



Original Contribution

The Changing Epidemiology of Methicillin-Resistant *Staphylococcus aureus* in the United States: A National Observational Study

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Methicillin-resistant *Staphylococcus aureus* (MRSA) can cause major illness and death and impose serious economic costs on patients and hospitals. Community-associated MRSA (CA-MRSA) is a growing problem in US hospitals, which are already dealing with high levels of hospital-associated MRSA (HA-MRSA), but little is known about how patient age and seasonal differences in the incidence of these 2 forms of MRSA affect the epidemic. By using national data on hospitalizations and antibiotic resistance, we estimated the magnitude and trends in annual *S. aureus* and MRSA hospitalization rates from 2005–2009 by patient age, infection type, and resistance phenotype (CA-MRSA vs. HA-MRSA). Although no statistically significant increase in the hospitalization rate was seen over the study period, the total number of infections increased. In 2009, there were an estimated 463,017 (95% confidence interval: 441,595, 484,439) MRSA-related hospitalizations at a rate of 11.74 (95% confidence interval: 11.20, 12.28) per 1,000 hospitalizations. We observed significant differences in infection type by age, with HA-MRSA-related hospitalizations being more common in older individuals. We also noted significant seasonality in incidence, particularly in children, with CA-MRSA peaking in the late summer and HA-MRSA peaking in the winter, which may be caused by seasonal shifts in antibiotic prescribing patterns.

age differences; community-acquired infection; cross infection; methicillin-resistant *Staphylococcus aureus*; seasonality

Abbreviations: CA-MRSA, community-associated methicillin-resistant *Staphylococcus aureus*; CI, confidence interval; HA-MRSA, hospital-associated methicillin-resistant *Staphylococcus aureus*; ICD-9, *International Classification of Diseases, Ninth Revision, Clinical Modification*; MRSA, methicillin-resistant *Staphylococcus aureus*; NIS, Nationwide Inpatient Sample; TSN, The Surveillance Network.

Infections caused by methicillin-resistant *Staphylococcus aureus* (MRSA) are a global phenomenon (1). Previous studies indicate that patients with MRSA infections of the bloodstream are more likely to be seriously ill, have longer hospital stays, face a higher risk of death (2), and incur significantly higher treatment costs than patients with methicillin-susceptible *S. aureus* infections of the bloodstream (3, 4). These findings are largely relevant to hospital-associated MRSA (HA-MRSA) infections. In recent years, the epidemiology of MRSA has changed from infections acquired primarily in health care settings to infections that are also acquired in the community (5).

Between 1999 and 2005, the estimated number of hospitalizations associated with MRSA infections in the United States more than doubled (6). This increase was attributable largely to skin and soft-tissue infections, which are most often caused by community-associated MRSA (CA-MRSA) (6, 7). CA-MRSA strains are genetically distinct from HA-MRSA strains and are thought to have evolved separately (5). The lack of any distinguishable fitness difference between the most common CA-MRSA subtypes (e.g., USA300) and similar nonresistant strains (8, 9) likely contributes to their wide distribution (5). This contrasts sharply with HA-MRSA clones, which have not spread widely

beyond hospitals because of the presumed growth and transmission costs associated with maintaining the chromosomal cassette that confers resistance (5).

Recent studies suggest that implementation of preventive interventions for HA-MRSA has reduced the incidence of MRSA central line-associated bloodstream infections in the United States (10) as well as the rates of invasive MRSA infections in 9 US metropolitan areas (11), but these studies were not national in scope. In addition, it is not clear how changes in the incidence of invasive MRSA infection have been associated with changes in the incidence of CA-MRSA hospitalization rates.

This paper aims to expand our understanding of MRSA epidemiology by estimating the incidence and patterns of HA-MRSA- and CA-MRSA-related hospitalizations in inpatients in the United States between 2005 and 2009. In addition, we explore the relationship between patient age and type of bacteria strain as well as the influence of seasonal variations. Although no seasonal relationship has been noted for *S. aureus* carriage (12), a recent review found several studies that noted a summer peak for CA-MRSA infections in the United States (13). These studies were limited in geographical scope and did not investigate seasonal patterns of HA-MRSA infection or how patient age affected seasonal patterns of MRSA infection.

MATERIALS AND METHODS

By using previously reported methods (6, 14), we computed national stratified estimates of *S. aureus*-related hospitalizations by combining national hospitalization data and surveillance data on drug susceptibility. Antimicrobial susceptibility data were obtained from The Surveillance Network (TSN) Database-USA (Focus Diagnostics, Inc., Herndon, Virginia), an electronic repository of susceptibility test results collected from more than 300 microbiology laboratories in the United States. TSN data have been used extensively to evaluate patterns and trends of antimicrobial drug resistance (6, 7, 14–19). Participating laboratories are geographically dispersed throughout the 9 US Census Bureau regions (16) and collect samples from patients treated in hospitals that are representative of the distribution of hospital bed sizes and patient population characteristics (i.e., age, sex, race) (15, 16). Isolates are tested on site as part of routine diagnostic testing for susceptibility to different antimicrobial agents by using standards established by the Clinical and Laboratory Standards Institute (Wayne, Pennsylvania) and approved by the US Food and Drug Administration (Silver Spring, Maryland). Results are filtered to remove repeat isolates and to identify microbiologically atypical results for confirmation or verification before being included.

