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Risk factors for non-invasive (skin and soft tissue) and invasive *Staphylococcus aureus* infections among children and adults living in southeastern USA: a retrospective cohort study

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ABSTRACT

Objective To characterise individual and area-level risks associated with invasive or skin and soft tissue (SSTIs) *Staphylococcus aureus* infections comparing methicillin-resistant *S. aureus* (MRSA) with methicillin-sensitive *S. aureus* (MSSA); and highlight differences between children and adults.

Setting A population-based study from 21 reporting laboratories located in Georgia Health District 3 (HD3), an eight-county catchment area around metro Atlanta.

Participants A case is a resident of HD3 from whom *S. aureus* had been isolated in 2017.

Primary outcome Culture-confirmed *S. aureus* infections, classified as skin and soft tissue (proxy for non-invasive) or invasive, by methicillin-sensitivity status.

Results The incidence of SSTIs was 19.7/100 000, compared with 5.2/100 000 for invasive infections. Adults experienced higher rates of SSTIs (22.3/100 000) and invasive infections (6.7/100 000) compared with children with SSTIs (13.0/100 000) and invasive infections (1.3/100 000). Risks of MRSA versus MSSA SSTIs were similar for children and adults. Black individuals with SSTIs were more likely to have MRSA than white individuals (children (OR 1.43, 95% CI 1.16 to 1.76); adults (OR 1.24, 95% CI 1.08 to 1.42)). Adults with invasive MRSA were more likely to be black (adjusted OR 1.69, 95% CI 1.25 to 2.29) compared with those with invasive MSSA. Children with invasive MRSA were more likely from a racial-ethnic concentrated area (OR 4.66, 95% CI 1.85 to 11.71). Hotspots of MRSA were found in crowded areas with higher rates of black populations.

Conclusions The risk of MRSA infections in children and adults can be defined by unique area-level sociodemographic characteristics which were distinct for those areas associated with MSSA infections. Place-based risks of MRSA or MSSA can be used to develop target public health interventions to decrease transmission and incidence.

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ Use of a large georeferenced dataset of laboratory-confirmed methicillin-resistant *Staphylococcus aureus* or methicillin-sensitive *S. aureus* to identify individual and neighbourhood sociodemographic risk factors.

⇒ Captured smaller clusters of socioenvironmental characteristics for individuals with confirmed infections by using reliable population estimates by census tract.

⇒ Exclusion of laboratory sites due to incomplete skin and soft tissue infection-related data or lack of geo-referenced cases.

⇒ Surveillance conducted in metro Atlanta may not be representative of other areas in the USA.

INTRODUCTION

Methicillin-resistant *Staphylococcus aureus* (MRSA) infections present challenges to treatment and prevention in both hospital and community settings. In 2017, an estimated 323 700 hospitalised cases of MRSA infections occurred in the USA, with 10 600 related deaths.[1] Hospital-associated MRSA (HA-MRSA) and community-associated MRSA (CA-MRSA) infections have been well described in previous literature,[2 3] highlighting the risks associated with invasive HA-MRSA infections (hospitalisation, extreme age groups, males, black race and haemodialysis patients)[4–7] and CA-MRSA infections (crowding, athletic facilities, military individuals, poor hygiene, previous antibiotic use and socioeconomic factors (households with low income, medically underserved area and area with low education attainment)).[8 9] Skin and soft tissue infections (SSTIs) likely account for at least 90% of non-invasive CA-MRSA and result in more than 14 million ambulatory visits per year.[2 8 10–15] Although evidence from one study in 2016 showed that the incidence of invasive methicillin-sensitive *S. aureus* (MSSA) infections in eight US counties across five states is higher than the incidence of invasive MRSA infections across all demographic

groups,[16] data evaluating non-invasive MSSA infections are less available.

This is the first large population-based study comparing adults with children with *S. aureus,* living in the southeastern USA. No previous studies have compared paediatric place-based risks with those of adults, among those with either MRSA or MSSA infections. In this study, we (1) characterise individual and area-level risks associated with invasive infections or SSTIs caused by *S. aureus* comparing MRSA with MSSA; and (2) highlight differences between children and adults with these infections.

METHODS
Study design
This is a retrospective study using data from Georgia Emerging Infections Program (EIP) laboratory-based surveillance of *S. aureus* infections from 21 reporting laboratories (18 hospital based and 3 referral) located in Georgia Health District 3 (HD3), an eight-county catchment area of approximately 3 951 039.[17] This area is shown on a map of the USA in online supplemental figure 1. Georgia's EIP has been ongoing since 2005, but in 2017, a time-limited expansion of its surveillance was initiated to include additional infections, for example, *S. aureus.*

Case definition
A case was defined as a resident of HD3 from whom *S. aureus* had been isolated from any clinical culture; cases were distinguished as MRSA or MSSA. Specimen sources were further categorised as invasive, non-invasive or other/uncertain infection based on a review of culture source.

