Association of Methicillin-Resistant *Staphylococcus aureus* (MRSA) with Hospitalization from Community-onset and Healthcare-associated Infections in Fulton County, Georgia, 2017

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Abstract

Objectives – To examine an association between MRSA and hospitalization, after adjusting for pre-existing health conditions among patients with S. aureus infections from community-onset (CO) and healthcare-associated settings in Fulton County, Georgia in 2017.

Methods –A retrospective, cohort study of patients with positive *S. aureus* (SA) infection in Fulton County, Georgia in 2017 was conducted by the Georgia Emerging Infections Program with survey weights. Patients with invasive infections were weighted 1:1, whereas those with non-invasive infections were weighted 1:4. The primary outcome was hospitalization following infection, including hospital admission, ICU admission, or re-admission. Weighted logistic regressions were used to evaluate MRSA-associated hospitalizations, adjusting for underlying health conditions by CO or HA infection.

Results – MRSA was more prevalent among HA infections (36.5%) than CO infections (24.1%). The odds of hospitalization from MRSA were 2.16 times higher than that of methicillin-susceptible SA (MSSA) among CO infections, after adjusting for bloodstream infections, diabetes, smoking status, and wounds (95% CI = 1.36-3.42). Similarly, the odds of hospitalization of MRSA were 2.09 times higher percent higher than that of MSSA among HA infections, after adjusting for bloodstream infections, diabetes, kidney dialysis, and smoking status (95% CI = 1.26-3.48). No significant differences were found in the odds of hospitalization in MRSA across CO and HA infections.

Conclusions – MRSA was significantly associated with hospitalization in both HA and CO infections, adjusting for bloodstream infections, diabetes, kidney dialysis, current smoking status, and wounds.

Introduction

Staphylococcus aureus is a bacterial pathogen that can cause infection in humans (Taylor et al., 2023). Severe infections generally require extensive medical treatment and hospitalization (Noskin et al., 2005; Taylor et al., 2023). For most healthy individuals, *S. aureus* colonization is asymptomatic in 20-30% of all human adults (Piewngam et al., 2024). However, vulnerable populations, such as those with comorbidities, are at risk of *S. aureus* colonization and often require clinical treatment for infection (Tong et al., 2015; Piewngam et al., 2024). For example, people who use needles frequently, including diabetics and hemodialysis patients, are at increased risk of *S. aureus* infection (Piewngam et al., 2024). Other underlying conditions, such as open wounds and chronic obstructive pulmonary disease (COPD) increase the likelihood of infection (Siddiqui et al., 2023; Piewngam et al., 2024). In addition, cigarette smoking elevates risk of infection by facilitating *S. aureus* biofilm formation and oxidative stress in human cells (Laniado-Laborín, 2009; Kulkarni et al., 2012; McEachern et al., 2015). Invasive *S. aureus* infections, including bacteremia and infective endocarditis, are associated with aggressive treatment and hospitalization (Tong et al., 2015). Same-day treatments, such as antibiotics and antiseptic drainage are known to be effective against infection; however, severe infections usually require more specialized treatments and hospitalization (Tong et al., 2015; Piewngam et al., 2024).

Antimicrobial strains, such as MRSA (methicillin-resistant *S. aureus*), complicate the prognosis of infection due to the limited selection of treatments available as a result of resistance to specific antibiotics, including methicillin, nafcillin, oxacillin, and cephalosporins (Klein et al., 2017; Taylor et al., 2023). From the National Inpatient Sample (NIS) of nonfederal hospitals in the United States, MRSA infections accounted for a higher estimate of 2.81 more discharges per 1,000 hospitalizations than MSSA infections in 2014 (Klein et al., 2017). Although the overall number of hospital discharges of MRSA is larger than MSSA, the annual trend of MRSA-related hospitalizations significantly declined between 2010 and 2014 ($p=0.03$) (Dantes et al., 2013; Klein et al., 2017). One study on HA bacteremia found that the median length of hospital stay was significantly higher among MRSA (12 days) than MSSA (4 days) ($p<0.0001$) (Abramson et al., 1999). The same study found that MRSA infections were associated with a

3-fold increase in direct cost compared to MSSA ($p<0.0001$) (Abramson et al., 1999). From these prior studies, we strengthen the assumption that MRSA infections are associated with poorer prognosis, longer hospital stays, and increased health costs compared to MSSA infections (Shorr et al., 2007).

