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Burden and Risk Factors for Hospitalization among *Staphylococcus aureus* Infections in the Southeastern USA

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2021

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An abstract of
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Rollins School of Public Health of Emory University
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Abstract

Burden and Risk Factors for Hospitalization among *Staphylococcus aureus* Infections in the Southeastern USA

By Katherine Phillip

Background – *Staphylococcus Aureus* is a common cause of infection both in community and hospital settings but is not extensively characterized. We extrapolated survey data to estimate overall and specific burden of *S. aureus* infections and estimate exposures associated with S. aureus hospitalization.

Methods – We analyzed a retrospective cohort of cases from the Georgia Emerging Infections Program consisting of cases from Fulton County, GA who had a positive culture of *S.aureus* in 2017. Cases were identified as invasive (originating from a normally sterile site), sampled 1:1, or non-invasive, sampled 1:4, and specific infection and clinical characteristics were collected. Survey and logistic regression analysis were used to evaluate the incidence of infection and predictors of hospitalization in patients, adjusting for demographic, clinical, and exposure factors.

Results – Incidence of clinically relevant *S. aureus* infection in 2017 was 405.7 cases per 100,000 people (SE 5.62, range 400.1 - 411.3). Invasive infections of all types had an incidence of 58.5 cases per 100,000 people (SE 2.34). Skin and soft tissue infections (SSTI) were the most common type of infection (225.8 cases per 100,000 people, SE 7.06). Black race, diabetes, MRSA, prior healthcare exposure, prior hospitalization, and homelessness were significant independent predictors of hospitalization across all models.

Conclusions – We found that there was a high incidence of *S. aureus* infections in Fulton County, GA and determined several independent predictors of hospitalization. Risks associated with prior healthcare exposures should be explored further to determine more specific sources of risk and develop prevention efforts.

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Introduction

Methicillin-resistant *Staphylococcus aureus* (MRSA) and methicillin-resistant *Staphylococcus aureus* (MSSA) are common causes of infection both in community and hospital settings. Invasive MRSA infections are well characterized, with national burden studies estimates of 119,247 cases of *S. aureus* bloodstream infections in 2017 and 80,461 invasive MRSA infections in 2011, as well as many studies and reviews completed on risk factors, trends, and clinical presentations (Dantes, 2013; Jenkins et al., 2010; Kourtis, 2019; LEE et al., 2016; van Hal et al., 2012).

Skin and soft tissue infections (SSTI) are common community-associated *S. aureus* infections that make up a large proportion of overall infections. However, SSTI are often not invasive in nature and therefore not a main focus of many *S. aureus* studies. Similarly, infections of the lungs, urinary tract, and surgical sites are other common foci of infections that don't receive frequent study.

Recent reports on bloodstream infections and healthcare related infections document decreasing rates of MRSA and MSSA over the past decade in part due to infection control efforts in hospitals (Dantes, 2013; Jacobs & Shaver, 2017; Kourtis, 2019; Landrum et al., 2012). *S aureus* still causes many infections, hospitalizations, and deaths each year (Kourtis, 2019; van Hal et al., 2012). Despite *S. aureus* being a common infection, current incidence and burden data tends to be limited to estimates based on administrative billing data with limited clinical or demographic data on all types of *S. aureus* infection.

This study is a novel approach to assessing the burden and clinical characteristics of all clinically significant *S. aureus* infections in a southeastern county of the United States, as well as assessing predictors for hospitalization due to *S. aureus* among clinically relevant SSTIs. By

applying sampling and weighting, we are able to extrapolate and estimate exposures and clinical factors without assessment of each individual case, while still providing robust estimates of incidence and frequency. In this study, we determine the burden of overall and specific infections of *S. aureus* in Fulton County, GA based on a complex sample of cases, highlight the clinical characteristics of SSTI, and determine predictors of hospitalization due to SST infections.