Invasive infection included isolation of *S. aureus* from a normally sterile site (ie, blood, bone, cerebrospinal fluid, pleural fluid, pericardial fluid, peritoneal fluid, joint/synovial fluid, internal organ site (lymph node, brain, heart, liver, spleen, kidney, pancreas, ovary or vitreous fluid) or other normally sterile site).[5] Non-invasive infections included those from lower respiratory tract, skin abscess and sinuses. *S. aureus* isolated from other sites, for example, wound, skin and 'unknown' sites, were assessed for clinical relevance. 'Free text' and 'comment' fields associated with culture report were then reviewed by an infectious disease physician (AW) to classify specimens into respective categories. SSTIs included skin abscess and superficial skin infections (wounds, rashes, cellulitis, swabs and drainage). For this study, SSTIs are a proxy for 'non-invasive' infection. For each unique patient, if multiple non-invasive cultures occurred within a 14-day period or if multiple invasive cultures occurred within a 30-day period, cases were assigned as a single incident infection (see figure 1 for enrolment scheme).

Patient and public involvement
It was not appropriate or possible to involve patients or the public in the design, conduct, reporting or dissemination plans of our research.

Patient-level data
Antibiotic susceptibility testing results and demographics (age, race, ethnicity, gender and home address) were obtained from culture reports. Age was grouped into eight clinically relevant categories: 0–2, >2–5, >5–13, >13–18, 19–25, >25–45, >45–65 and >65 years.
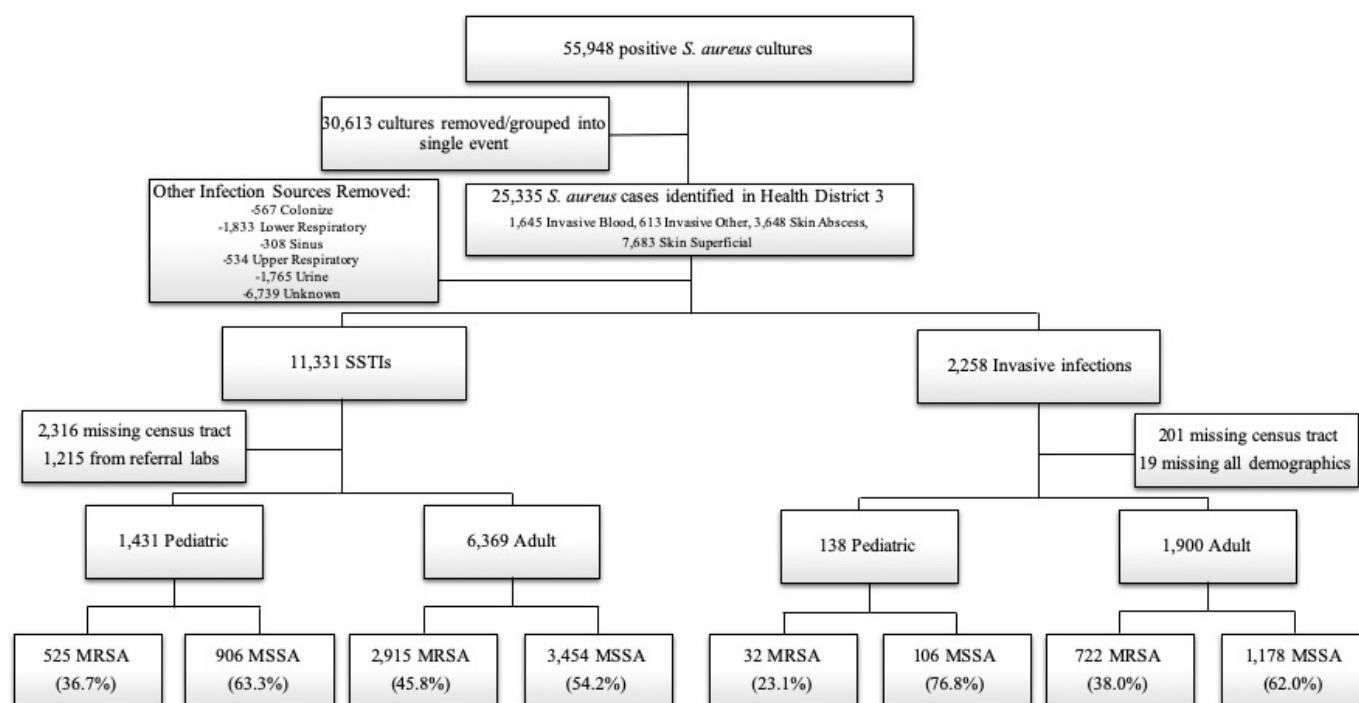

Figure 1 Enrolment scheme for all *Staphylococcus aureus* cultures in adults and children, based on distribution of type of infection (invasive vs non-invasive) and resistance to methicillin, 2017. MRSA, methicillin-resistant *S. aureus*; MSSA, methicillin-sensitive *S. aureus*; SSTIs, skin and soft tissue infections.

Geocoding

World Geocoding Service in ArcMap V.10.7 software (ArcGIS Desktop, Redlands, California, USA: Environmental Systems Research Institute) was used to georeference cases to the census tract level.

Missing data

Two referral laboratories' data for patients with SSTIs were excluded from the analyses due to missing race assignments for 84.4% and 95.5%, respectively. From 13 of 21 remaining laboratories, a total of 429 (2.3%) cultures were missing infection source. Age, gender, race and ethnicity were missing in less than 20% of remaining SSTI and invasive cases. Missing demographic data were adjusted through five iterations[18] of multiple imputations based on distributions of age category, gender, race, ethnicity, methicillin sensitivity and county of residence using SAS V.9.4 (SAS Institute). Imputed demographics were used for logistic regression and incidence rates.

Area-level data

Area variables at census tract level were abstracted from the 2017 US Census Bureau American Community Survey 5-Year Data.