Our data comprised *S. aureus* isolates that were collected from inpatient areas between January 2005 and December 2008 and that were tested for susceptibility to oxacillin (a proxy for all β -lactam antimicrobial drugs including methicillin). Isolates classified as “resistant” according to the Clinical and Laboratory Standards Institute breakpoint criteria were considered to be MRSA (<0.01% had intermediate resistance and were conservatively classified as “susceptible”). Because

CA-MRSA isolates are generally susceptible to more antimicrobial agents (5, 20), we defined CA-MRSA isolates by using methods similar to those of prior studies (7, 21). Briefly, genotypic analysis of phenotypically defined CA-MRSA strains has found that the number of antimicrobial drugs to which an isolate is susceptible is a reliable predictor of the genotype (20). MRSA isolates that were tested against ciprofloxacin or clindamycin and at least 4 other drugs and found to be resistant to ciprofloxacin or clindamycin and at least 1 other drug were classified as HA-MRSA. Isolates resistant to oxacillin only or at most 1 other drug were classified as CA-MRSA. Other drugs tested were gentamicin, tetracycline, sulfamethoxazole/trimethoprim, erythromycin, and vancomycin. Isolates were stratified by infection site (blood, lower respiratory tract, and “other”) and patient age (0–19, 20–64, and ≥ 65 years).

Hospitalization incidence estimates for *S. aureus* infection for the years 2005–2009 were derived from the Nationwide Inpatient Sample (NIS), Healthcare Cost and Utilization Project, Agency for Healthcare Research and Quality (Rockville, Maryland). The NIS contains data on approximately 8 million hospital stays annually from about 1,000 hospitals, approximating a 20% stratified sample of US community hospitals, and includes all nonfederal, short-term, general, and specialty hospitals, such as obstetrics-gynecology, ear-nose-throat, orthopedic, and pediatric institutions. The NIS includes public hospitals and academic medical centers but excludes long- and short-term acute rehabilitation facilities, psychiatric hospitals, and alcohol and chemical dependency treatment facilities. NIS data are standardized across years, and each discharge record contains up to 15 discharge diagnosis codes as established by the *International Classification of Diseases, Ninth Revision, Clinical Modification* (ICD-9). Each record is weighted on the basis of the probability of sample selection and is adjusted for nonresponse, which allows for an estimate of the total number of hospitalizations in the United States. All records containing *S. aureus* infection codes 038.11, 482.41, and 041.11 were included. Records that contained multiple *S. aureus*-related diagnosis codes were counted only once, with preferential inclusion of the first infection listed. In October 2008, new MRSA-specific codes 038.12, 482.42, and 041.12 were added for each infection type. Because adoption of new codes lags behind their introduction, we aggregated all *S. aureus*-related discharges whether or not they were coded as MRSA (e.g., we counted all infections coded 038.11 and 038.12 as *S. aureus* septicemias) for 2008.

The number of MRSA-related hospitalizations for 2005 through 2008 was estimated by multiplying the number of *S. aureus*-related hospitalizations by the estimated percentage of *S. aureus* isolates that were resistant for the years that they overlapped. Results were stratified by patient age and infection type; that is, we matched the culture source (e.g., blood, sputum, etc.) to the infection type (e.g., sepsis, pneumonia) for each age group. For 2009, we estimated the incidence of MRSA-related hospitalizations by using data from the NIS database only. Hospitalization rates were calculated as the number of MRSA-related hospitalizations divided by the total number of hospitalizations stratified by

age. Estimates were calculated for the full year as well as for each month. Relative standard errors for incidence of *S. aureus*-related hospitalizations in the NIS database were calculated in STATA, version 10, software (StataCorp LP, College Station, Texas) as detailed by Houchens and Elixhauser (22). Confidence intervals for TSN data were calculated by using the Wilson score method and incorporating continuity correction, as detailed by Newcombe (23). The variance of MRSA incidence was estimated by using the method described by Barnett (24) and Goodman (25). Significance of differences between years was assessed by using Student's *t* tests. Analysis of seasonal time trends was done by using a seasonal-trend decomposition method based on a locally weighted regression scatterplot smoother, which robustly detects both trends and seasonal variations (26). The seasonal-trend decomposition method uses a sequence of smoothing fits on localized subsets of data to generate a seasonal component, a trend component, and a remainder. We ran our analysis over the entire range of data so the seasonal component is an annually repeating pattern of the mean fitted seasonal change for each month. All seasonal analysis was performed using R statistical software (R Foundation for Statistical Computing, Vienna, Austria).