Pathogenic strains of *S. aureus* are continually evolving due to their antimicrobial resistant nature (Piewngam et al., 2024). Through this study, we can improve our understanding of emerging *S. aureus* strains and their relationship to hospitalizations in metropolitan areas of the United States with respect to CO and HA infections. In one study, HA bacteremia was associated with a higher mortality rate and a longer length of stay compared to CO bacteremia, so examining differences between CO and HA infections is justifiable (Kollef et al., 2011). Finally, a better characterization of this comparison can help us prevent *S. aureus* infection among high-risk populations and reduce hospital burden from infections acquired from the community and/or healthcare systems (Noskin et al., 2005).

In this study, we will retrospectively examine associations between MRSA and hospitalizations in Fulton County, Georgia in 2017 with respect to CO and HA infections, after adjusting for bloodstream infections, diabetes, kidney dialysis, smoking status, and wounds at the time of infection.

Methods:

Study Population

The Georgia Emerging Infections Program (EIP) conducts active surveillance of *S. aureus* infections to estimate incidence in various metropolitan areas across the United States (Fridkin, 2015). In 2017, the EIP surveyed patients with *S.aureus* infection from all 19 acute care hospitals, 1 pediatric hospital, and 2 referral laboratories in Fulton County, Georgia (Phillip, 2023). Clinical and demographic data were abstracted only from patient medical records that indicated a positive test of *S.aureus* infection (Fridkin, 2015). Trained surveillance staff de-identified patients and transcribed data to a standardized form (Phillip, 2023). They also reported other clinical diagnoses associated with *S aureus* infection based on a patient's medical record (Phillip, 2023). In addition, the EIP distinguished MRSA, MSSA, hospital-onset (HO), HA, and CO infections (Fridkin, 2015). Cases were identified as hospitalized patients, while controls were non-hospitalized patients in this retrospective, cohort study.

Eligibility Criteria

Only patients with HA infection (i.e., a positive *S. aureus* test was obtained as an outpatient or as a hospitalized patient with less than or equal to 3 days length of stay and prior health care exposure in the past 12 months), CO infection (i.e., a positive *S. aureus* test was obtained as an outpatient or as a hospitalized patient with less than or equal to 3 days length of stay and without prior health care exposure in the past 12 months), and patients receiving antibiotics and/or drainage treatment were included in the study. We excluded patients with HO infections (i.e. a positive *S. aureus* test was obtained as a hospitalized patient with more than 3 days length of stay).

Survey-Weighted Sampling Design

Sample weights were provided by the investigators to obtain a more representative sample of the population of patients with invasive or non-invasive *S. aureus* infections in Fulton County, Georgia (Phillip, 2023). Non-invasive *S. aureus* infections affect non-sterile sites (e.g. skin and nasal membrane), while invasive infections affect sterile sites (e.g. blood cardiac tissue, or bone tissue). If infections were found on both sterile and non-sterile sites, then the infection was considered invasive. The data set includes a weighted sampling design, where non-invasive infections were randomly sampled with a 1:4 weight and invasive infections were assigned a 1:1 weight (Phillip, 2023).

According to a 2017 US census, 1,041,432 people resided in Fulton County, Georgia (Phillip, 2023). The number of patients surveyed with *S. aureus* infection was 5,001 residents, adjusting for weights (Figure 1). The unweighted total number of infections was 1,647 patients (Figure 1). Missing values from variables of interest were excluded prior to analysis to perform complete case analysis. The final analysis set was stratified between CO and HA infections (Figure 1).

