7%) were due to ESC-nonsusceptible *Klebsiella*, and carbapenem susceptibility test results were available in 661 isolates, of which 70 (10.6%) were due to

carbapenem-nonsusceptible *Klebsiella*. For all phenotypes, there was no significant difference in the percent nonsusceptible among males and females, while increasing age was significantly associated with decreasing susceptibility (Table 2). There was a significant difference in the percent nonsusceptible among the patient locations for all phenotypes, with adult locations having higher levels of resistance than neonatal and pediatric locations. However, differences between adult ICU and non-ICU locations, and between pediatric ICU and non-ICU locations, were in most cases small and not statistically significant (data not shown). Isolates from smaller hospitals and those without medical school affiliations were significantly more likely to be nonsusceptible than isolates from larger hospitals or hospitals with medical school affiliations (Table 2). Approximately 37% of *Staphylococcus aureus* isolates and 27% of *Klebsiella* species in medical school–affiliated hospitals came from infants. Similar proportions of study isolates in large hospitals (>200 beds) were obtained regarding infants.

Adjusted State-Specific Summary Measure of Non-susceptibility

Although the proportion of isolates tested for the relevant antibiotic susceptibility varied between facilities (and states), this variation was not significantly associated with the percent nonsusceptible and was dropped from the model-building process. The final regression models included age divided into 3 or 4 categories, depending on the resistant phenotype (Table 3). Controlling for age in these models, the adjusted percent non-susceptible of each resistant phenotype was calculated. The crude infection rate, crude percent nonsusceptible, and adjusted percent nonsusceptible values are plotted in Figure 1 (and the Appendix).

For MRSA, 24 states had sufficient data to calculate an adjusted measure. The adjusted percent nonsusceptible values differed only slightly from crude percent nonsusceptible values (Figure 1A), in all cases by fewer than 5%, and usually within 1%–2%. The variability of the state-specific crude percent nonsusceptible (range: 26%–64%) and adjusted percent nonsusceptible (range: 27%–66%) was large (Figure 2), with only a slight narrowing of the interquartile range in the adjusted measure compared to the crude measure (~19%–16%). In 5 instances (states 2, 13, 18, 27, and 35), a state's rank shifted relative to the position of other states based on the respective measure (Figure 3A).

For ESC-nonsusceptible *Klebsiella* spp., 11 states had sufficient data to calculate an adjusted measure. Compared to crude percent nonsusceptible measures, the adjusted percent nonsusceptible values differed appreciably in only 2 states: state 15 with a lower adjusted value by 7%, and state 3 with a lower adjusted value by 17% (Figure 1B); otherwise, differences were minor (0–4%). The variability of the state-specific measures of crude percent nonsusceptible (range: 20%–80%) and adjusted percent nonsusceptible (range: 21%–63%) was large (Figure 2), but the interquartile range in the adjusted measure was narrower (17%) compared with that in the crude measure (25%). In only 1 instance did the state's value shift ranking relative to the position of other states based on the respective measure (ie, only 1 line crossed other lines in state 36) (Figure 3B).

For carbapenem-nonsusceptible *Klebsiella* spp., 9 states had sufficient data to calculate an adjusted measure. The adjusted percent nonsusceptible values differed appreciably from the

crude percent nonsusceptible only in state 3, with a lower adjusted value by 10%; this state happened to be the same state with a large difference between adjusted and crude measures for ESC-nonsusceptible *Klebsiella* spp. (Figure 1C). Differences in all other states were minor (1%–4%). The variability of the state-specific measures of crude percent nonsusceptible (range: 2%–35%) and adjusted percent nonsusceptible (range: 3%–25.3%) was again large (Figure 2). There was essentially no difference in the size of the interquartile range between the adjusted measure and the crude measure (Figure 2). In only 1 instance (state 3) did the state's value shift in rank (Figure 3C).

DISCUSSION

Using susceptibility data for *S. aureus* and *Klebsiella* CLABSIs reported from ICUs to the NHSN in 2011, we have demonstrated that the extent of antibiotic resistance varies considerably between different states. Among the 3 state-level summary measures of nonsusceptibility that we explored, the most state-to-state variability was seen for the crude percent of isolates testing nonsusceptible. However, the age-adjusted state-summary resistance measure (ie, adjusted percent nonsusceptible), with few exceptions, did not appreciably change the state-specific values either in magnitude or relative to other states compared to the crude measure.

State-level summary antibiotic resistance measures have public health implications. Summary measures have the potential to inform empiric treatment recommendations where local representative data are not available. Second, utilizing a state-specific summary measure should allow providers and public health agencies at the state level to gain situational awareness around the magnitude of the resistance problem in their jurisdictions, more so than if they relied on data from a few selected healthcare facilities. This is especially true regarding resistant phenotypes of an urgent threat nature, such as carbapenem-resistant *Enterobacteriaceae* (CRE). The variability in resistance measures reflected in these data supports other studies' findings of regional variability in resistance related to HAIs. It also supports the notion that 1 single approach to reducing infections with antibiotic-resistant bacteria may not be appropriate for all locales.[10,12,29]

Unique to this analysis is our adjustment of a summary measure of antibiotic resistance through a modeling process, which allows for valid comparisons between state-specific measures. The direct standardization method that summarizes the measure across adjusting categories is commonly used for comparison between groups.[30] However, in states with small values for tested isolates, many categories have small cell sizes or empty cells, leading to unstable category-specific rates to calculate adjusted summary measures. In addition, some of the adjusting variables may be continuous in nature, and it may be difficult to optimize the categorization of these variables, making direct standardization less feasible. The model-based approach can circumvent these inherent limitations in the direct standardization method. Unfortunately, even with the model-based method, the lack of appreciable changes in the adjusted measure compared to the crude measure likely reflects an absence of adequate factors to incorporate into the modeling process (residual confounding). Such factors, those that are associated with resistance at the patient level but are not confounded by facility-specific infection control activity, are limited in our current

data set (eg, age, gender). Additional opportunities for improved adjustment of state summary resistance measures include incorporation of patient-level or ward-level severity measures or more likely hospital-wide severity of illness measures such as a case mix index.[31] Ideally, measures used to compare one state to another should be as risk adjusted as possible. For now, given the limited availability of adjustment factors that systematically influence the values, crude summary measures of resistance appear to be a reasonable approach to evaluating geographic differences in summary resistance patterns.