Methods

Study design and population

This is a retrospective study using data collected by the Georgia Emerging Infections Program Active Bacterial Core (ABC) laboratory-based surveillance for *S. aureus*. EIP surveillance practices for *S. aureus* are described in detail elsewhere (Klevens et al., 2007). The study population for this analysis consists of the 1,041,432 people living in Fulton County, GA in 2017.

Definitions

A case was defined as a resident of Fulton County, GA from whom a positive *S. aureus* case was isolated from any clinical culture. Patients could be residing in long-term care facilities, institutionalized, or homeless, in addition to private residences. Cases were categorized as MRSA or MSSA based on laboratory testing at a clinical laboratory. Cases of invasive *S. aureus* were defined as a positive culture from a normally sterile site, such as the blood, cerebrospinal fluid, pleural fluid, pericardial fluid, peritoneal fluid, bone, joint or synovial fluid, internal body sites (liver, heart, brain, kidneys, spleen, pancreas, ovary, lymph node, or vitreous fluid), or other normally sterile sites. Non-invasive cases were defined as any positive culture from a non-sterile

site. Cases could have more than one clinical diagnosis. If any positive culture was collected from a normally sterile site, the case was considered invasive regardless of other positive cultures from non-sterile sites in the same patient.

Cases were considered hospital-onset (HO) if the patient was hospitalized and had a positive culture collected greater than three calendar days after admission. Cases were considered hospital-associated, community-onset (HACO) if a patient had a prior healthcare exposure within the last 12 months and was not identified as a hospital-onset case. Cases were considered community-associated (CA) if positive cultures were obtained as an outpatient or hospitalized patients had a positive culture within three calendar days of admission without any healthcare exposure in the prior 12 months.

Sampling

All invasive cases received a full medical chart review and were sampled 1:1. Non-invasive cases were randomly sampled in a 1:4 method and received a full medical chart review. Additional information was recorded based on invasive status, infection type, and outcome. The total number of observations sampled was 1647, comprised of 550 invasive and 1097 non-invasive cases. Specimens obtained solely for the purpose of surveillance or testing of carriage were considered 'surveillance testing' and were excluded from analysis. Clinician derived diagnoses were determined by mapping clinical documentation from treatment notes to pre-determined clinical conditions associated with *S. aureus* infection. Cases were identified as clinically significant if they received treatment, such as antibiotics or drainage. Cases that were not identified as clinically significant were dropped, resulting in an unweighted sample size of 1453 people (550 invasive and 903 non-invasive). Discrepancy between counts of invasive cases

before and after weights were accounted for can be attributed to *S. aureus* bloodstream infections being marked and weighted as non-invasive cases in some report forms when present with other non-invasive *S. aureus* infections. All bloodstream infections were considered invasive and assessed as such.

Missing data

Race information was missing from 18% of the sample, while ethnicity was missing from 20% of the sample. For incidence calculations, cases where race and ethnicity were unknown were assigned to race and age strata in proportion to 2017 Fulton County population distributions stratified by age and sex (*Georgia Department of Public Health, Office of Health Indicators for Planning OASIS*, n.d.).

Statistical analyses

All analyses were performed on clinically significant cases exclusively. Cases that were not clinically significant were excluded from all analyses. Incidence and logistic regression analysis included all infection types. Clinical description analysis limited cases to SSTI only. Cases with overlap between SSTI and surgical site infection (SSI) were omitted for this part of analysis due to the inability to distinguish if the SSI was clinically the same as the SSTI or if they were separate infections.

All survey analysis, including accounting for weights, generating values with error, and regression analysis were completed using the R package {survey} (ver. 4.1.1), created by Thomas Lumley. This package accounts for survey weights specified in the dataset, which were based on invasive vs non-invasive status. Invasive status infections were counted as-is with a

weight of 1, while non-invasive infections were given a weight of 4 to account for the 1:4 sampling method. Other analyses, data cleaning, and data visualization were completed using R statistical software (ver. 4.2.2) and other necessary packages.