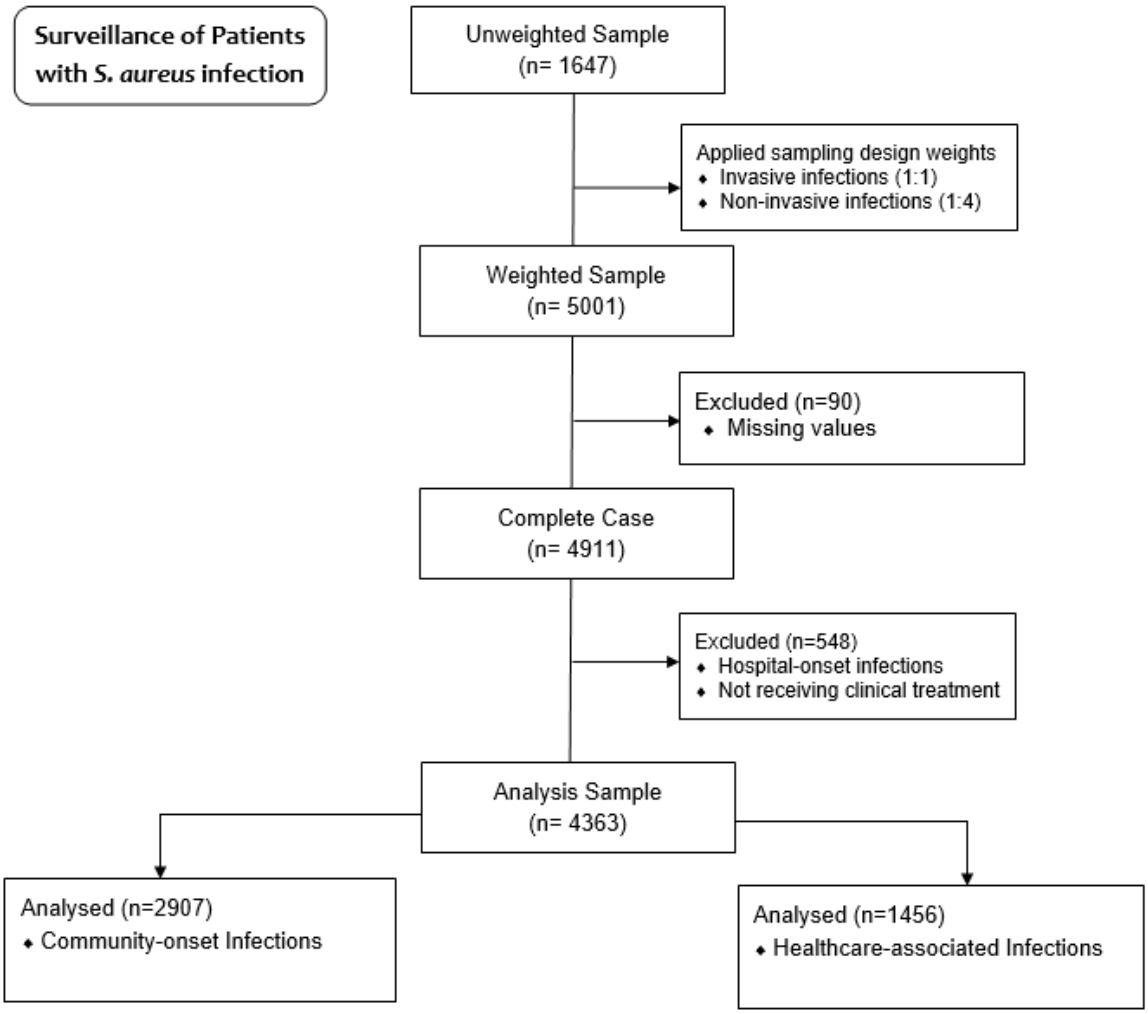

Figure 1. Patient Flow Diagram: Surveillance of Patients with S. aureus infection

Variables

As the binary outcome, hospitalization was defined collectively as hospital admission, ICU admission, or re-admission. Antimicrobial strain (i.e., MRSA vs. MSSA) was the primary exposure. Potential confounders were bloodstream infections, diabetes, kidney dialysis, smoking status, and wounds at the time of infection.

Statistical Analysis

All analyses were performed at a two-sided significance level of 0.05. Weighted descriptive statistics were stratified by HA and CO infections (Table 1). A two-sample Wilcoxon rank sum test compared

median age differences by strata, and Pearson's chi-square test compared proportional differences of hospitalization, antimicrobial strain, kidney dialysis, diabetes, current smoker, bloodstream infection, and wound variables by strata.