There were notable differences in the impact of adjustment on specific resistant phenotypes. For MRSA there was minor impact: although 5 states shifted their relative ranking to one another, the change in the value of the resistance measure was small. In contrast, for the most uncommon resistant phenotype, carbapenem-nonsusceptible *Klebsiella* spp., the state with the highest crude value had a substantial decrease (10%) in the percent nonsusceptible after age adjustment because, unlike other states, all ICU patients with *Klebsiella* CLABSIs in that state were 21 years and older, apparently inflating the crude percent nonsusceptible. Despite this, the overall variability in the percent nonsusceptible did not change with adjustment; the range and interquartile range essentially stayed the same. This finding suggests that the variability of antimicrobial resistance among the states is likely related to factors (other than age) such as cross-transmission between patients or facilities.

A notable observation that CLABSIs reported from large, academic hospitals have less-resistant pathogens than those from smaller non-academic hospitals could be partly explained by the presence of large proportions of infants represented in the patient population with CLABSIs in these large, academic hospitals, and these infants least often had resistant pathogens.

Overall, these data indicate that crude summary measures of resistance may suffice at present for assessing geographic variability. However, the generalizability of this finding is constrained by several study limitations. The isolates obtained from CLABSI do not represent hospital patients in general. Although we adjusted for state differences in age distributions, additional explanation for regional variability in antibiotic resistance could range from differences in laboratory testing standards and reporting bias to differences in patient mix. Data used in the analysis are for a small fraction of HAIs; CLABSIs account for <10% of HAIs occurring in acute care hospitals.[32] Therefore, the magnitudes of the proportions presented in this paper do not reflect the magnitude of resistance problem accurately; however, we believe they do reflect the impact of adjusting these summary measures accurately. It is possible that the variability of, and impact of adjustment on, resistance measures may differ for other HAI types, and this topic requires further analysis.

Additional limitations include the relatively small number of states represented in some comparisons. Although eliminating summary values comprised of fewer than 20 isolates helped to exclude outliers, it reduced the number of states included in each analysis. Similarly, although all facilities within a state reporting to NHSN could have contributed data to the state summary value, only those that did report a CLABSI are represented in the percent nonsusceptible measure. However, we did also construct crude resistance infection incidence measures that included exposure data (ie, cumulative central line days) from all

facilities reporting CLABSI data to NHSN and is more representative of facilities within the state. This measure has an added advantage of better reflecting infection burden compared to the percent nonsusceptible.[33]

Reducing the transmission of antibiotic-resistant bacteria in healthcare settings remains a high priority for patients, healthcare providers, and public health agencies. Although the relative value of the different tools in place for hospitals and local health departments to reduce these infections is still uncertain, state-specific summary measures (which ideally include all infection types) should be able to provide health authorities and healthcare providers within a region or state situational awareness of the magnitude of the resistance problem in their area. The improvement of such measures by identifying and applying factors such as laboratory practices and patient mix into a risk adjustment strategy and by incorporating test results from more clinical cultures is needed. However, producing state summary resistance measures and assessing their utility using existing national data will be a critical first step toward reducing the emergence and spread of antibiotic resistance in US hospitals.

Acknowledgments

We thank the NHSN participants for their ongoing efforts to monitor infections and improve patient safety, and our colleagues in the Division of Healthcare Quality Promotion, who tirelessly support this unique public health network.

Financial support. The NHSN surveillance system is supported by the Division of Healthcare Quality Promotion, Centers for Disease Control and Prevention.

References

1. U.S. Department of health and Human Services & Centers for Disease Control and Prevention. Antibiotic resistance threats in the United States, 2013. Centers for Disease Control and Prevention; website http://www.cdc.gov/drugresistance/threat-report-2013/index.html. Published 2013 [Accessed February 3, 2014]
2. Cosgrove SE. The relationship between antimicrobial resistance and patient outcomes: mortality, length of hospital stay, and health care costs. Clin Infect Dis. 2006; 42(Suppl 2):S82–S89. [PubMed: 16355321]
3. Maragakis LL, Perencevich EN, Cosgrove SE. Clinical and economic burden of antimicrobial resistance. Expert Rev Anti Infect Ther. 2008; 6:751–763. [PubMed: 18847410]
4. Shorr AF. Review of studies of the impact on Gram-negative bacterial resistance on outcomes in the intensive care unit. Crit Care Med. 2009; 37:1463–1469. [PubMed: 19242341]
5. European Centre for Disease Prevention and Control. Annual Report of the European Antimicrobial Resistance Surveillance Network (EARS-Net). Stockholm: European Centre for Disease Control and Prvention; 2012. Antimicrobial resistance surveillance in Europe 2011.
6. Molton JS, Tambyah PA, Ang BS, Ling ML, Fisher DA. The global spread of healthcare-associated multidrug-resistant bacteria: a perspective from Asia. Clin Infect Dis. 2013; 56:1310–1318. [PubMed: 23334810]
7. Master RN, Deane J, Opiela C, Sahm DF. Recent trends in resistance to cell envelope-active antibacterial agents among key bacterial pathogens. Ann N Y Acad Sci. 2013; 1277:1–7. [PubMed: 23346857]
8. Stelling JM, Travers K, Jones RN, Turner PJ, O'Brien TF, Levy SB. Integrating *Escherichia coli* antimicrobial susceptibility data from multiple surveillance programs. Emerg Infect Dis. 2005; 11:873–882. [PubMed: 15963282]