Logistic regression models were built starting with factors that were statistically significant in univariate analysis (not shown) or deemed important for analysis and built forward to include factors of interest. Factors that were not statistically significant in the previous models were not carried on to further models. Not all foundational models and outputs used to build the models presented in this analysis are shown. Hospital-onset cases were omitted from regression analyses since all hospital-onset cases are hospitalized by nature. Statistical significance was defined as $P \leq 0.05$.

Results

Counts and Incidence

After weights were applied, there were 4225 (SE 55.04) cases of clinically relevant *S. aureus* in Fulton County Georgia in 2017, comprised of 609 invasive and 3616 non-invasive cases (SE 24.38 and 73.951, respective). Of the 4225 cases, 1315 were MRSA (SE 58.23) and 2910 were MSSA (SE 70.1). Invasive MRSA made up 243 (SE 15.83), or 5.7% of the total cases and 40% of all invasive cases.

Incidence of clinically relevant *S. aureus* infection was 405.7 cases per 100,000 people (SE 5.62, range 400.1 - 411.3) and invasive infections of all types had an incidence of 58.5 cases per 100,000 people (SE 2.34). Overall MRSA and MSSA infections had respective incidences of 122.27 (SE 5.59) and 270.43 (SE 6.73) per 100,000 people. Rates of bloodstream infection (BSI), surgical site infection (SSI), *S. aureus* pneumonia (PNE) and urinary tract infection (UTI)

were 46.47 (SE 2.28), 38.70 (SE 3.45), 30.06 (SE 3.09), and 25.35 (SE 2.92) per 100,000 people, respectively (Figure 1).

Skin and soft tissue infections (SSTI) were the most common type of infection (225.8 cases per 100,000 people, SE 7.06), with 2351 identified (SE 73.5). Rates of invasive SSTI were 8.35 per 100,000 people (SE 1.12) and MRSA rates were 73.94 per 100,000 people (SE 4.36).

Incidence rates were highest in the Black race, with 500.84 cases per 100,000 people (SE 14.55) for overall infections and 295.73 cases per 100,000 people (SE 13.72) for SST-specific infections (Figure 2, Table 1). Other races had the lowest incidences by race, at 165.54 per 100,000 (SE 24.74) and 100.72 per 100,000 (SE 19.80) for overall and SST infections. Males had higher incidence compared with females for both infection categories. In overall infections, incidence increases as age increases. However, for SSTI, the lowest incidence is found in those aged 18-39 (188.12 per 100,000 people, SE 13.53), followed by those under the age of 18 (218.33 per 100,000, SE 18.29). Proportions of MRSA infections is consistent between overall infection (31% of cases) and SSTI (33% of cases), but invasive cases occur less frequently for SSTI (14% vs 3.7%).

Clinical

Assessment of clinical presentation of SSTIs show that 48% of presentations included abscess and 30% of presentations included cellulitis as symptoms (Table 2). Uncommon infection types include mastitis, myositis, and infant pustulosis. Infant pustulosis was not reported in 2017. Cases could have more than one infection presentation.

Community-associated (CA) infections make up majority of all infection types, excluding chronic wounds/decubitus ulcers and necrotizing fasciitis, both of which have 50% of their cases

considered hospital-associated, community onset (HACO) infections. Hospital-onset (HO) infections are highest in burn-related infections, chronic wound/decubitus ulcers, and cellulitis, making up 33%, 10%, and 4.6% of respective infections (Table 2). Out of the 702 hospitalized with SSTI, 49% received drainage as part of their treatment (Table 3).

Predictors of Hospitalization among SSTI

After adjusting for patient demographics, infection characteristics, and prior healthcare exposures in model 1, the odds of hospitalization for those with MRSA infections is 1.6 (95% CI 1.03-2.5, $p = 0.037$)(Table 4). Invasive infections, cellulitis or necrotizing fasciitis infection, sex, Black race, and prior healthcare exposure within the last 12 months were independent predictors of hospitalization.