We applied weighted logistic regression to analyze association measures between MRSA strain and hospitalization with respect to HA and CO infections, adjusting for bloodstream infections, diabetes, kidney dialysis, smoking status, and wounds. Variables were selected *a priori* from clinical knowledge and literature to date. Weight-adjusted Wald tests were used to determine whether a variable should be included in the model and whether the fit was adequate. Interaction terms between covariates were tested, and ultimately, excluded due to their non-significance. Additionally, the covariates in the logistic regression models were assessed by their variance inflation factors to detect any violations of strongly-correlated covariates, The residuals and outliers were examined for verifying model assumptions and noting influential observations. To evaluate model performance, sensitivity, specificity, and AUROC (area under the receiver operating curve) metrics were reported using weight-adjusted rescaling bootstrap method. All analyses were done using R statistical software (version 4.4.1).

Results

Descriptive Statistics

Table 1 describes clinical and demographic characteristics stratified by HA and CO infections. Overall, there were 2,907 CO infections and 1,456 HA infections. HA infections (64.1%) had a significantly higher proportion of hospitalizations compared to CO infections (22.6%; $p < 0.0001$). Median age was significantly higher in HA infections (56 years) than that of CO infections (38 years; $p < 0.0001$). Male and female sex did not significantly differ by HA and CO infections ($p = 0.6$). MRSA was significantly higher in proportion among HA infections (36.5%) than that of CO infections (24.1%; $p < 0.0001$). HA infections had a significantly higher proportion of kidney dialysis patients (22.7%) compared to CO infections (4.1%; $p < 0.0001$). HA infections also had a significantly higher proportion of diabetic patients (36.0%) than that of CO infections (13.8%; $p <0.0001$) Current smokers were significantly higher in proportion among HA infections (16.8%) compared to CO infections (12.3 %; $p = 0.030$). Bloodstream

infections were significantly higher in proportion among HA infections (21.1%) than that of CO infections (5.2%; $p < 0.0001$). Wounds present at the time of infection were significantly higher among HA infections (34.9%) than that of CO infections (18.3%; $p < 0.0001$).

Table 1. Weighted Descriptive Statistics of Demographic and Clinical Characteristics

	Overall N = 4,363[1]	**Healthcare-associated** N = 1,456[1]	**Community-onset** N = 2,907[1]	**p-value**
Hospitalization				<0.001
No	2,808 (64.4)	523 (35.9)	2,285 (78.6)	
Yes	1,555 (35.6)	933 (64.1)	622 (21.4)	
Age (years)	45 (22.6)	56 (19.7)	38 (22.6)	<0.001
Sex				0.6
Male	2,266 (51.9)	771 (53.0)	1,495 (51.4)	
Female	2,097 (48.1)	685 (47.0)	1,412 (48.6)	
Strain				<0.001
MSSA	3,130 (71.7)	924 (63.5)	2,206 (75.9)	
MRSA	1,233 (28.3)	532 (36.5)	701 (24.1)	
Kidney Dialysis				<0.001
No	3,913 (89.7)	1,126 (77.3)	2,787 (95.9)	
Yes	450 (10.3)	330 (22.7)	120 (4.1)	
Diabetes				<0.001
No	3,438 (78.8)	932 (64.0)	2,506 (86.2)	
Yes	925 (21.2)	524 (36.0)	401 (13.8)	
Current Smoker				0.030
No	3,760 (86.2)	1,212 (83.2)	2,548 (87.7)	
Yes	603 (13.8)	244 (16.8)	359 (12.3)	
Bloodstream Infection				<0.001
No	3,906 (89.5)	1,149 (78.9)	2,757 (94.8)	
Yes	457 (10.5)	307 (21.1)	150 (5.2)	
Wound Present				<0.001
No	3,323 (76.2)	948 (65.1)	2,375 (81.7)	
Yes	1,040 (23.8)	508 (34.9)	532 (18.3)	

[1] n (%); Median (SD)

Model Fit and Evaluation Metrics

For weighted logistic regression analysis, we used weight-adjusted Wald tests to build models of adequate fit for CO and HA infections. Selected variables were MRSA status, BSI, diabetes, kidney dialysis, current smoker status, and wound status. In the CO subset, the weight-adjusted Wald test showed that dialysis was not necessary in the model ($p = 0.155$). In the HA subset, the weight-adjusted Wald test showed that wound was not necessary in the model ($p = 0.555$). Furthermore, we tested variance inflation factors (VIF) of each potential variable to assess correlations between variables that could destabilize model estimation. In both models, the VIF were below 2, indicating little to no concern of multicollinearity (Table 2).