9. Sannes MR, Kuskowski MA, Johnson JR. Geographical distribution of antimicrobial resistance among *Escherichia coli* causing acute uncomplicated pyelonephritis in the United States. FEMS Immunol Med Microbiol. 2004; 42:213–218. [PubMed: 15364106]
10. Zilberberg MD, Shorr AF, Kollef MH. Growth and geographic variation in hospitalizations with resistant infections, United States, 2000–2005. Emerg Infect Dis. 2008; 14:1756–1758. [PubMed: 18976563]
11. Zhanel GG, DeCorby M, Adam H, et al. Prevalence of antimicrobial-resistant pathogens in Canadian hospitals: results of the Canadian Ward Surveillance Study (CANWARD 2008). Antimicrob Agents Chemother. 2010; 54:4684–4693. [PubMed: 20805395]
12. Kallen AJ, Hidron AI, Patel J, Srinivasan A. Multidrug resistance among Gram-negative pathogens that caused healthcare-associated infections reported to the National Healthcare Safety Network, 2006–2008. Infect Control Hosp Epidemiol. 2010; 31:528–531. [PubMed: 20334552]
13. Gales AC, Jones RN, Sader HS. Contemporary activity of colistin and polymyxin B against a worldwide collection of Gram-negative pathogens: results from the SENTRY Antimicrobial Surveillance Program (2006–09). J Antimicrob Chemother. 2011; 66:2070–2074. [PubMed: 21715434]
14. Diekema DJ, Pfaller MA, Schmitz FJ, et al. Survey of infections due to *Staphylococcus* species: frequency of occurrence and antimicrobial susceptibility of isolates collected in the United States, Canada, Latin America, Europe, and the Western Pacific region for the SENTRY Antimicrobial Surveillance Program, 1997–1999. Clin Infect Dis. 2001; 32(Suppl 2):S114–132. [PubMed: 11320452]
15. Centers for Disease Control and Prevention. CDC vital signs. Making health care safer. Centers for Disease Control and Prevention; website http://www.cdc.gov/vitalsigns/pdf/2011-03-vitalsigns.pdf [Accessed April 2014]
16. Siegel, JD.; Rhinehart, E.; Jackson, M.; Chiarello, L. Committee tHICPA. Management of multidrug-resistant organisms in healthcare settings. Centers for Disease Control and Prevention; 2006. website http://www.cdc.gov/hicpac/pdf/MDRO/MDROGuideline2006.pdf. Published 2006 [Accessed February 3, 2014]
17. Smith DL, Dushoff J, Perencevich EN, Harris AD, Levin SA. Persistent colonization and the spread of antibiotic resistance in nosocomial pathogens: Resistance is a regional problem. Proc Soc Natl Acad Sci USA. 2004; 101:5696–5696.
18. Schwaber MJ, Lev B, Israeli A, et al. Containment of a countrywide outbreak of carbapenem-resistant *Klebsiella pneumoniae* in Israeli Hospitals via a nationally implemented intervention. Clin Infect Dis. 2011; 52:848–855. [PubMed: 21317398]
19. Won SY, Munoz-Price LS, Lolans K, et al. Emergence and rapid regional spread of *Klebsiella pneumoniae* carbapenemase-producing Enterobacteriaceae. Clin Infect Dis. 2011; 53:532–540. [PubMed: 21865189]
20. Wisconsin Division of Public Health. Guidance for preventing transmission of carbapenem-resistant Enterobacteriaceae (CRE) in acute care and long-term care hospitals. Wisconsin Division of Public Health; website http://www.dhs.wisconsin.gov/publications/P0/p00532A.pdf. Published 2014 [Accessed February 3, 2014]
21. Centers for Disease Control and Prevention. National and state healthcare associated infections: Progress Report. Centers for Disease Control and Prevention; website http://www.cdc.gov/HAI/pdfs/progress-report/hai-progress-report.pdf. Published 2014 [Accessed April 2014]
22. Council of state and territorial epidemiologists. [Accessed August 2014] Placing central line-associated bloodstream infections (CLABSI) under nationwide surveillance through the National Healthcare Safety Network (NHSN). http://c.ymcdn.com/sites/www.cste.org/resource/resmgr/PS/12-ID-06FINAL.pdf
23. Virginia department of health's healthcare-associated infections (HAI) program. [Accessed August 2014] SYNERGY: combining efforts for HAI prevention. http://www.vdh.virginia.gov/Epidemiology/Surveillance/HAI/documents/pdf/VDH%20HAI%20NewsletterVol5Issue3FINAL.pdf
24. U.S. Government Accountability Office. Antibiotic Resistance: Data Gaps Will Remain Despite HHS Taking Steps to Improve Monitoring. GAO-11-406, 2011. Washington D.C: Government

Accountability Office; website http://www.gao.gov/assets/320-/319110.pdf. Published 2011 [Accessed February 3, 2014]