Household crowding

The US Department of Housing and Urban Development defines household crowding as more than one person per room per dwelling unit, regardless of unit size, structure type, location or lot size.[19]

Racial-ethnic groups

Based on proportions of non-Hispanic, non-white individuals per census tract, 'concentrated' areas of this racial-ethnic group were determined by adding 10% to the percentage of non-Hispanic, non-white population for the state.[20] For example, in Georgia, the average rate of non-Hispanic, non-white population is 37.8%, so any census tract >47.8% was defined as a 'concentrated' area of this racial-ethnic group.

Poverty

Census tracts where >40% of the population falls below the national poverty line.[21]

Other area-level variables

Index of income inequality uses the Gini index to represent wealth dispersal, where 0 indicates perfect equality and 1, perfect inequality. Proportions in each census tract with no health insurance, <18 years old and foreign born (defined by US Census) were calculated. The proportion of individuals with no high school diploma was calculated among the population >25 years old.

Statistical analyses

Overview

Patients who met the case definition for either MRSA or MSSA were stratified by individual patient-level and area-level variables. Comparison of incident SSTIs with invasive infections, overall and by resistance, was then examined by χ^2 test for categorical variables and two-sample t-test for continuous variables. Additional comparisons were done between paediatric versus adult infections. Incidence calculations used 2017 US Census data for the study area as the denominator. Incidence (per 100 000 HD3 population) of SSTIs and invasive infections was calculated by age group, race and ethnicity. Statistical analysis was performed using SAS V.9.4 (SAS Institute).

Statistical models

Bivariate analyses were performed to test associations of variables with MRSA compared with MSSA. Individual patient-level and area-level demographic variables, based on risks or proxies for risks reported in the literature,[9 22] were selected for inclusion. Three types of multivariable logistic regression models were created: individual factors only, area factors only and multilevel (individual and area) factors. Multilevel logistic regression used random intercepts for census tract; area-level variables with a p value of <0.15 in adjusted models were included for initial consideration. These model types were applied to SSTIs and invasive infections among both children and adults. ORs were used as estimates of relative risks, and 95% CIs were determined. All tests were two tailed and a p value of <0.05 was considered significant.

Spatial analyses

Georeferencing of all data was previously done[17] and census tract ID was determined for each case; geocode match accuracy was 98% overall. Standardised incidence ratios (SIRs) using county rate were determined. Observations of zero incidents in a census tract were adjusted by adding an arbitrarily small value (0.5) to the observed and expected incidents as risk in any census tract was not likely to be zero for any infection. Ratios were calculated and mapped by type of infection (invasive vs SSTIs), adjusted for age and race. Using Getis-Ord Gi* statistic, MRSA and MSSA hotspot and cold spot analyses were performed on incidence rates and non-aggregated data to determine significant spatial clustering. Significance was tested at various confidence levels (99%, 95% or 90%) for each spatial cluster.

RESULTS

During 2017, 25 335 unique *S. aureus* infections were reported for HD3. Of these, 11 746 infections were removed as they were isolated from a source that did not meet our definition for invasive infection or SSTI (figure 1). The remaining infections included 11 331 (44.7%) SSTIs and 2258 (8.9%) invasive infections; 3531 SSTIs and 220 invasive infections were removed due to missing census tract, demographic information or incomplete reports from referral laboratories. Our final analysis included 2915 adults (45.8%) with MRSA SSTIs and 3454 adults (54.2%) with MSSA SSTIs, as well as 525 children (36.8%) with MRSA SSTIs and 906 children (63.3%) with

MSSA SSTIs. For invasive infections, 722 adults (38.0%) with MRSA and 1178 adults (62.0%) with MSSA were identified, compared with 32 children (23.2%) with MRSA and 106 children (76.8%) with MSSA.

Population characteristics

Individual demographics and risks determined a priori are shown in table 1, stratified by SSTI versus invasive infection (see online supplemental table 1 for imputed demographics by imputation iteration and online supplemental table 2, which further examines demographic differences in children vs adults). The incidence of SSTIs in HD3 was 19.7/100 000, compared with 5.2/100 000 for invasive infections. Adults experienced higher incidence of SSTIs (22.3/100 000) and invasive infections (6.7/100 000) compared with children with SSTIs (13.0/100 000) and invasive infections (1.3/100 000). The incidence of MRSA SSTIs among adults (10.2/100 000) was more than twice that of children (4.8/100 000), and the incidence of invasive MRSA (2.5/100 000) was almost nine times that of children (0.3/100 000). The rates of infection types by methicillin resistance are displayed by demographics in online supplemental figure 2.

Risk factors among children and adults

Risks of MRSA versus MSSA SSTIs were similar for children and adults. Black persons with SSTIs were more likely to have MRSA than white persons (children (OR 1.43, 95% CI 1.16 to 1.76); adults (OR 1.24, 95% CI 1.08 to 1.42)), and both adults and children with MRSA SSTIs were less likely to be Hispanic (children (OR 0.76, 95% CI 0.65 to 0.89); adults (OR 0.88, 95% CI 0.78 to 1.00)) (table 2). Highest risk of MRSA SSTIs (over MSSA) was found in children <2 years, children >2–5 years and adults >65 years. At the area level, since the rate of no health insurance was highly correlated with no high school diploma, health insurance was dropped from adjusted models. After adjusting for crowding and foreign born, higher proportions with no high school degree increased adult risk of MRSA SSTIs (adjusted OR (aOR) 2.47, 95% CI 1.29 to 4.74); living in a racial-ethnic concentrated area increased paediatric risk of MRSA SSTIs (aOR 1.31, 95% CI 1.03 to 1.65) not seen with adults.