Model 2 additionally adjusts for diabetes, a known risk factor for *S. aureus* infection, potential indicator of further healthcare exposures like dialysis. Diabetes was also evaluated to try to identify an additional factor that may influence the odds of hospitalization among those of Black race, as diabetes disproportionately affects those of Black race compared with other races. The odds of hospitalization for those with MRSA infections increases slightly to 1.8 (95% CI 1.15 - 2.9, $p = 0.01$). Diabetes is a strong independent predictor of hospitalization (OR 3.64, 95% CI 2.10 - 6.30, $p < 0.001$) and did reduce the odds of hospitalization among those of Black race when included in the model.

Models 3 and 4 were made to evaluate if other prior healthcare or high-risk exposures were stronger predictors for hospitalization over MRSA infection. Both models 3 and 4 evaluate hospitalization in the last 12 months and homelessness as specific exposures in place of overall healthcare exposure. Model 3 evaluates long-term care (LTC) exposure in the previous 12

months and model 4 evaluates an additional nursing home healthcare exposure. Hospitalization in the last 12 months and homelessness were independent predictors of hospitalization and had stronger predictive values than MRSA in both models. Previous LTC stay and admission or treatment from a LTC facility were not significant predictors of hospitalization ($p = 0.5$, $p = 0.9$).

Black race, invasive status, and cellulitis and necrotizing fasciitis were consistently significant positive predictors of hospitalization across all models. Invasive infections are the strongest predictor of hospitalization of the predictors evaluated, with odds of hospitalization between 25.6 and 27.6 for all models. Female sex was protective and significant in model 1 but loses significance after adjusting for diabetes and other healthcare exposures in models 2-4.

Discussion

This analysis uses a novel surveillance sampling method to evaluate incidence and burden of specific and overall *S. aureus* infections and clinical factors in a large population. We found that there was a high incidence of *S. aureus* infections in Fulton County, GA, and that more than half of all infections were skin and soft tissue infections. Incidence was also calculated for other common infection types, such as *S. aureus* pneumonia, bloodstream infections, surgical site infections, and urinary tract infections. Non-invasive infections and MSSA infections make up a significant portion of overall infections as well, causing major health issues and burden on healthcare systems.

We found that after controlling for common risk factors, including age, sex, diabetes, and previous healthcare exposures, MRSA infection was a significant predictor of hospitalization at presentation or within 30 days of admission. Invasive infections and cellulitis and necrotizing fasciitis were significant predictors of hospitalization consistent with the clinical severity that is

typical for these infections. Diabetes is an independent predictor of hospitalization that does not explain all risk associated with Black race. Incidence of all infections assessed were higher in Black race compared to white and other races, reinforcing the presence of racial disparities in *S. aureus* infections (Gualandi et al., 2018; Portela et al., 2022; See et al., 2017). Healthcare exposures in the previous 12 months were consistently more predictive of hospitalization than MRSA infection or race over all models, suggesting that healthcare exposure is a major factor in *S. aureus* infections.

A potential limitation for this analysis is that each case could have multiple infection locations and clinical presentations. Invasive status was based on whether a positive *S. aureus* culture was identified, regardless of the presence of other non-invasive infections. This could result in higher numbers of invasive status SST infections due to pairings of SSTI with other invasive infections like bloodstream infections. This may also influence the frequency of more severe outcomes like hospitalization that may be a result of a different non-SST invasive infection. However, we observe a decreased percentage of invasive SSTI compared with invasive overall infections, from 14% of overall infections to 3.7% of SSTI, suggesting that majority of invasive infections did not have overlap with SSTI, or that overlap was minimal.

This study was completed in Fulton County, GA, which contains the large and diverse urban city center of Atlanta. The population studied may not be representative of the state of Georgia or other areas in the US, particularly in racial make-up. Over 44% of the total population studied identified as black, which is higher than the percentage of black people in the state of Georgia and in the country (*U.S. Census Bureau, 2017 American Community Survey 1-Year Estimates*, n.d.).