Model performance metrics, such as AUROC (area under receiver operating curve), sensitivity, and specificity were calculated for each subset. The CO infections model showed an AUROC of 0.778, sensitivity of 0.313, and specificity of 0.988; the HA infections model showed an AUROC of 0.791, sensitivity of 0.852, and specificity of 0.572 (Table 3). Although the AUROC scores were comparable between models, the sensitivity and specificity scores were lacking. The AUROC scores of 0.778 and 0.798 indicate that the models have acceptable discriminatory power for estimating the likelihood that a patient who is hospitalized will have a higher probability of hospitalization than an individual who was not hospitalized. Low sensitivity of the CO model indicates an underestimation of true hospitalization. Low specificity of the HA model indicates an underestimation of true non-hospitalization and an overestimation of false hospitalization.

Table 2. Comparison of Potential Variables and their Variance Inflation Factors

Infection Model	**MRSA**	**BSI**	**Diabetes**	**Kidney dialysis**	**Current Smoker**	**Wound**
Community-onset	1.574	1.143	1.338	1.133	1.278	1.440
Healthcare-associated	1.414	1.153	1.357	1.239	1.136	1.695

Table 3. Comparison of Model Performance Metrics

Infection Model	**AUROC**	**Specificity**	**Sensitivity**
Community-onset	0.778	0.988	0.313
Healthcare-associated	0.791	0.572	0.852

Model Estimates: Association Measures

In CO infections, MRSA was positively associated with hospitalization, after adjusting for bloodstream infections (BSI), diabetes, dialysis, smoking status, and wound (p=0.001); the estimated odds of hospitalization of MRSA were 2.16 times higher than the odds of hospitalization of MSSA (95% CI = 1.36-3.42). Remarkably, BSI was also positively associated with hospitalization, after adjusting for MRSA strain, diabetes, dialysis, smoking status, and wound ($p < 0.0001$); the estimated odds of hospitalization in BSI were 94.1 times higher than the odds of hospitalization without BSI in CO infections(95% CI = 41.84-211.65). Additionally, patients with diabetes ($p < 0.0001$), current smoking status ($p = 0.002$), and present wound ($p < 0.0001$) were significantly associated with hospitalization.

In HA infections, MRSA was positively associated with hospitalization, after adjusting for BSI, diabetes, dialysis, smoking status, and wound (p=0.005); the estimated odds of hospitalization of MRSA were 2.09 times higher than the odds of hospitalization of MSSA (95% CI = 1.26-3.48). HA infections also show that BSI was positively associated with hospitalization, although the effect size in HA infections is significantly less than that of CO infections ($p < 0.0001$); the estimated odds of hospitalization in BSI was 10.4 times higher than the odds of hospitalization without BSI in HA infections (95% CI = 4.96-21.77). Additionally, patients with diabetes ($p < 0.0001$), current smoking status ($p = 0.037$), and dialysis ($p = 0.021$) were significantly associated with hospitalization.

There was no significant difference between the odds ratios of hospitalization by MRSA in CO and HA infections, after adjusting for BSI, diabetes, dialysis, current smoking status, and wound (Figure 2). However, there was a significant difference in odds ratios of hospitalization by BSI in CO and HA

infections ($p < 0.0001$). In CO BSI, the estimated odds of hospitalization were 9 times higher than the odds of hospitalization in HA BSI ($p < 0.0001$).