Additional multilevel model analyses revealed that black race was no longer a significant determinant of MRSA infection among children or adults (online supplemental table 3). Only crowding remained a significant area-level risk for paediatric MRSA SSTIs (aOR 1.44, 95% CI 1.02 to 2.04), while crowding (aOR 1.35, 95% CI 1.14 to 1.59) and no high school degree (aOR 2.98, 95% CI 1.35 to 6.56) remained significant area predictors of adult MRSA SSTIs.

After adjusting for individual demographics, adults with invasive MRSA were more likely to be black (aOR 1.69, 95% CI 1.25 to 2.29) compared with those with invasive MSSA (table 3). Children with invasive MRSA were more likely from racial-ethnic concentrated areas (OR 4.66, 95% CI 1.85 to 11.71); no factors were significant in

area level-adjusted models for invasive disease. A multilevel model indicated adults with MRSA (compared with MSSA) invasive infections were more likely black (aOR 1.52, 95% CI 1.21 to 1.92) and persons living in areas without health insurance (aOR 3.95, 95% CI 1.07 to 14.55) after adjusting for age, ethnicity and poverty.

Spatial densities of skin and soft tissue and invasive MRSA and MSSA infections

After adjusting for age and race, invasive *S. aureus* (MRSA and MSSA) was distributed across fewer census tracts than SSTIs (figure 2). Although many census tracts had higher SIRs for SSTIs, particularly in central and northern HD3, the highest invasive SIRs were aggregated in smaller spatial areas. More census tracts had SIRs >2.0 for MRSA SSTIs and invasive infections than MSSA, while more areas had a ratio of 1.2–2.0 for MSSA infections of both types (online supplemental figure 3). MRSA was greatest in south-central Atlanta around Fulton, DeKalb and Clayton counties, three of the four counties with the highest population densities. The distribution of *S. aureus* for adults compared with children was similar, except in Douglas and Newton counties where there were high SIRs of adult *S. aureus* but low for paediatric (figure 3A,B). More census tracts with SIRs >2.0 were seen with children, even though infected adults covered a greater region of HD3 (online supplemental figure 4).

Among 634 census tracts with adult MRSA, 30% (193) were identified as hotspots and within these hotspots, 79% (152 of 193) were in areas with ≥40% black population and 66% (128 of 193) were in hotspots with ≥50% black population. Figure 3C,D demonstrates these hotspots and shows the preponderance of cold spots in tracts where there are more white persons than black persons. Paediatric MRSA hotspots were similar in distribution as adults, with hotspots seen in 33% (166 of 504) of census tracts with paediatric MRSA, and 78% (130 of 166) and 65% (108 of 166) of these hotspots with ≥40% and >50% black population, respectively. In general, this appears to correspond to population density; exception to this was seen in Cobb and Douglas counties. We found evidence that highly black, densely populated regions of south-central Fulton–DeKalb counties and the south-side of the city of Atlanta were areas with significant MRSA hotspots and less significant MRSA hotspots in the less densely populated areas of east and south DeKalb county. Within the north-side of the city of Atlanta, we saw no significant hotspots and only a few significant cold spots.

DISCUSSION

S. aureus SSTIs occurred more often than invasive disease for both adults (nearly 4-fold higher rate) and children (roughly 10-fold higher rate); this was consistent for both MRSA and MSSA. Since many SSTIs are not standardly or routinely cultured, our findings are an underestimation of true SSTI incidence and therefore, an under-reporting of the likely even greater disparity between SSTIs and

Table 1 Population characteristics between skin and soft tissue and invasive infections by methicillin sensitivity