RESULTS

In 2009, there were an estimated 39,434,956 (95% confidence interval (CI): 37,810,324, 41,059,588) hospitalizations in the United States, of which 697,248 (95% CI: 633,338, 761,159) were *S. aureus* related, for a rate of 17.68 (95% CI: 16.06, 19.30) per 1,000 hospitalizations. Though this is an increase of 1.37 *S. aureus*-related hospitalizations per 1,000 hospitalizations since 2005 when the rate was 16.31 (95% CI: 15.52, 17.10), this change is not statistically significant ($P = 0.22$).

Though the total number of MRSA-related hospitalizations increased by ~30,000 between 2005 and 2008 ($P = 0.01$), the estimated rate of MRSA-related hospitalizations did not change significantly ($P = 0.45$), and the proportion of HA-MRSA (55%) and CA-MRSA (45%) phenotypes remained approximately constant (Figure 1). We calculated the rate of MRSA-related hospitalizations during this period by multiplying the percentage of resistant *S. aureus* isolates by the total number of *S. aureus*-related hospitalizations. In 2009, using the new MRSA-specific diagnosis code added in 2008, we estimated that there were 463,017 (95% CI: 441,595, 484,439) MRSA-related hospitalizations, or a rate of 11.74 MRSA infections (95% CI: 11.20, 12.28) per 1,000 hospitalizations.

Despite an increase in 2006 ($P = 0.05$), the estimated hospitalization rate for MRSA-related bloodstream infections in 2008 remained statistically unchanged from 2005 as did the proportion of each phenotype: Of all MRSA-related bloodstream infections, ~64% were caused by HA-MRSA and ~36% were caused by CA-MRSA (Figure 2). The estimated rate of 1.59 (95% CI: 1.50, 1.68) hospitalizations for MRSA-related bloodstream infections per 1,000 hospitalizations in 2009 was slightly higher than the estimated rate of 1.47 (95% CI: 1.38, 1.55) hospitalizations for MRSA-related bloodstream infections per 1,000 hospitalizations in

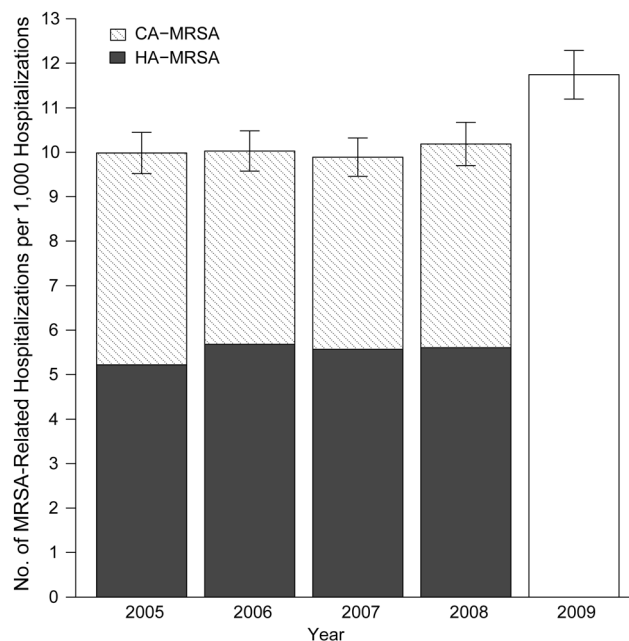


Figure 1. Estimated MRSA-related hospitalization rates, United States, 2005–2009. Estimated rates of MRSA-related discharges with a hospital-associated (dark) and a community-associated (hatched) phenotype. The rate of MRSA-related hospitalizations from 2005 to 2008 was calculated by multiplying the percentage of resistant *Staphylococcus aureus* isolates from The Surveillance Network Database-USA (Focus Diagnostics, Herndon, Virginia) by the total number of *S. aureus*-related hospitalizations from the Nationwide Inpatient Sample, Healthcare Cost and Utilization Project, Agency for Healthcare Research and Quality. Data in 2009 (white bar) were estimated directly from the Nationwide Inpatient Sample. Error bars show the 95% confidence intervals for total MRSA-related hospitalizations. CA-MRSA, community-associated methicillin-resistant *S. aureus*; HA-MRSA, hospital-associated methicillin-resistant *S. aureus*; MRSA, methicillin-resistant *S. aureus*.