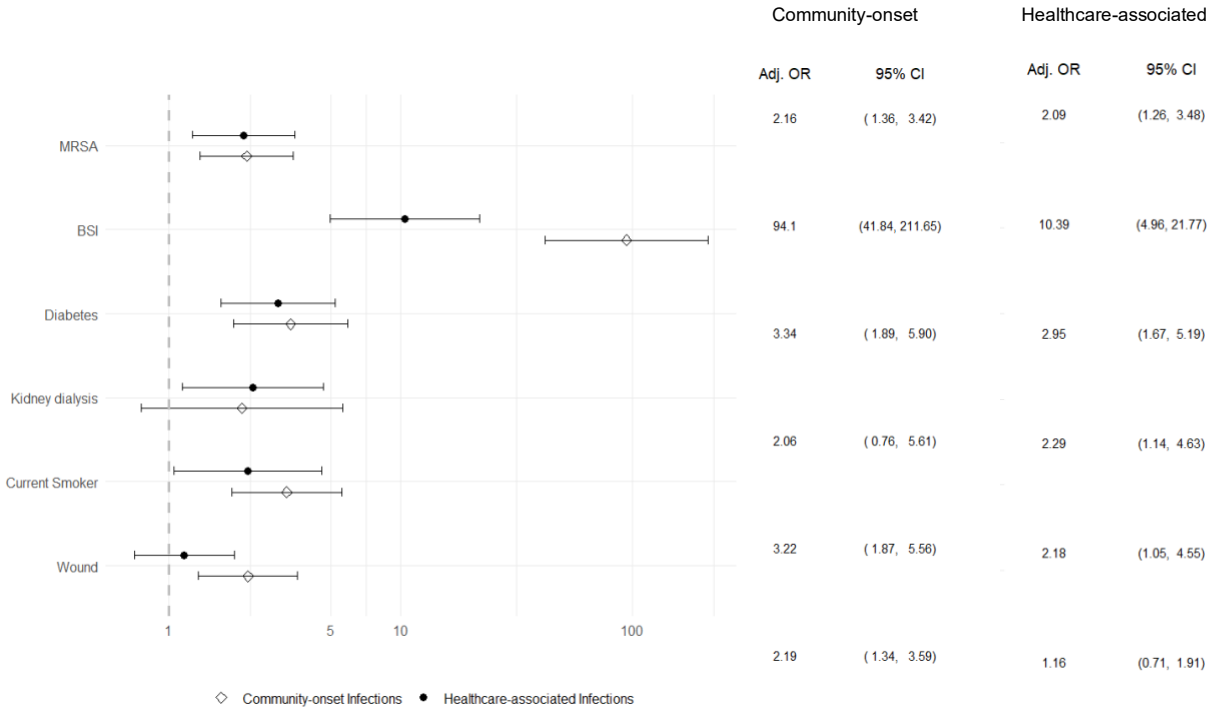

Figure 2. Odds Ratio Estimates and 95% Confidence Intervals by Community-Onset and Healthcare-Associated Infections

Estimated Probabilities of Hospitalization

To further examine the effect size of BSI between HA and CO infections by strain, we estimated their probabilities of hospitalization. Although interactions between BSI and strain were not significant, we noticed that BSI significantly increased the risk of hospitalization in both CO and HA infections (Figure 3).

The estimated probabilities of hospitalization from BSI CO infections that were MRSA and MSSA were respectively, 0.94 (95% CI = 0.87-0.97) and 0.88 (95% CI = 0.77-0.94). The estimated probabilities of hospitalization from non-BSI CO infections that were MRSA and MSSA were respectively, 0.15 (95% CI = 0.10-0.21) and 0.07 (95% CI = 0.05 – 0.10). In CO infections, BSI is a highly positive factor of hospitalization regardless of strain.

The estimated probabilities of hospitalization from BSI HA infections that were MRSA and MSSA were respectively, 0.92 (95% CI = 0.84-0.96) and 0.85 (95% CI = 0.73-0.92). The estimated probabilities of hospitalization from non-BSI HA infections that were MRSA and MSSA were respectively, 0.54 (95% CI = 0.43-0.66) and 0.37 (95% CI = 0.29 – 0.45). BSI is a positive factor of hospitalization regardless of strain in HA infections, but the effect size is not as large as in CO infections.

Additionally, the estimated probabilities of hospitalization from non-BSI are relatively higher in HA infections than CO infections (Figure 3). In both infections, the risk of hospitalization increases at a steeper rate among non-BSI than BSI when the strain is MRSA rather than MSSA (Figure 3).