Individual level, no (%)	SSTIs				Invasive infections				
	All (n=7800)	MRSA (n=3440)	MSSA (n=4360)	P value	All (n=2038)	MRSA (n=754)	MSSA (n=1284)	P value	All P value
Age				<0.001				<0.001	<0.001
Paediatric	1431 (18.3)	525 (15.3)	906 (20.8)		138 (6.8)	32 (4.2)	106 (8.3)		
Adult	6369 (81.7)	2915 (84.7)	3454 (79.2)		1900 (93.2)	722 (95.8)	1178 (91.7)		
County				<0.001				0.001	<0.001
Clayton	644 (8.3)	311 (9.0)	333 (7.6)		167 (8.2)	77 (10.2)	90 (7.0)		
Cobb	1884 (24.2)	823 (23.9)	1061 (24.3)		388 (19.0)	122 (16.2)	266 (20.7)		
DeKalb	1336 (17.1)	565 (16.4)	771 (17.7)		436 (21.4)	151 (20.0)	285 (22.2)		
Douglas	482 (6.2)	265 (7.7)	217 (5.0)		101 (5.0)	33 (4.4)	68 (5.3)		
Fulton	1488 (19.1)	667 (19.4)	821 (18.8)		530 (26.0)	228 (30.2)	302 (23.5)		
Gwinnett	1490 (19.1)	629 (18.3)	861 (19.7)		311 (15.3)	104 (13.8)	207 (16.1)		
Newton	258 (3.3)	87 (2.5)	171 (3.9)		57 (2.8)	19 (2.5)	38 (3.0)		
Rockdale	218 (2.8)	93 (2.7)	125 (2.9)		48 (2.4)	20 (2.7)	28 (2.2)		
Race				<0.001				<0.001	0.09
White	3759 (48.2)	1606 (46.7)	2153 (49.4)		943 (46.3)	303 (40.2)	640 (49.8)		
Black	3825 (49.0)	1762 (51.2)	2063 (47.3)		1049 (51.5)	442 (58.6)	607 (47.3)		
Other	216 (2.8)	72 (2.1)	144 (3.3)		46 (2.3)	9 (1.2)	37 (2.9)		
Ethnicity				<0.001				0.0025	0.19
Non-Hispanic	7238 (92.8)	3246 (94.4)	3992 (91.6)		1908 (93.6)	722 (95.8)	1186 (92.4)		
Hispanic	562 (7.2)	194 (5.6)	368 (8.4)		130 (6.4)	32 (4.2)	98 (7.6)		
Gender				0.65				0.088	<0.001
Female	3542 (45.4)	1572 (45.7)	1970 (45.2)		821 (40.3)	322 (42.7)	499 (38.9)		
Male	4258 (54.6)	1868 (54.3)	2390 (54.8)		1217 (59.7)	432 (57.3)	785 (61.1)		
Area level (census tract), mean (SD)									
Income Inequality Index	0.41 (0.05)	0.41 (0.05)	0.41 (0.05)	0.44	0.42 (0.06)	0.42 (0.06)	0.42 (0.06)	0.05	<0.001
Crowding, no (%)	6455 (82.8)	2926 (85.1)	3529 (80.9)	<0.001	1704 (83.6)	636 (84.4)	1068 (83.2)	0.49	0.36
Racial-ethnic concentration, no (%)				0.04				0.24	<0.001
>47.8	3884 (49.8)	1757 (51.1)	2127 (48.8)		1109 (54.4)	423 (56.1)	686 (53.4)		
Proportion no high school diploma	0.12 (0.09)	0.13 (0.09)	0.12 (0.09)	0.001	0.12 (0.08)	0.13 (0.09)	0.12 (0.08)	0.19	0.48
Poverty concentration, no (%)				0.51				0.04	<0.001
>40	247 (3.2)	114 (3.3)	133 (3.1)		98 (4.8)	46 (6.1)	52 (4.1)		
Proportion no health insurance	0.17 (0.09)	0.17 (0.09)	0.16 (0.09)	0.46	0.16 (0.09)	0.17 (0.09)	0.16 (0.09)	0.08	0.06
Proportion under 18 years old	0.25 (0.06)	0.25 (0.06)	0.25 (0.06)	0.44	0.25 (0.06)	0.24 (0.07)	0.25 (0.06)	0.18	<0.001
Proportion foreign born	0.15 (0.11)	0.15 (0.11)	0.16 (0.11)	0.09	0.14 (0.11)	0.13 (0.11)	0.14 (0.11)	0.15	<0.001

MRSA, methicillin-resistant *Staphylococcus aureus*; MSSA, methicillin-sensitive *Staphylococcus aureus*; SSTIs, skin and soft tissue infections.

Table 2 MRSA compared with MSSA infections (skin and soft tissue infection only) by paediatric and adult incidence for bivariate and multivariable models

Individual level	Paediatric skin and soft tissue infections				Adult skin and soft tissue infections			
	Crude OR (95% CI)	P value	Adjusted OR (95% CI)	P value	Crude OR (95% CI)	P value	Adjusted OR (95% CI)	P value
Individual level								
Age*								
Level 1	Referent		Referent		Referent		Referent	
Level 2	1.05 (0.75 to 1.48)	0.78	1.01 (0.71 to 1.42)	0.97	1.21 (0.98 to 1.49)	0.08	1.21 (0.98 to 1.50)	0.08
Level 3	0.55 (0.41 to 0.73)	<0.001	0.55 (0.41 to 0.74)	<0.001	0.98 (0.79 to 1.20)	0.81	0.98 (0.79 to 1.20)	0.82
Level 4	0.63 (0.47 to 0.85)	0.002	0.64 (0.47 to 0.87)	0.003	1.25 (1.00 to 1.55)	0.05	1.27 (1.02 to 1.58)	0.04
Gender								
Female	Referent		Referent		Referent		Referent	
Male	0.87 (0.70 to 1.08)	0.21	0.96 (0.86 to 1.07)	0.45	1.00 (0.90 to 1.10)	0.91	1.01 (0.96 to 1.06)	0.68
Race								
White	Referent		Referent		Referent		Referent	
Black	1.43 (1.16 to 1.76)	0.001	1.35 (1.09 to 1.67)	0.007	1.24 (1.08 to 1.42)	0.003	1.24 (1.08 to 1.43)	0.002
Other	0.72 (0.48 to 1.06)	0.09	0.69 (0.46 to 1.02)	0.06	0.74 (0.58 to 0.95)	0.02	0.73 (0.57 to 0.94)	0.02
Ethnicity								
Non-Hispanic	Referent		Referent		Referent		Referent	
Hispanic	0.76 (0.65 to 0.89)	0.001	0.80 (0.67 to 0.95)	0.01	0.88 (0.78 to 1.00)	0.04	0.90 (0.80 to 1.02)	0.09
Area level (census tract)								
Income Inequality Index	1.40 (0.19 to 10.57)	0.74			1.35 (0.53 to 3.44)	0.53		
Crowding								
No	Referent		Referent		Referent		Referent	
Yes	1.41 (1.04 to 1.90)	0.03	1.40 (1.01 to 1.93)	0.04	1.34 (1.17 to 1.53)	<0.001	1.29 (1.12 to 1.48)	<0.001
Racial-ethnic concentration								
≤47.8%	Referent		Referent		Referent		Referent	
>47.8%	1.47 (1.19 to 1.83)	<0.001	1.31 (1.03 to 1.65)	0.03	1.03 (0.94 to 1.14)	0.52		
Proportion no HS diploma	1.94 (0.65 to 5.75)	0.23			2.60 (1.49 to 4.54)	<0.001	2.47 (1.29 to 4.74)	0.007
Proportion under 18 years old	0.29 (0.04 to 2.15)	0.22			1.06 (0.44 to 2.52)	0.90		
Poverty concentration								
≤40%	Referent		Referent		Referent		Referent	
>40%	1.40 (0.81 to 2.42)	0.23			1.04 (0.78 to 1.38)	0.81		
Proportion no health insurance	2.30 (0.78 to 6.84)	0.13			2.43 (1.42 to 4.17)	0.001		
Proportion under 18 years old	0.29 (0.04 to 2.15)	0.22			1.06 (0.44 to 2.52)	0.90		
Proportion foreign born	0.31 (0.13 to 0.76)	0.01	0.35 (0.13 to 0.90)	0.03	0.95 (0.61 to 1.49)	0.82	0.58 (0.35 to 0.96)	0.03