25. Centers for Disease Control and Prevention. Operational guidance for acute care hospitals to report central line-associated bloodstream infection (CLABSI) data to CDC's NHSN for the purpose of fulfilling CMS's hospital inpatient quality reporting (IQR) Requirements. Centers for Disease Control and Prevention; website http://www.cdc.gov/nhsn/PDFs/HPS-manual/Operational-Guidance-HPS-Flu-Vaccination-Sum-Acute-Care.pdf. Published 2012 [Accessed January 2014]
26. Rothman, KJ.; Boice, JDJ. Epidemiologic analysis with a programmable calculator. Bethesda, MD: National Institutes of Health; 1979. NIH Pub No. 79-1649
27. Graubard BI, Korn EL. Predictive margins with survey data. Biometrics. 1999; 55:652–659. [PubMed: 11318229]
28. Wolter, KM. Introduction to Variance Estimation. 2. New York, NY: Springer; 2007.
29. Tillotson GS, Draghi DC, Sahm DF, Tomfohrde KM, del Fabro T, Critchley IA. Susceptibility of *Staphylococcus aureus* isolated from skin and wound infections in the United States 2005–07: laboratory-based surveillance study. J Antimicrob Chemother. 2008; 62:109–115. [PubMed: 18397923]
30. Hennekens, CH.; Buring, JE.; Mayrent, SL. Epidemiology in Medicine. Boston, MA: Little, Brown and Co; 1987.
31. Kuster SP, Ruef C, Bollinger AK, et al. Correlation between case mix index and antibiotic use in hospitals. J Antimicrob Chemother. Oct.2008 62:837–842. [PubMed: 18617509]
32. Magill SS, Edwards JR, Bamberg W, et al. Multi-state point prevalence survey and national burden of healthcare-associated infections. N Engl J Med. 2014; 370:1198–1208. [PubMed: 24670166]
33. Schwaber MJ, De-Medina T, Carmeli Y. Epidemiological interpretation of antibiotic resistance studies—what are we missing? Nature Rev Microbiol. 2004; 2:979–983. [PubMed: 15550943]

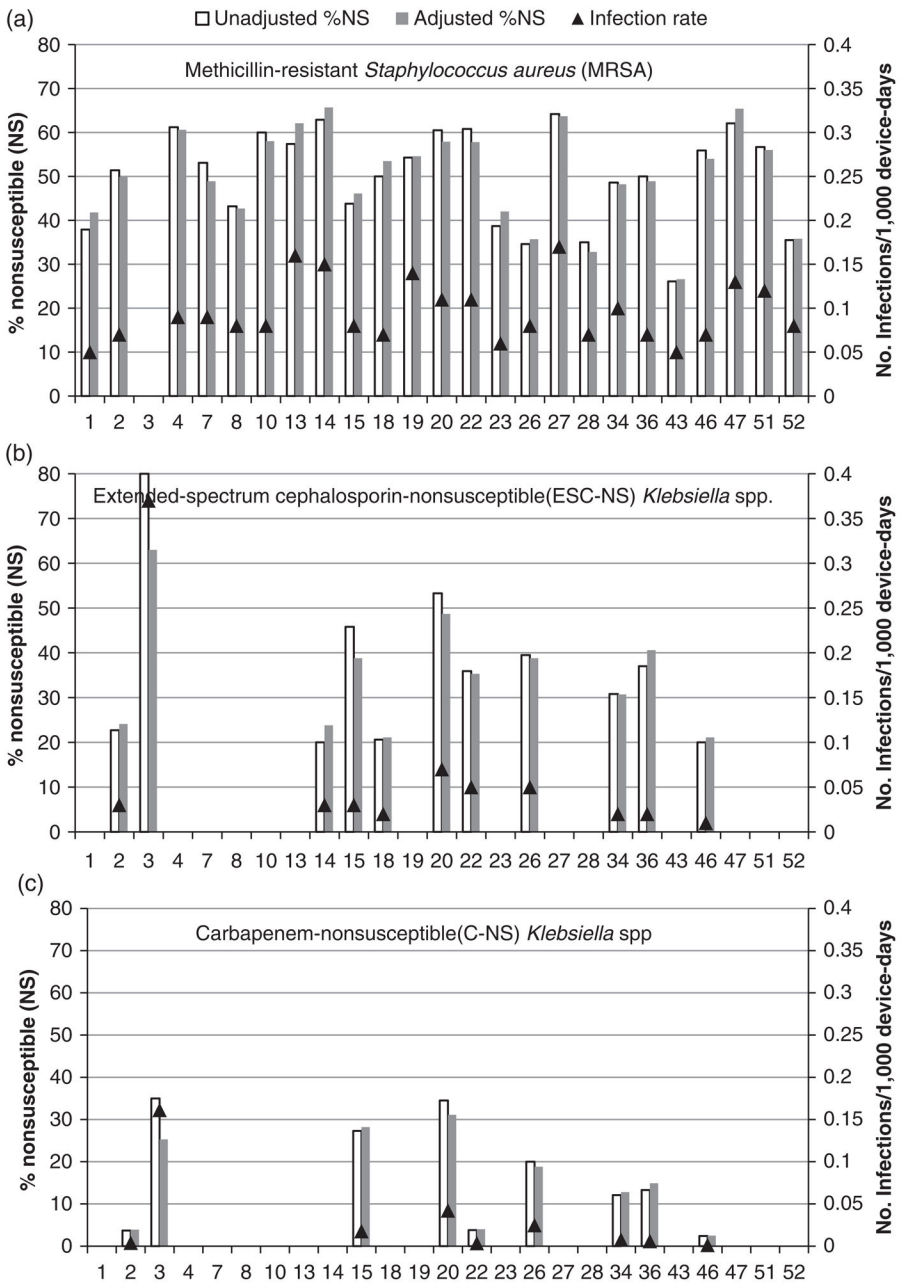

FIGURE 1.