2008. The hospitalization rate for MRSA-related pneumonia, which consisted of ~74% hospital-associated phenotypes and ~26% community-associated phenotypes, also remained largely unchanged ($P = 0.16$) over this period, though the estimated rate of 1.81 (95% CI: 1.70, 1.91) MRSA-related pneumonia hospitalizations per 1,000 hospitalizations in 2009 was slightly higher than the estimated rate of 1.52 (95% CI: 1.41, 1.62) MRSA-related pneumonia hospitalizations per 1,000 hospitalizations in 2008. “Other” (not bloodstream or upper respiratory tract) MRSA-related hospitalizations, however, increased from a rate of 6.61 (95% CI: 6.26, 6.97) per 1,000 hospitalizations in 2005 to a rate of 7.16 (95% CI: 6.78, 7.53) per 1,000 hospitalizations in 2008 ($P = 0.01$). The proportion of phenotypes also changed: The percentage of hospitalizations for infection with a hospital-associated phenotype increased from ~44% in 2005 to ~49% in 2008 while the percentage of hospitalizations for infection with a community-associated phenotype fell from ~56% in 2005 to ~51% in 2008 ($P < 0.01$).

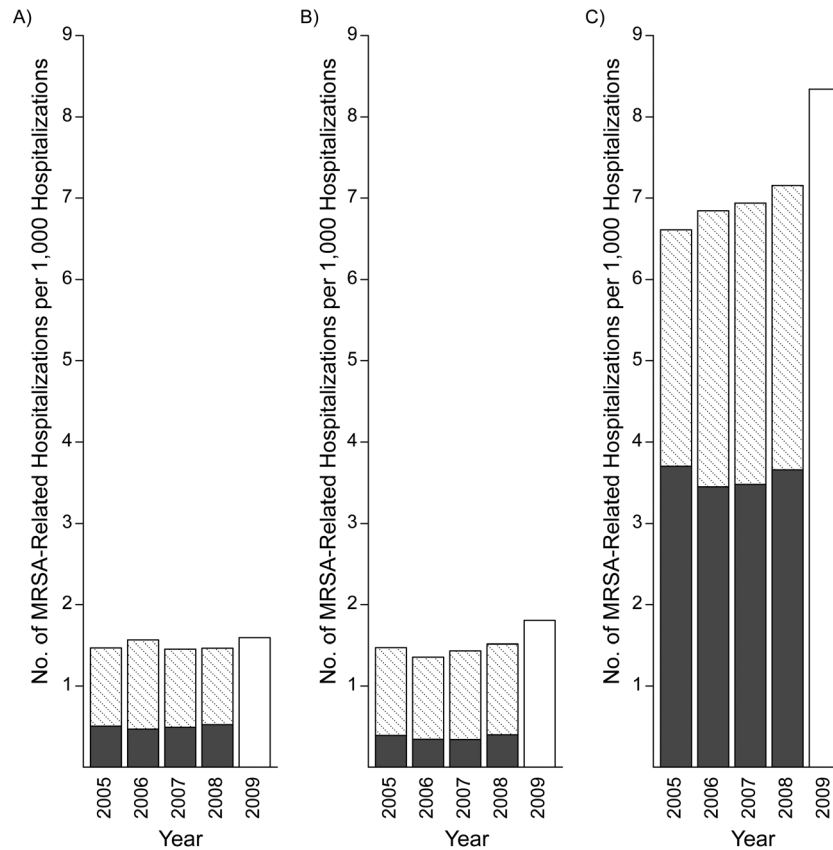


Figure 2. Estimated MRSA-related hospitalization rates, United States, 2005–2009, by source of infection. Estimated rates of MRSA-related discharges for A) blood infections, B) pneumonia infections, and C) other infections, with a hospital-associated (dark) and a community-associated (hatched) phenotype. The rate of MRSA-related hospitalizations from 2005 to 2008 was calculated by multiplying the percentage of resistant *Staphylococcus aureus* isolates from The Surveillance Network Database-USA (Focus Diagnostics, Herndon, Virginia) by the total number of *S. aureus*-related hospitalizations from the Nationwide Inpatient Sample, Healthcare Cost and Utilization Project, Agency for Healthcare Research and Quality, stratified by source. Data in 2009 (white bar) were estimated directly from the Nationwide Inpatient Sample. MRSA, methicillin-resistant *Staphylococcus aureus*.

Additionally, data from 2009 suggested an even higher rate of “other” MRSA-related hospitalizations, at 8.34 (95% CI, 7.92, 8.76) per 1,000 hospitalizations.

The most frequent primary diagnoses associated with “other” *S. aureus*-related infections were carbuncles, furuncles, cellulitis, and abscesses (ICD-9 codes 680–682), which were the primary diagnoses listed in 30% of “other” *S. aureus*-related infections in 2009. The next most frequent primary diagnosis code was for infections from an implanted device or graft (ICD-9 code 996) at 7%, followed by postoperative infections (ICD-9 code 998.59) at 6%, diabetes mellitus (ICD-9 code 250) at 5%, and osteomyelitis (ICD-9 code 730) at 3%.