*Pediatric: level 1=0–2 years, level 2=>2–5 years, level 3=>5–13 years, level 4=>13–18 years (inclusive); adult: level 1=19–25 years (inclusive), level 2=>25–45 years (inclusive), level 3=>45–65 years, level 4=65+ years (non-inclusive).
HS, high school; MRSA, methicillin-resistant *Staphylococcus aureus*; MSSA, methicillin-sensitive *Staphylococcus aureus*.

Table 3 MRSA compared with MSSA infections (invasive infection only) by paediatric and adult incidence for bivariate and multivariable models

Individual level	Invasive paediatric				Invasive adult			
	Crude OR (95% CI)	P value	Adjusted OR (95% CI)	P value	Crude OR (95% CI)	P value	Adjusted OR (95% CI)	P value
Individual level								
Age*								
Level 1	Referent		Referent		Referent		Referent	
Level 2	2.21 (0.58 to 8.51)	0.25	2.64 (0.61 to 11.40)	0.19	0.70 (0.39 to 1.26)	0.23	0.68 (0.37 to 1.22)	0.20
Level 3	1.19 (0.46 to 3.13)	0.72	2.25 (0.76 to 6.69)	0.14	0.63 (0.36 to 1.11)	0.11	0.64 (0.36 to 1.13)	0.13
Level 4	1.41 (0.40 to 5.02)	0.60	2.11 (0.64 to 12.03)	0.17	1.03 (0.58 to 1.81)	0.93	1.09 (0.61 to 1.94)	0.77
Gender								
Female	Referent		Referent		Referent		Referent	
Male	0.90 (0.41 to 2.00)	0.80	1.05 (0.68 to 1.62)	0.82	0.84 (0.70 to 1.02)	0.07	0.94 (0.86 to 1.04)	0.24
Race								
White	Referent		Referent		Referent		Referent	
Black	1.85 (0.91 to 3.77)	0.09	2.05 (0.95 to 4.45)	0.07	1.63 (1.21 to 2.19)	0.001	1.69 (1.25 to 2.29)	<0.001
Other	1.21 (0.40 to 3.69)	0.73	1.58 (0.48 to 5.13)	0.45	0.55 (0.31 to 0.97)	0.04	0.54 (0.30 to 0.96)	0.04
Ethnicity								
Non-Hispanic	Referent		Referent		Referent		Referent	
Hispanic	0.76 (0.42 to 1.35)	0.34	1.21 (0.61 to 2.42)	0.58	0.77 (0.62 to 0.97)	0.02	0.89 (0.70 to 1.12)	0.31
Census tract level								
Income Inequality Index	2.65 (0.00 to 999.99)	0.81			4.34 (0.86 to 21.98)	0.08		
Crowding								
No	Referent				Referent			
Yes	6.34 (0.81 to 49.49)	0.08			1.05 (0.81 to 1.34)	0.73		
Racial ethnic concentration								
≤47.8%	Referent				Referent			
>47.8%	4.66 (1.85 to 11.71)	0.001			1.03 (0.86 to 1.24)	0.74		
Proportion no HS diploma	3.79 (0.07 to 214.15)	0.52			2.24 (0.74 to 6.73)	0.15		
Poverty concentration								
≤40%	Referent				Referent			
>40%	3.55 (0.68 to 18.54)	0.13			1.46 (0.96 to 2.22)	0.08		
Proportion no health insurance	11.60 (0.32 to 425.26)	0.18			2.68 (0.93 to 7.75)	0.07		
Proportion under 18 years old	0.45 (0.00 to 999.99)	0.84			0.43 (0.10 to 1.80)	0.25		
Proportion foreign born	0.20 (0.01 to 5.04)	0.33			0.67 (0.27 to 1.65)	0.38		