State-specific rate and percentage of isolates with resistant phenotypes, reported as central line-associated bloodstream infections (CLEBSIs) from intensive care units, National Healthcare Safety Network, 2011. Triangle represents point estimate of rate per 1,000 device days, open bar represents crude proportion and grey bar represents adjusted proportion. Graph 1A represents methicillin-resistant *Staphylococcus aureus* (MRSA). Graph 1B represents extended-spectrum cephalosporin-nonsusceptible (ESC-NS) *Klebsiella* spp. Graph 1C represents carbapenem-nonsusceptible (C-NS) *Klebsiella* spp.

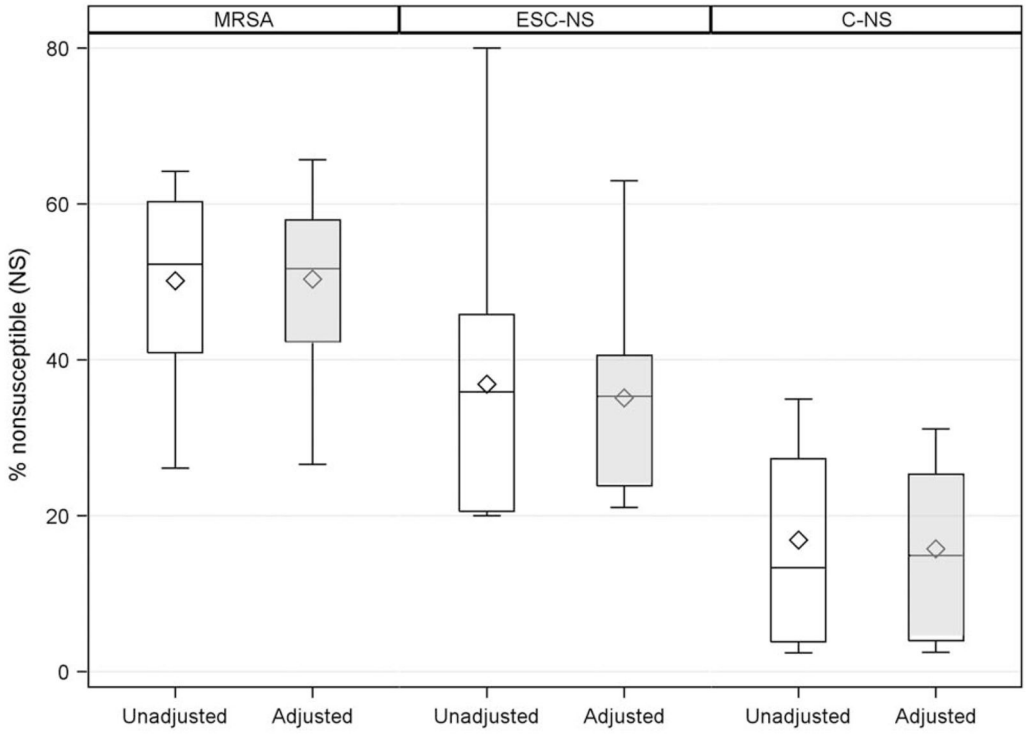

FIGURE 2.

Distributions of state-specific percentage of pathogenic central line-associated bloodstream infection (CLEBSI) isolates nonsusceptible to selected antibiotics in intensive care units, unadjusted (crude) vs. adjusted (model-based) values, National Healthcare Safety Network, 2011. MRSA, methicillin resistant *S. aureus*; ESC-NS, extended-spectrum cephalosporin-nonsusceptible *Klebsiella* spp.; C-NS, carbapenem-nonsusceptible *Klebsiella* spp. Horizontal lines represent maximum, minimum, 75th, 50th, and 25th percentile values. Diamond represents the mean value.

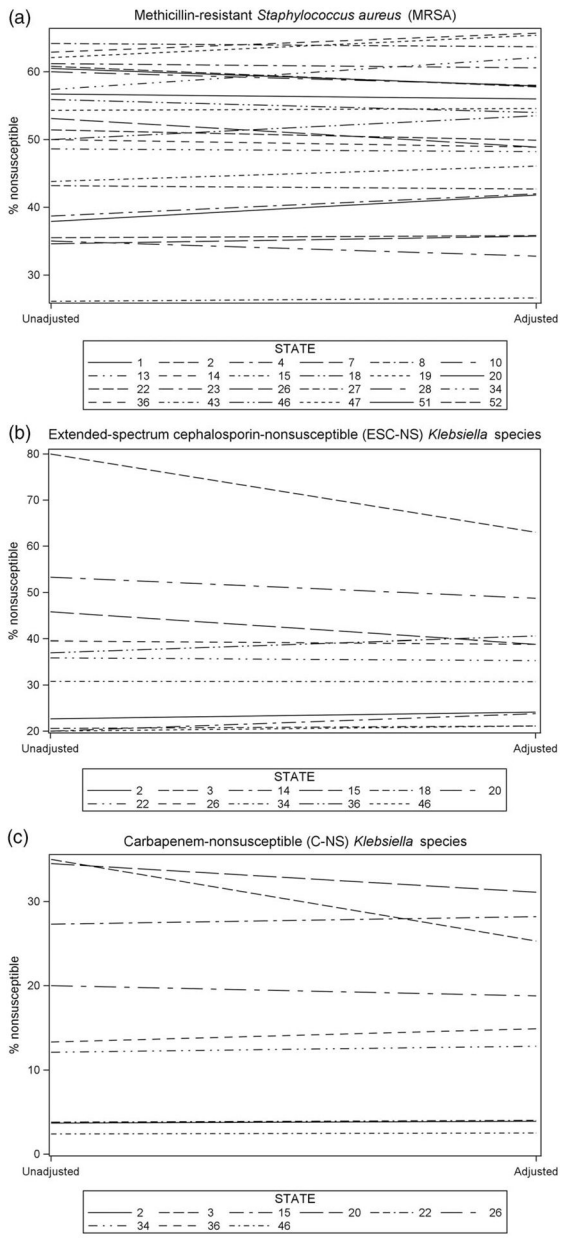

FIGURE 3.