The distribution of HA-MRSA and CA-MRSA hospitalizations was not constant across age groups. In 2008, “other” *S. aureus*-related infections were more likely to be caused by CA-MRSA in younger patients, with 74% and 55% of infections estimated to be caused by CA-MRSA in patients aged 0–19 years and 20–64 years, respectively, whereas only 37% of infections were caused by CA-MRSA

in patients over age 65 years (Figure 3). Distribution of MRSA-related bloodstream infections followed a similar pattern with 61%, 42%, and 27% of infections in 2008 being caused by CA-MRSA in patients aged 0–19, 20–64, and ≥ 65 years, respectively. However, MRSA-related pneumonia infections were more likely to be caused by HA-MRSA in all patients, with 68%, 69%, and 79% of infections being caused by HA-MRSA in patients aged 0–19, 20–64, and ≥ 65 years, respectively. Estimates of the MRSA-related hospitalization rate in 2009 were approximately the same as in prior years for younger patients but were higher for older patients. This is most pronounced in MRSA-related pneumonia hospitalizations for patients aged 20–64 years, which were $\sim 28\%$ higher, and for “other” MRSA-related infections, which were $\sim 18\%$ and $\sim 25\%$ higher for patients aged 20–64 and ≥ 65 years, respectively.

Analysis of seasonal patterns of MRSA-related hospitalizations found that the frequency of CA-MRSA isolates among all MRSA isolates peaked in the summer (Figure 4), changing by more than 3 percentage points

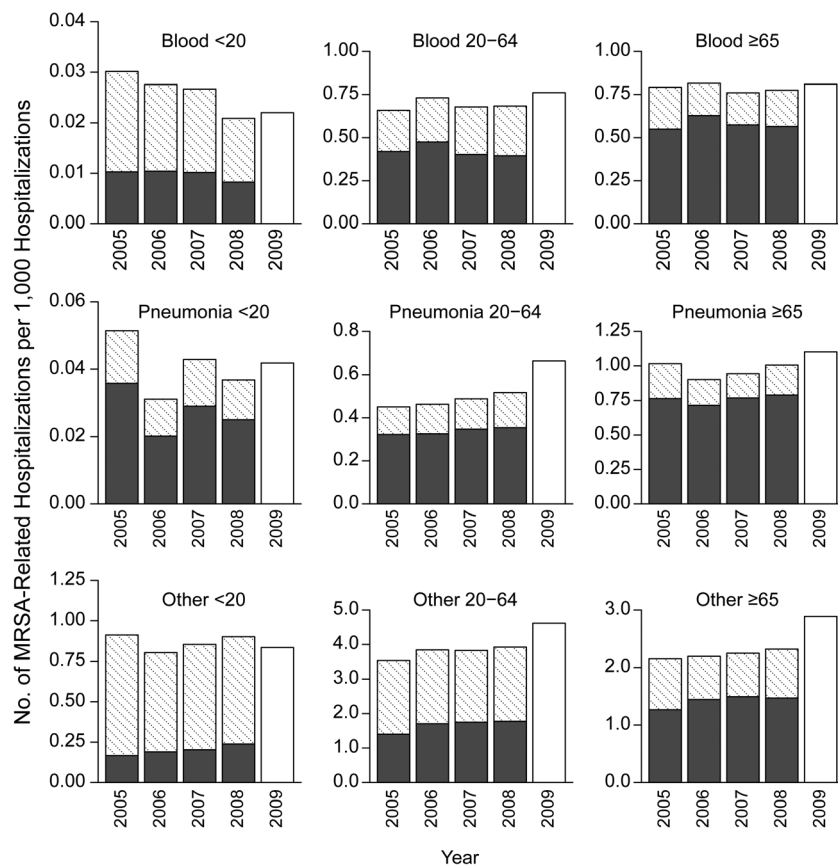


Figure 3. Estimated MRSA-related hospitalization rates, United States, 2005–2008, by source of infection and patient age. Estimated rates of MRSA-related discharges by age (<20, 20–64, and ≥65 years) with a hospital-associated (dark) and a community-associated (hatched) phenotype for blood infections (top row), pneumonia infections (middle row), and other infections (bottom row). The rate of MRSA-related hospitalizations from 2005 to 2008 was calculated by multiplying the percentage of resistant *Staphylococcus aureus* isolates from The Surveillance Network Database-USA (Focus Diagnostics, Herndon, Virginia) by the total number of *S. aureus*-related hospitalizations from the Nationwide Inpatient Sample, Healthcare Cost and Utilization Project, Agency for Healthcare Research and Quality. Data in 2009 (white bar) were estimated directly from the Nationwide Inpatient Sample. Note that the y-axis varies by plot. MRSA, methicillin-resistant *S. aureus*.

between summer and winter. Similar patterns were seen in hospitalizations for different types of infection. “Other” *S. aureus*-related hospitalizations significantly increased in the summer months, peaking in August at a hospitalization rate that was more than 2 hospitalizations per 1,000 higher than the rate in February. In contrast, *S. aureus*-related pneumonia hospitalizations peaked in the winter, with an increase of more than 1.15 hospitalizations per 1,000 hospitalizations for February compared with August. Comparatively, *S. aureus*-related septicemia has a limited seasonal pattern, with a difference of only 0.29 hospitalizations per 1,000 from a low in February to a high in September. The observed seasonal patterns also differed vastly with patient age. MRSA-related pneumonia hospitalizations were primarily seasonal in older individuals and only weakly seasonal for younger individuals. “Other” MRSA-related hospitalizations, however, had only a limited seasonal pattern for older individuals but were significantly seasonal for younger individuals (Figure 5).