All values presented in this study are based on estimates with error. This study is based on a sample of cases, and error is produced when analyzing and extrapolating the sample data. Sampling provides the ability to make these estimates based on a smaller number of cases chosen randomly in a population and uses error to accommodate for natural variations in case data.

Sampling is unable to collect all variations in clinical disease that occur, which may reduce our ability to detect and report more rare clinical factors since not all cases are evaluated. Recording and reporting of more intricate clinical diagnoses is better suited to different study designs such as case control studies, but for large-scale, population level incidence and diagnosis information, sampling cases provides a reliable method of collecting information without reliance on administrative data. Sampling as a method of data collection and extrapolation is applicable to many other surveillance settings and may prove highly useful in investigating other infections.

Additional studies and documentation are needed to further characterize S. aureus infection presentations such as pneumonia and surgical site infections, which can aid prevention efforts in hospital and acute care settings. Findings from this study can help inform efforts to reduce risk of S. aureus infection by targeting interventions at healthcare exposures, including non-hospital and outpatient exposures, and at minimizing long-term effects, as high-risk factors weren't exclusive to prior hospitalization and could be up to 12 months prior to admission. Additional studies are needed to determine other risk factors within the healthcare sector that may be influencing hospitalization.

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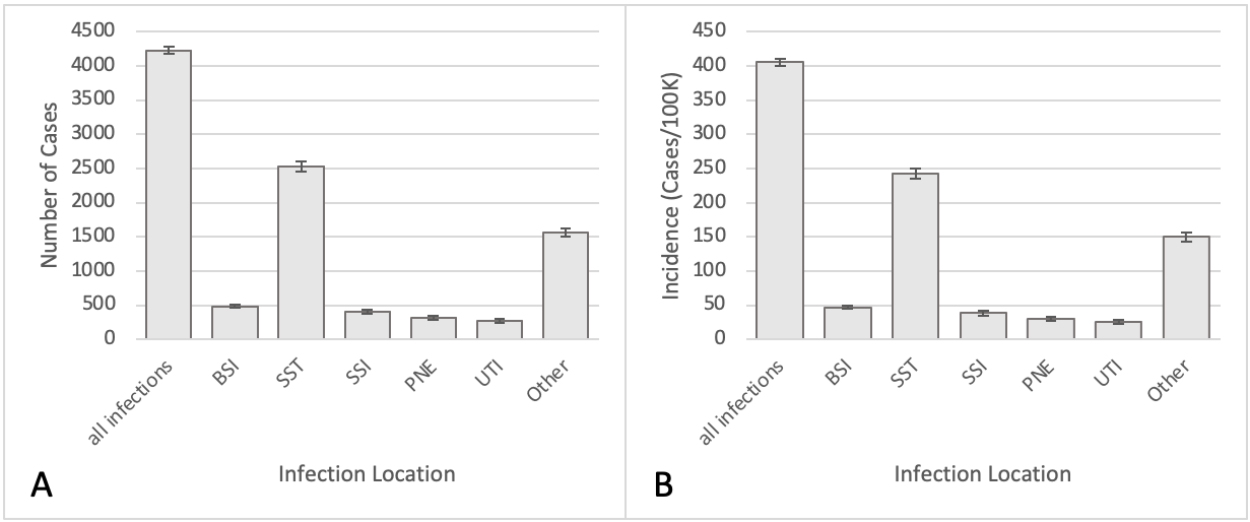

Figure 1: Count and Incidence of Clinically Relevant Staphylococcus Aureus Cases by Infection Location in Fulton County, GA in 2017. This figure shows counts (A) and infection incidence (B) with error of S. Aureus cases after survey weighting has been taken into account. Error bars are specific to each infection type and measure and are based on standard sampling error. Cases can have more than one infection location. N = 4225.