Linked values of unadjusted (crude) and adjusted (model-based) state-specific percentage of isolates with selected resistance phenotype among central line-associated bloodstream infections (CLEBSIs) from intensive care units, by state, National Healthcare Safety Network, 2011. Graph 3A represents methicillin-resistant *Staphylococcus aureus* (MRSA). Graph 3B represents extended-spectrum cephalosporin-nonsusceptible (ESC-NS) *Klebsiella* spp. Graph 3C represents carbapenem-nonsusceptible (C-NS) *Klebsiella* spp.

TABLE 1

Characteristics of Hospitals Reporting Central Line-Associated Bloodstream Infections (CLABSIs) from Intensive Care Units to the National Healthcare Safety Network, 2011

	No. hospitals reporting ≥ 1 CLABSI					
	Reporting any isolate n = 2,212		Reporting study isolates n = 1,356		Reporting other isolatesn = 857	
Characteristics	**n**	**(%)**	**n**	**(%)**	**n**	**(%)**
Hospital type						
Children's	54	(2.4)	45	(3.3)	9	(1.1)
General	1,890	(85.4)	1124	(82.9)	766	(89.5)
Military	8	(0.4)	4	(0.3)	4	(0.5)
Veterans affairs	11	(0.5)	6	(0.4)	5	(0.6)
Long-term acute care	179	(8.1)	140	(10.3)	39	(4.6)
Other[a]	70	(3.2)	37	(2.7)	33	(3.9)
Facility size (no. beds)						
<100	412	(18.6)	233	(17.2)	179	(20.9)
100–199	571	(25.8)	280	(20.7)	291	(34.0)
200–299	477	(21.6)	259	(19.1)	218	(25.5)
300–399	297	(13.4)	200	(14.8)	97	(11.3)
400–499	199	(9.0)	149	(10.9)	50	(5.8)
500–599	104	(4.7)	91	(6.7)	13	(1.5)
600 +	152	(6.9)	144	(10.6)	8	(0.9)
Medical School Affiliation						
Affiliated	882	(39.9)	625	(46.1)	257	(30.0)
Not Affiliated	1,330	(60.1)	731	(53.9)	599	(70.0)
US Census regions[b]						
Northeast	428	(19.4)	273	(20.1)	155	(18.1)
Midwest	430	(19.4)	236	(17.4)	194	(22.7)
South	844	(38.2)	501	(36.9)	343	(40.1)
West	490	(22.2)	329	(24.3)	161	(18.8)
Other[c]	20	(0.9)	17	(1.3)	3	(0.4)

[a] Oncology hospitals, orthopedic hospitals, psychiatric hospitals, inpatient rehabilitation hospitals, surgical hospitals, women's hospitals, women's & children's hospitals, critical access hospitals.

[b] Northeast: Connecticut, Maine, Massachusetts, New Hampshire, New Jersey, New York, Pennsylvania, Rhode Island, and Vermont; Midwest: Illinois, Indiana, Iowa, Kansas, Michigan, Minnesota, Missouri, Nebraska, North Dakota, Ohio, South Dakota, and Wisconsin; South: Alabama, Arkansas, Delaware, District of Columbia, Florida, Georgia, Kentucky, Louisiana, Maryland, Mississippi, North Carolina, Oklahoma, South Carolina, Tennessee, Texas, Virginia, and West Virginia; West: Alaska, Arizona, California, Colorado, Hawaii, Idaho, Montana, Nevada, New Mexico, Oregon, Utah, Washington, and Wyoming.

[c] Armed Forces, Puerto Rico, and US Virgin Islands

Infect Control Hosp Epidemiol. Author manuscript; available in PMC 2016 January 01.

TABLE 2

Percent of Isolates Associated with Central Line-Associated Bloodstream Infections (CLABSIs) Reported from Intensive Care Units Testing Nonsusceptible to Select Antimicrobial Agents, by Patient and Facility Characteristics, National Healthcare Safety Network, 2011

	S. aureus			*Klebsiella* spp.					
	Methicillin resistant			Extended-spectrum cephalosporin-nonsusceptible			Carbapenem-nonsusceptible		
Characteristic	**No. Tested**	**%R**	**χ^2 *P***	**No. Tested**	**%NS**	**χ^2 *p***	**No. Tested**	**%NS**	**χ^2 *P***
Gender									
Male	957	(48.4)	0.62	430	(29.3)	0.24	373	(11.0)	0.70
Female	661	(49.6)		326	(25.5)		288	(10.1)	
Age group[a]									
<1	506	(32.2)	<0.01	186	(1.1)	<0.01	172	(0.6)	<0.01
1–20	62	(38.7)		44	(34.1)		36	(8.3)	
21–29	57	(63.2)		23	(43.5)		19	(5.3)	
30–44	125	(52.8)		50	(34.0)		45	(13.3)	
45–54	165	(55.8)		89	(37.1)		76	(9.2)	
55–64	245	(56.7)		118	(32.2)		102	(13.7)	
65–74	227	(56.8)		129	(35.7)		110	(14.5)	
75–84	173	(59.0)		85	(38.8)		73	(20.5)	
85 +	58	(69.0)		32	(46.9)		28	(25.0)	
Hospital size (beds)[a]									
<100	78	(56.4)	<0.01	28	(35.7)	<0.01	28	(3.6)	0.0002
100–199	164	(62.2)		70	(52.9)		63	(25.4)	
200–299	241	(52.3)		107	(29.0)		91	(11.0)	
300–399	282	(44.0)		124	(31.5)		118	(10.2)	
400–499	242	(43.4)		99	(26.3)		90	(15.6)	
500–599	175	(56.6)		88	(26.1)		69	(11.6)	
600 +	436	(43.8)		240	(17.9)		202	(4.5)	
Major medical school affiliation[a]									
Affiliated	1,165	(45.2)	<0.01	571	(25.6)	0.02	498	(9.0)	0.02
Not Affiliated	453	(58.5)		185	(34.1)		163	(15.3)	
Patient location[a]									