DISCUSSION

During the past decade, the epidemiology of MRSA has been altered by the emergence of community-associated strains of MRSA. Since 1999, the number of MRSA-associated hospitalizations has more than doubled (6), driven primarily by skin and soft-tissue infections caused by CA-MRSA (7). However, between 2005 and 2008 the rate of growth in MRSA-related hospitalizations slowed considerably and remained static for hospitalizations with MRSA-related bloodstream infections. Though not directly comparable, estimated MRSA-related hospitalizations in 2009, for which MRSA ICD-9 codes were available, were higher than in prior years, particularly for MRSA-related infections other than pneumonia and septicemia, suggesting that prior analyses (6, 14) may have underestimated the extent of the problem; however, this does not significantly affect the estimated trends.

The stability of the rate of MRSA-related hospitalizations for pneumonia and septicemia differs from recent national

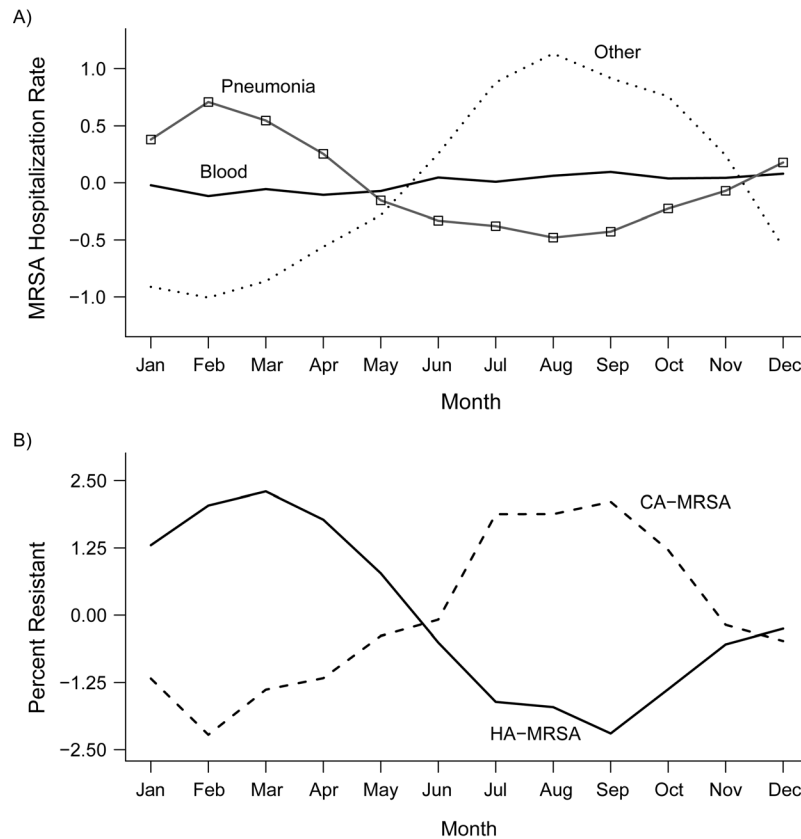


Figure 4. Seasonality of *Staphylococcus aureus* infection, United States, 2005–2008. A) Seasonal patterns of *S. aureus* infection rates were calculated by using a seasonal-trend decomposition method based on a locally weighted regression scatterplot smoother from the Nationwide Inpatient Sample, Healthcare Cost and Utilization Project, Agency for Healthcare Research and Quality, by source for the years 2005–2008. B) The seasonal percentage change in isolates that have the hospital-associated methicillin-resistant *S. aureus* and community-associated methicillin-resistant *S. aureus* phenotypes from The Surveillance Network Database-USA (Focus Diagnostics, Herndon, Virginia) was calculated by using the seasonal-trend decomposition method based on loess for the years 2005–2008. CA-MRSA, community-associated methicillin-resistant *S. aureus*; HA-MRSA, hospital-associated methicillin-resistant *S. aureus*; MRSA, methicillin-resistant *S. aureus*.

reports from the United States showing decreasing rates of MRSA central line-associated bloodstream infections in intensive care units (10), as well as decreases in the rate of invasive MRSA infections (11). This difference may reflect the broader nature of our data, which encompass both intensive care unit and non-intensive care unit patients; the latter make up the majority of patients and thus the majority of central line-associated bloodstream infections (27). In addition, a prior report (11) on invasive infections covered only approximately 15 million people. The greater geographical representation of our study suggests that geographic variability may play a role in these differing results—a matter that deserves more study.