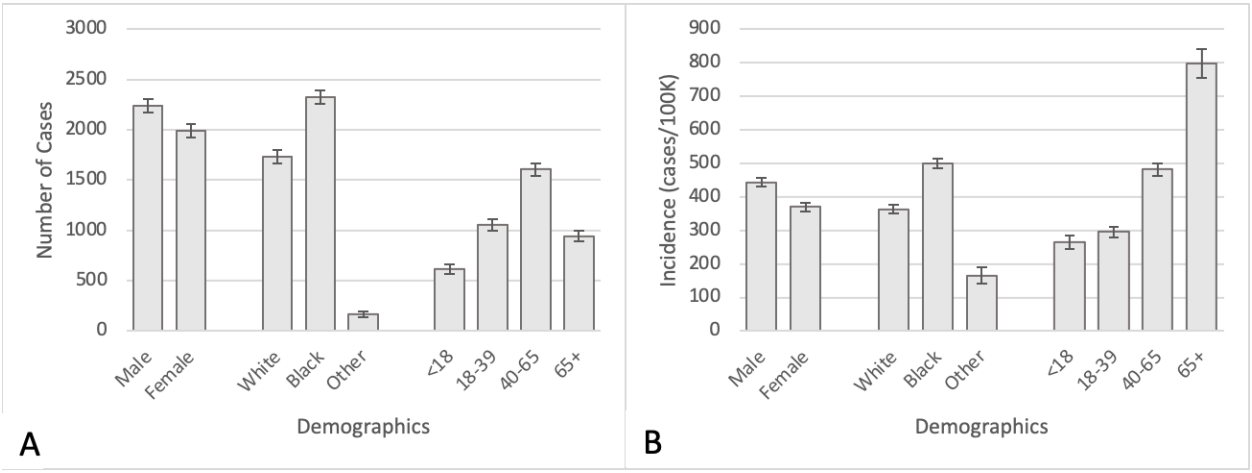

Figure 2. Count and Incidence of Clinically Relevant Staphylococcus Aureus Cases by Demographic Category in Fulton County, GA, in 2017. This figure shows counts (A) and incidence (B) of combined infection locations by demographic category after survey weighting has been taken into account. Error bars are specific to each demographic category count and incidence and error values are based on standard sampling error. N = 4225.

		Overall Infection (n = 4225)				SST Infection (n = 2351)			
		Count (%)	Error ±	Incidence	Error ±	Count (%)	Error ±	Incidence	Error ±
Sex									
	Male	2237 (53)	68.031	443.49	13.49	1297 (55)	62.626	257.13	12.42
	Female	1988 (47)	67.284	370.20	12.53	1054 (45)	57.998	196.27	10.80
Race									
	White	1733 (47)	65.765	363.67	13.80	876 (37)	54.017	183.83	11.34
	Black	2327 (55)	67.583	500.84	14.55	1374 (58)	63.73	295.73	13.72
	Other	166 (3.9)	24.808	165.54	24.74	101 (4.3)	19.856	100.72	19.80
Age									
	<18	616 (15)	45.916	265.27	19.77	507 (22)	42.934	218.33	18.49
	18-39	1059 (25)	56.933	296.02	15.91	673 (29)	48.403	188.12	13.53
	40-65	1606 (38)	62.941	481.94	18.89	826 (35)	52.634	247.87	15.79
	65+	944 (22)	50.877	798.50	43.04	345 (15)	34.813	291.83	29.45
Status									
	Invasive	609 (14)	24.375	58.48	2.34	87 (3.7)	11.634	8.35	1.12
	MRSA	1315 (31)	58.234	279.43	6.73	770 (33)	45.43	73.94	4.36

Table 1. Incidence and case count by demographic category for overall infections and skin and soft tissue infections. Errors are specific to each value and are based on standard sampling error. Incidence is N/100K.