	S. aureus			*Klebsiella* spp.					
	Methicillin resistant			Extended-spectrum cephalosporin-nonsusceptible			Carbapenem-nonsusceptible		
Characteristic	**No. Tested**	**%R**	**χ^2 *P***	**No. Tested**	**%NS**	**χ^2 *p***	**No. Tested**	**%NS**	**χ^2 *P***
Adult Intensive Care	1058	(57.1)	<0.01	531	(36.2)	<0.01	457	(14.4)	<0.01
Neonatal/pediatric Intensive care	560	(33.4)		225	(7.6)		204	(2.0)	
Total	1,618	(48.9)		756	(27.7)		661	(10.6)	

NOTE. Methicillin resistance was defined as resistance to oxacillin, cefoxitin, or methicillin. Extended-spectrum cephalosporin-nonsusceptible was defined as *K. pneumoniae* or *K. oxytoca* testing intermediate (I) or resistant (R) to cefotaxime, ceftazidime, ceftriaxone or cefepime. Carbapenem-nonsusceptible was defined as *K. pneumoniae* or *K. oxytoca* reported as I or R to imipenem, meropenem, or doripenem. R, resistant; NS, nonsusceptible.

[a] χ^2 P <0.05, all phenotypes.

TABLE 3

Multivariable Analysis of Factors associated with Resistant Phenotypes among Isolates associated with Central Line-Associated Bloodstream Infections from Intensive Care Units, National Healthcare Safety Network, 2011

Phenotype, parameter [a]	Age, yrs	% nonsusceptible	Parameter estimate	Adjusted OR (95% CI)
Methicillin resistant *Staphylococcus aureus* (N = 1,618)				
Age group [b]	85 +	69.0	1.5	4.7 (2.6–8.4)
	30–84	56.5	1.0	2.7 (2.2–3.4)
	21–29	63.2	1.3	3.6 (2.0–6.4)
	1–20	38.7	0.3	1.3 (0.8–2.3)
	<1	32.2		Reference
Extended-spectrum cephalosporin- nonsusceptible *Klebsiella* spp. (N = 756)				
Age group [b]	65 +	38.2	4.0	56.9 (13.8–234.7)
	1–64	34.9	3.9	49.3 (12.0–202.2)
	<1	1.1		Reference
Carbapenem-nonsusceptible *Klebsiella* spp. (N = 661)				
Age group [b]	65 +	18.0	2.4	11.2 (3.9–32.0)
	21–65	11.6	1.9	6.7 (2.3–19.3)
	<21	1.9		Reference

NOTE. Methicillin resistance was defined as resistant to oxacillin, cefoxitin, or methicillin. Extended-spectrum cephalosporin-nonsusceptible was defined as *K. pneumoniae* or *K. oxytoca* testing intermediate (I) or resistant (R) to cefotaxime, ceftazidime, ceftriaxone or cefepime.

Carbapenem-nonsusceptible was defined as *K. pneumoniae* or *K. oxytoca* reported as I or R to imipenem, meropenem, or doripenem. OR, odds ratio; CI, confidence interval; N, number of isolates.

[a] Eligible parameters gender and facility-level percentage of isolates tested for antibiotic resistance, were not statistically significant and therefore dropped in the final models of all 3 phenotypes.

[b] This final model with specified age groups is the best fit model with the smallest AIC and −2 log likelihood value after different age parameter categorizations were examined including age as a continuous variable.

APPENDIX

State-Specific Rate and Percentage of Isolates with Select Resistant Phenotypes, reported as Central Line-Associated Bloodstream Infections from Intensive Care Units, National Healthcare Safety Network, 2011