By using a phenotypic rule, we examined trends in the occurrence of CA-MRSA and HA-MRSA phenotypes. Similar to the rate data, the proportion of hospitalizations for MRSA-related bloodstream infections and MRSA-related pneumonia that were caused by community-associated and hospital-associated phenotypes remained largely constant. However, the proportion of “other” MRSA-related hospitalizations that were resistant to multiple antibiotics, which

was our assumed hospital-associated phenotype, actually increased. This may reflect changes in the underlying resistance phenotype of CA-MRSA, for which increased clindamycin and quinolone resistance has been reported (28). However, an analysis of changes in resistance to clindamycin and ciprofloxacin in methicillin-susceptible *S. aureus* isolates found that both increased by only ~2% over the study period (Web Figure 1, available at <http://aje.oxfordjournals.org/>). In addition, we did not see any changes in the proportion of CA-MRSA in blood or pneumonia infections, suggesting that the reliability of our phenotypic rule did not change significantly over the course of the survey.

Our results show a significant reduction in the growth rate of both *S. aureus*- and MRSA-related hospitalizations, which contrasts sharply with prior years, when *S. aureus*-related hospitalizations increased by approximately 1.17 per 1,000 hospitalizations per annum and MRSA-related hospitalizations more than doubled (6). This is true even when accounting for higher estimates for 2009. Our results also suggest that the epidemiology of CA-MRSA is markedly

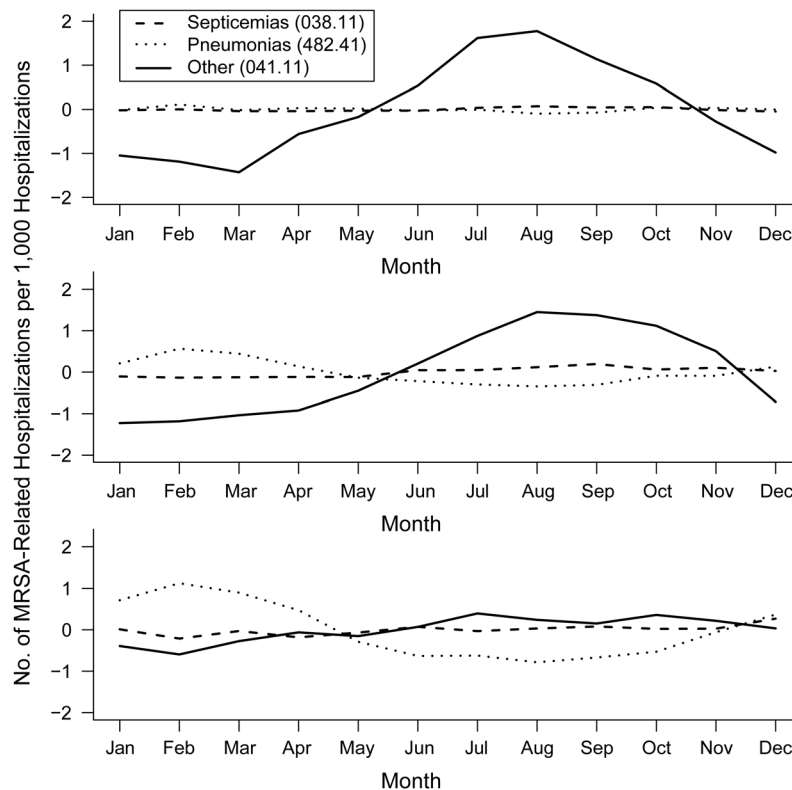


Figure 5. Seasonal hospitalization patterns by infection type and patient age, United States, 2005–2008. Seasonal patterns of *Staphylococcus aureus* infection rates were calculated by using the seasonal-trend decomposition method based on a locally weighted regression scatterplot smoother from the Nationwide Inpatient Sample, Healthcare Cost and Utilization Project, Agency for Healthcare Research and Quality, by source, for (top) patients aged 0–19 years; (middle) patients aged 20–64 years; and (bottom) patients ≥ 65 for the years 2005–2008. Numbers in parentheses are *International Classification of Diseases, Ninth Revision, Clinical Modification*, diagnosis codes. MRSA, methicillin-resistant *S. aureus*.

age dependent. MRSA-related hospitalizations in older individuals are more likely to be caused by HA-MRSA even when they are hospitalizations for skin and soft-tissue infections. One reason for this could be that older individuals are more likely to visit health care facilities or live in long-term care facilities (29).

Finally, our results show that the MRSA infection rate is highly seasonal: Infections with HA-MRSA phenotypes peak in the winter and infections with CA-MRSA phenotypes peak in the summer. This is true across all infection types (Web Figure 2). Hospitalization patterns follow a similar trend, with pneumonia hospitalizations peaking in the winter and nonblood and nonpneumonia hospitalizations, which are generally the result of skin and soft-tissue infections and generally associated with CA-MRSA, peaking in the summer. These patterns are also age dependent, with MRSA-related pneumonia hospitalizations having an extremely strong winter seasonal pattern in older adults and “other” MRSA-related hospitalizations having a strong summer seasonal pattern in children.