Infection Type	Count (%)	Error, ±	HO	HACO	CA
Abscess	1132 (48)	60.4	16	172	944
Acute Infected wound	380 (16)	37.7	12	116	252
Pustule or minor skin infection	404 (17)	38.8	0	68	336
Cellulitis	696 (30)	49.5	32	156	508
Chronic wound or decubitus ulcer infected	324 (14)	34.9	32	164	128
Necrotizing fasciitis	32 (1.4)	11.3	4	16	12
Burn related	12 (0.5)	6.9	4	4	4
Herpes/zoster related	8 (0.3)	5.65	0	0	8
Infant Pustulosis	0	0	0	0	0
Mastitis	4 (0.2)	4	0	0	4
Myositis	4 (0.2)	4	0	0	4

Table 2. Clinical Presentation of Skin Soft Tissue Infections. N = 2351. Cases can have more than one presentation form. Percentage of counts were taken out of total number of cases, not number of presentations. There were 2996 clinical presentations recorded.
Note: HO – Hospital Onset
HACO – Hospital-Associated, Community Onset
CA – Community-Associated.

		Hospitalization		
		No	Yes	**Total**
Treated via Drainage	No	945	358	1303
	Yes	704	344	1048
	Total	1649	702	2351

Table 3. Contingency Table of hospitalizations and drainage as treatment for SSTI. N = 2351.

	Model 1			Model 2			Model 3			Model 4		
Characteristic	**OR**[1]	**95% CI**[1]	**p-value**	**OR**[1]	**95% CI**[1]	**p-value**	**OR**[1]	**95% CI**[1]	**p-value**	**OR**[1]	**95% CI**[1]	**p-value**
MRSA	1.60	1.03, 2.50	0.037	1.83	1.15, 2.90	0.010	1.75	1.09, 2.81	0.020	1.79	1.12, 2.85	0.016
Invasive	27.6	7.18, 106	<0.001	25.6	6.30, 104	<0.001	27.5	6.65, 114	<0.001	27.2	6.61, 112	<0.001
Cellulitis or Necrotizing Fasciitis	2.38	1.50, 3.79	<0.001	2.57	1.59, 4.16	<0.001	2.41	1.48, 3.91	<0.001	2.40	1.48, 3.89	<0.001
Healthcare Exposure in Previous 12 Months	5.52	3.26, 9.36	<0.001	4.77	2.74, 8.31	<0.001						
Black	2.07	1.29, 3.34	0.003	1.72	1.06, 2.79	0.028	1.68	1.03, 2.74	0.037	1.67	1.03, 2.72	0.039
Female	0.64	0.41, 1.00	0.048	0.69	0.44, 1.09	0.11	0.73	0.46, 1.16	0.2	0.74	0.47, 1.16	0.2
Age												
0-17	—	—		—	—		—	—		—	—	
18-39	4.37	1.97, 9.67	<0.001	3.55	1.61, 7.82	0.002	3.48	1.57, 7.70	0.002	3.46	1.56, 7.66	0.002
40-64	4.05	1.82, 9.02	<0.001	2.64	1.15, 6.05	0.022	2.46	1.07, 5.67	0.034	2.43	1.05, 5.60	0.037
65+	4.42	1.72, 11.4	0.002	2.35	0.87, 6.39	0.093	2.06	0.73, 5.84	0.2	2.12	0.76, 5.96	0.2
Diabetes				3.64	2.10, 6.30	<0.001	3.81	2.17, 6.69	<0.001	3.88	2.22, 6.79	<0.001
Hospitalization in Previous 12 Months							5.49	2.98, 10.1	<0.001	5.66	3.09, 10.3	<0.001
Homeless							4.79	1.30, 17.6	0.018	4.79	1.30, 17.6	0.019
LTC Stay in Previous 12 Months							1.65	0.35, 7.75	0.5			
Admit/Treated from LTCF										1.15	0.23, 5.77	0.9

[1] OR = Odds Ratio, CI = Confidence Interval

Table 4: Logistic Regression for Hospitalization as an Outcome of MRSA infection. Hospital-onset cases are excluded from this analysis. N = 2283. Model 1 focused on patient demographic, pathogen, and clinical presentation; Model 2 added patient underlying illness; Model 3 added alternative healthcare or other high-risk exposures rather than summary healthcare exposure variable; Model 4 considered alternative nursing home exposure more readily captured during clinical assessment.