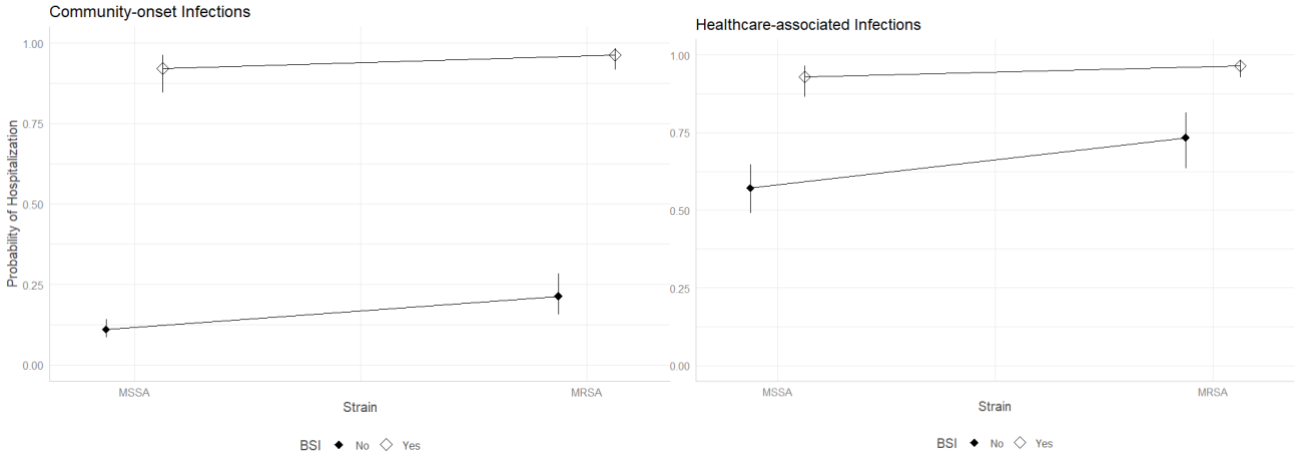

Figure 3. Estimated Probabilities of Hospitalization by Community-Onset and Healthcare-Associated Infections from Bloodstream Infection (BSI) and MRSA Plots

Discussion

MRSA infections were significantly associated with hospitalization compared to MSSA, after adjusting for risk factors, such as bloodstream infections (BSI), diabetes, kidney dialysis, smoking status, and wounds, in community-onset (CO) and healthcare-associated (HA) infections from Fulton County, Georgia in 2017. This result is consistent with the finding that MRSA infections are associated with prolonged hospitalization and more complex care than MSSA infections (Shorr et al., 2007; Siddiqui et

al., 2023). We also show that HA-MRSA and CO-MRSA were independently associated with hospitalization. This implies that MRSA infection significantly increases the risk of hospitalization in both healthcare systems and communities. In addition, BSI were associated with hospitalization, regardless of strain. We identify associations between MRSA and hospitalizations by CO and HA infection and related health conditions among patients with positive *S. aureus* infection to intervene on behalf of these populations at help and mitigate hospital burden among them.

The results of this study are not generalizable to other populations besides Fulton County, Georgia. The low sensitivity of the CO model indicates an underestimation of true hospitalizations. The low specificity of the HA model indicates an overestimation of false hospitalizations. As a result, the models are not guaranteed to perform reliably. Selection bias may be present due to the nature of the study, where certain hospitals and ambulatory clinics can report *S. aureus* infections at disproportionate rates. Confirmation bias may influence the results due to the variable selection process by literature review. Missing data from incomplete survey responses generate non-response bias. We purposefully excluded age from the logistic regression models because this covariate violated the linearity assumption. Age may need further transformation or need to be fit on a generalized linear mixed effects model to account for the variance between hospitals that the patient was treated.

For future directions, we can incorporate additional underlying health factors related to MRSA and hospitalization for a more complete understanding of targeted populations at risk. In addition, we can learn from the results of more recent studies in Fulton County, Georgia to compare with this study to determine the validity of our findings. Finally, we can assess patient correlation within hospital clusters, and account for random effects between hospitals to draw more reliable fixed effect estimates using a hierarchical mixed effects structure.

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