The reasons behind the observed seasonality remain unclear. Whereas incidence rates of Gram-negative bacterial infections have been shown to be strongly temperature

dependent (30), no seasonality has been found in *S. aureus* carriage (12) or infection (30). In addition, we found that trends in MRSA-related hospitalizations did not vary significantly by state or region, suggesting that temperature, and by extension behavioral or environmental differences, is unlikely to be the main cause of the observed seasonality. An alternative possibility, given that resistance profiles fluctuate for all infection types, is that increased exogenous antibiotic use because of an increased incidence of respiratory infections in the winter may reduce the infection rate of CA-MRSA, which has a reduced spectrum of resistance compared with HA-MRSA. This supposition stems from the fact that antibiotic use increases in the winter, both in the hospital (31) and in the community, where prescription rates have been observed to be strongly correlated with rates of influenza infection (32, 33). In addition, community antibiotic use has been shown to be strongly related to the resistant organisms present in hospitalized patients (34–36), and an analysis of ambulatory antibiotic prescribing patterns indicates that this linkage is age dependent, with younger individuals having the strongest seasonal usage pattern (Web Figure 3). This correlates with the age-dependent seasonality observed in hospitalization for skin and soft-tissue infections,

the patterns of which are also strongest in younger patients. Similarly, the age-dependent seasonality observed in HA-MRSA-related pneumonia is likely caused by secondary *S. aureus*-related pneumonia infections linked to influenza (37); these predominate in older individuals who are more likely to have contact with the health care system and are thus more likely to be infected with HA-MRSA.

Differential hospital contact patterns by different age groups may also explain why we see apparent coexistence of both MRSA strains, which is contrary to prior suggestions that CA-MRSA would replace HA-MRSA (38). Although CA-MRSA, in which little or no fitness cost has been detected (8, 9), may be spreading widely in individuals who have little contact with hospitals, HA-MRSA does not spread easily in the community but can infect individuals who have regular contact with hospitals, such as older individuals (aged ≥ 65 years).

Our results are subject to a number of limitations. First, although TSN is national in scope, it does not represent a fully stratified random sample of hospitals by type and region. Second, we have matched the location of isolates in TSN with infection codes in the NIS, but location may not always correspond with infection type. For example, some isolates taken from the blood or the lung area may not be associated with septicemia or pneumonia, respectively. In addition, isolates from TSN are not the same as clinical infections recorded in the NIS, and thus isolates from patients without infections could bias either the estimates of the percentage resistant or the phenotypic classification. However, the vast majority of "other" MRSA isolates were from wounds, suggesting that most isolates were from patients with infections, and our results are robust to alternative classifications (Web Table 1). Third, ICD-9 codes may not always accurately reflect a patient's medical condition and can vary over time if the provider's documentation, coding practice, or reimbursement incentives change. This may be particularly true in examining the differences between 2009 and prior years because reporting requirements have increased and reimbursement for treatment of infections deemed to be associated with the provision of health care has changed. Any of these limitations may explain the difference between data from 2009 and prior years, but we are unaware of a systematic source of bias in reported time trends.

Limitations in classification of isolates, which was based on phenotypic profiles rather than genotype, may also introduce bias. Although phenotypic rules have been strongly correlated with genotypic results in the past, evolutionary patterns and phenotype-genotype linkages can be affected by local variation in transmission, drug use, and hospitalization patterns. In addition, recent evidence suggests that CA-MRSA strains can acquire multiple resistance genes (28), though in general most CA-MRSA isolates are still susceptible to numerous antibiotics to which HA-MRSA is routinely resistant (5).

Our results suggest that although the number of MRSA-related hospitalizations continues to increase, the rate has slowed significantly, and for septicemia-related hospitalizations it has remained largely unchanged since 2005. The reasons behind stagnant MRSA rates are not clear, but increased attention to hospital-associated infections, particularly MRSA,

may be playing a significant role (39). This is reflected in the fact that hospitalizations for MRSA-related septicemia and pneumonia, which are largely hospital-associated, remained largely unchanged even when accounting for differences in methods, yet other MRSA-related hospitalizations, which are associated with community acquisition, continued to increase.

Our analysis also shows significant seasonality of MRSA infections and the rate at which they affect different age groups. Whereas younger individuals are more likely to experience CA-MRSA infections of the skin and soft tissue, older individuals are more likely to experience HA-MRSA infections. In addition, CA-MRSA infections may be more common in summer, particularly in younger individuals. Further validation of seasonal patterns of infection and resistance is warranted because understanding seasonal patterns can improve patient care by informing more prudent drug prescription practices, diagnoses, infection control programs, and seasonally appropriate treatment guidelines (30).

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