				Klebsiella spp.					
	Staphylococcus aureus % MRSA			% Extended-spectrum cephalosporin-nonsusceptible			% Carbapenem-nonsusceptible		
State	Rate	Crude	Adjusted[a]	Rate	Crude	Adjusted[a]	Rate	Crude	Adjusted[a]
1	0.05(0.03,0.09)	37.9(22.4,56.4)	41.8(26.1,59.4)						
2	0.07(0.05,0.09)	51.4(41.9,60.8)	49.9(40.7,59.1)	0.03(0.02,0.04)	22.7(15.1,32.6)	24.1(16.3,34.1)	0(0.00,0.01)	3.7(1.2,10.8)	3.9(1.2,11.8)
3	0.07(0.02,0.19)	60.0(20.0,90.0)		0.37(0.22,0.59)	80.0(57.2,92.3)	63.0(45.8,77.5)	0.16(0.07,0.32)	35.0(17.6,57.5)	25.3(12.9,43.7)
4	0.09(0.06,0.13)	61.2(47.0,73.7)	60.6(47.2,72.6)	0(0.00,0.02)	10.0(1.4,46.8)				
7	0.09(0.05,0.14)	53.1(36.1,69.4)	48.9(33.6,64.3)	0.02(0.01,0.05)	22.2(8.6,46.5)		0.02(0.00,0.04)	23.1(7.6,52.2)	
8	0.08(0.05,0.12)	43.2(28.4,59.4)	42.7(29.5,57.1)	0.03(0.01,0.06)	31.6(14.9,54.9)		0.01(0.00,0.03)	10.5(2.6,33.8)	
10	0.08(0.05,0.13)	60.0(43.3,74.7)	58.0(42.2,72.4)	0.01(0.00,0.03)	15.8(5.2,39.2)		0(0.00,0.02)	5.6(0.8,30.8)	
13	0.16(0.10,0.22)	57.4(43.1,70.7)	62.1(48.0,74.4)	0.03(0.01,0.06)	33.3(14.6,59.5)		0.01(0.00,0.03)	7.1(1.0,37.2)	
14	0.15(0.10,0.23)	62.9(46.0,77.1)	65.7(47.9,79.9)	0.03(0.01,0.07)	20.0(7.7,42.8)	23.8(9.6,47.8)			
15	0.08(0.06,0.12)	43.8(32.2,56.0)	46.1(34.5,58.2)	0.03(0.02,0.06)	45.8(27.5,65.4)	38.8(24.1,55.9)	0.02(0.01,0.04)	27.3(12.8,49)	28.2(13.2,50.3)
18	0.07(0.05,0.09)	50.0(37.2,62.8)	53.5(40.3,66.2)	0.02(0.01,0.03)	20.6(10.1,37.4)	21.1(10.7,37.3)	0.01(0.00,0.03)	26.3(11.4,49.9)	
19	0.14(0.09,0.21)	54.3(37.9,69.8)	54.6(39.4,69.0)	0.01(0.00,0.05)	14.3(3.6,42.8)				
20	0.11(0.07,0.16)	60.5(45.3,73.8)	57.9(43.1,71.4)	0.07(0.04,0.11)	53.3(35.8,70.1)	48.7(34.1,63.5)	0.04(0.02,0.08)	34.5(19.6,53.1)	31.1(18.5,47.4)
22	0.11(0.08,0.15)	60.8(46.9,73.1)	57.8(44.1,70.5)	0.05(0.03,0.08)	35.9(22.5,51.9)	35.3(23.0,49.9)	0(0.00,0.02)	3.8(0.5,22.9)	4.0(0.6,23.2)
23	0.06(0.03,0.10)	38.7(23.5,56.6)	42.0(26.1,59.8)						
26	0.08(0.06,0.10)	34.6(26.9,43.3)	35.7(27.8,44.6)	0.05(0.04,0.08)	39.5(29.1,50.8)	38.8(29.4,49.1)	0.02(0.01,0.04)	20(12.2,31.0)	18.8(11.6,28.9)
27	0.17(0.13,0.23)	64.2(52.1,74.7)	63.7(51.1,74.7)	0.01(0.00,0.03)	10.5(2.6,33.8)		0(0.00,0.02)	5.9(0.8,32.1)	
28	0.07(0.04,0.12)	35.0(21.9,50.8)	32.8(21.1,47.1)	0.03(0.01,0.06)	55.6(25.1,82.4)				
34	0.10(0.08,0.13)	48.6(39.5,57.9)	48.2(39.4,57.1)	0.02(0.01,0.04)	30.8(18.4,46.8)	30.7(18.9,45.7)	0.01(0.00,0.02)	12.1(4.6,28.2)	12.8(5.0,29.1)
36	0.07(0.05,0.08)	50.0(41.6,58.4)	48.9(41.2,56.7)	0.02(0.01,0.03)	37.0(25.3,50.6)	40.6(28.1,54.3)	0.01(0.00,0.01)	13.3(6.1,26.7)	14.9(7.0,28.9)
43	0.05(0.02,0.11)	26.1(12.2,47.3)	26.6(12.6,47.5)						
46	0.07(0.05,0.09)	55.9(45.7,65.6)	54.0(44.0,63.7)	0.01(0.01,0.02)	20.0(11.1,33.4)	21.1(12.0,34.4)	0(0.00,0.01)	2.4(0.3,15.1)	2.5(0.4,15.9)
47	0.13(0.08,0.20)	62.1(43.6,77.6)	65.4(48.9,78.9)	0.01(0.00,0.05)	25.0(6.3,62.4)				
51	0.12(0.07,0.18)	56.7(38.8,72.9)	56.0(39.2,71.6)	0.01(0.00,0.03)	16.7(2.3,63.2)				

	Klebsiella spp.								
	Staphylococcus aureus % MRSA			% Extended-spectrum cephalosporin-nonsusceptible			% Carbapenem-nonsusceptible		
State	Rate	Crude	Adjusted[a]	Rate	Crude	Adjusted[a]	Rate	Crude	Adjusted[a]
52	0.08(0.04,0.13)	35.5(20.8,53.5)	35.8(21.7,53.0)	0.01(0.00,0.05)	14.3(3.6,42.8)				

Rate, No. of isolates with resistance phenotype per 1,000 central line days.

NOTE. Methicillin resistance was defined as resistant to oxacillin, cefoxitin, or methicillin. Extended-spectrum cephalosporin-nonsusceptible was defined as *K. pneumoniae* or *K. oxytoca* testing intermediate (I) or resistant (R) to cefotaxime, ceftazidime, ceftriaxone or cefepime. Carbapenem-nonsusceptible was defined as *K. pneumoniae* or *K. oxytoca* reported as I or R to imipenem, meropenem, or doripenem.

[a] Adjusted percent nonsusceptible was calculated for the states with a minimum of 20 isolates with antibiotic susceptibility test results reported.