*Paediatric: level 1=0–2 years, level 2=>2–5 years, level 3=>5–13 years, level 4=>13–18 years (inclusive); adult: level 1=19–25 years (inclusive), level 2=>25–45 years, level 3=>45–65 years, level 4=65+ years (non-inclusive).
HS, high school; MRSA, methicillin-resistant *Staphylococcus aureus*; MSSA, methicillin-sensitive *Staphylococcus aureus*.
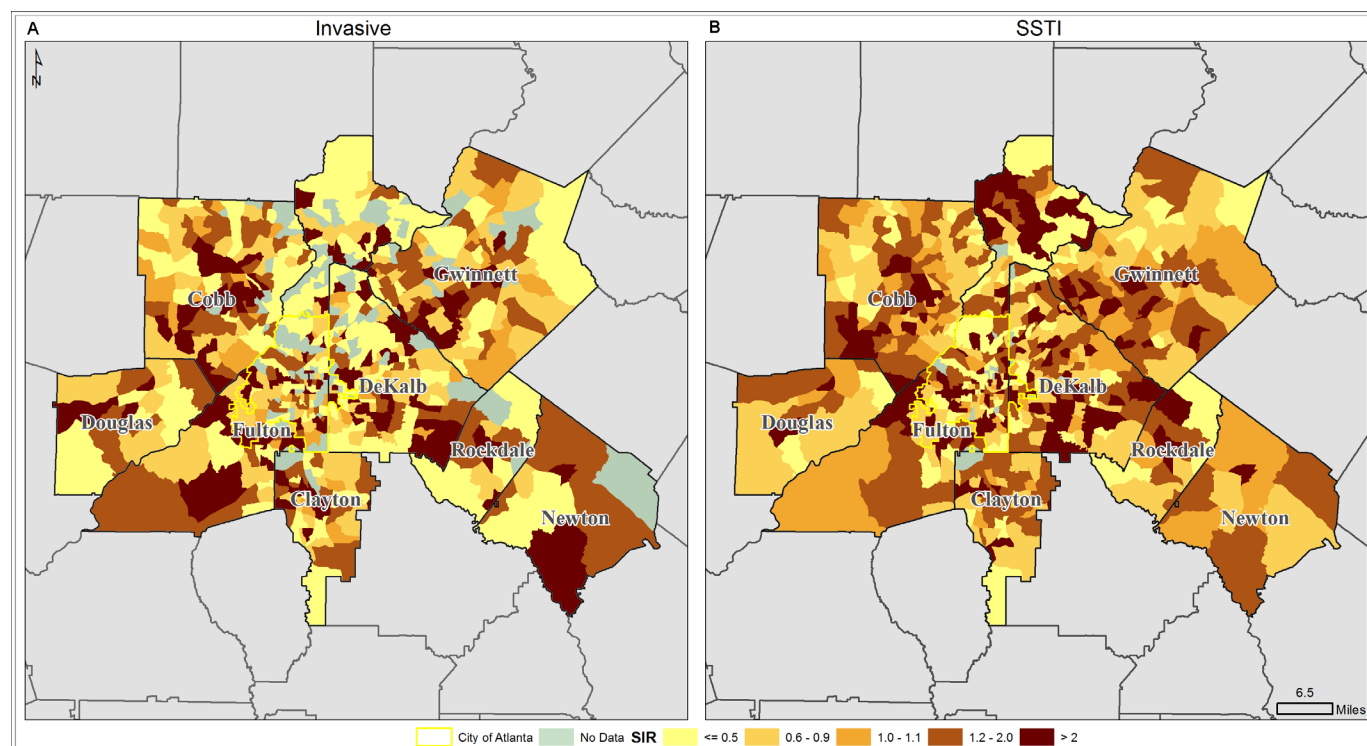
Figure 2 Standardised incidence ratio (SIR) for *Staphylococcus aureus* infections, stratified by type of infection (invasive (A) and skin and soft tissue, (B)). SSTI, skin and soft tissue infection.

invasive disease. Among children, MRSA-related SSTIs were >10 times that of invasive MRSA. Infants have been shown to be colonised with *S. aureus* in up to 60%,[23–26] which is consistent with our results that young children (0–2 years) are at increased risk of MRSA SSTIs; perinatal colonisation coupled with possible common paediatric conditions of eczema or diaper dermatitis may be explanatory of this finding.

A number of studies have reported on racial/ethnic disparities associated with MRSA-related infections.[3 9 22] In our analysis, we also found the rate of MRSA infections increased among black adults and children, regardless of the type of infection; however, this disparity was no longer evident once we adjusted for spatial clustering through the random effect of census tract and the area-level crowding variable. By controlling for place-based crowding, we demonstrate decreased racial differences at the community or area level, since most densely populated census tracts in our catchment include predominantly black communities. Population crowding (household or community level) has been previously cited as a risk for all *S. aureus*, regardless of age, gender or race.[22 27] As such, allocation of prevention resources, particularly in areas with high levels of household crowding, may reduce the burden of MRSA infections disproportionately affecting black communities living in crowded settings.

We observed the 'Hispanic paradox' in MRSA SSTIs among both Hispanic adults and children. This 'protective effect' has been reported by others.[28 29] Reasons for this may be similar to those factors seen in other conditions where Hispanics have better health outcomes (eg,

overall, Hispanics living in the USA tend to have better diets and lower smoking rates, though they are twice as likely to be living below poverty and more likely to be uninsured[30]). Cultural practices in communities where the majority of residents are of similar ethnicity may lower risk of developing MRSA-related infections.[31 32] For example, decreased utilisation of antimicrobials to treat an infection where there might be a culturally based remedy may indirectly decrease the risk of development of MRSA. Further research into specific cultural influences is needed.

Areas of concentrated poverty did not appear to be a risk factor for MRSA SSTIs at the community level. However, transmission dynamics of SSTIs are directly related to the spatial proximity of individuals. Our findings are consistent with others in associating crowding with MRSA SSTIs for both children and adults.[22 27] About 85% of children and adults with MRSA lived in areas with evidence of crowding. Our hotspot analyses demonstrated a 'band' inside the city of Atlanta, running from northwest to southeast, devoid of any hot or cold spots. This band mapped to a predominantly industrial section with little crowding. In comparison, other areas have socioenvironmental conditions of increased opportunities for person-to-person transmission (eg, neighbourhoods with concentrated multiunit housing, K-12 schools, or daycare centres inhabited by children and adults alike); these place-based factors and their degree of contribution to risks need further investigation.

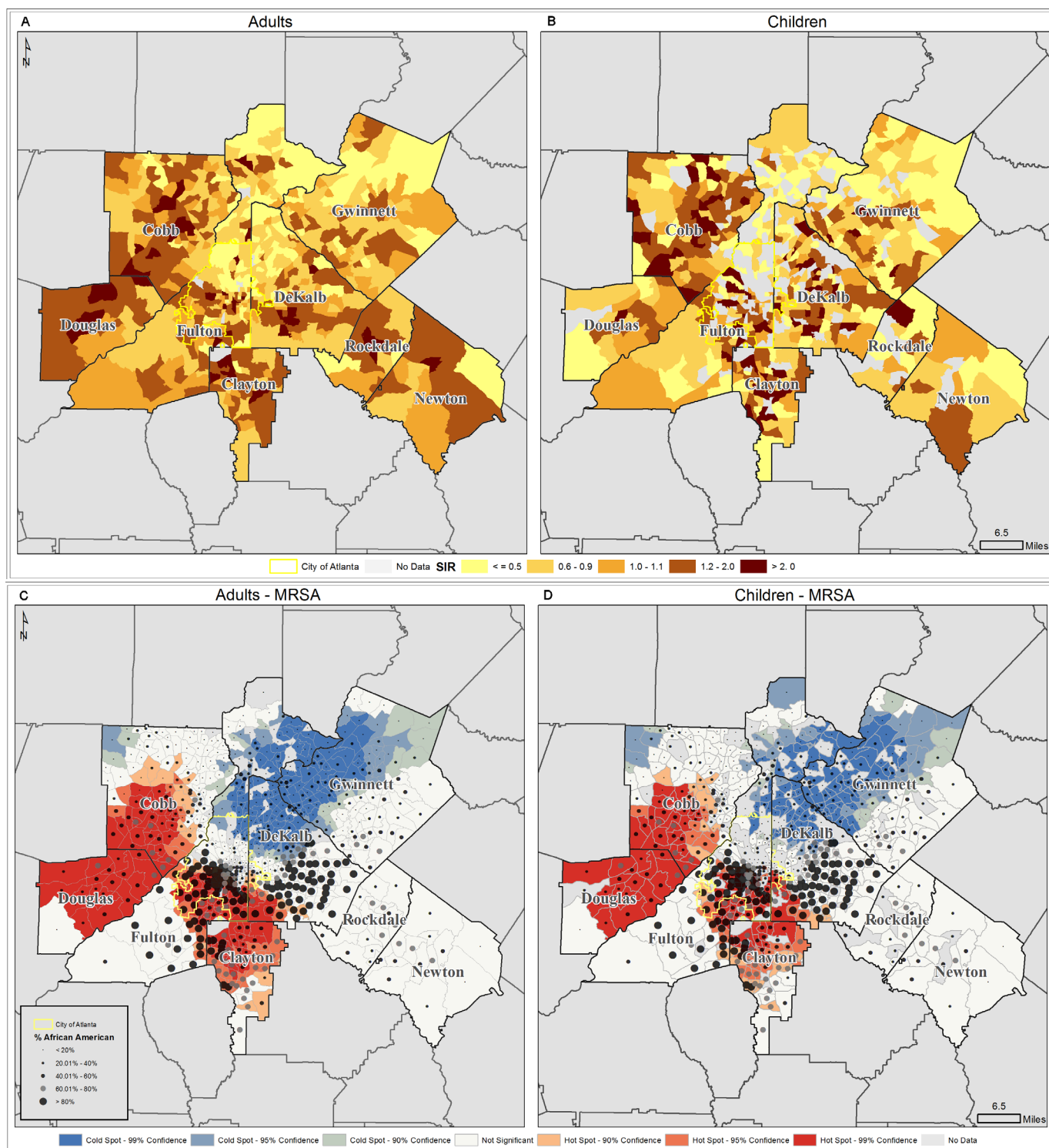Communities with higher rates of foreign-born populations were protective against MRSA SSTIs in

Figure 3 Standardised incidence ratio (SIR) for *Staphylococcus aureus* infections, stratified by adults and children (A,B) and hot and cold spots of MRSA infections in Health District 3, comparing adults and children (C,D). MRSA, methicillin-resistant *S. aureus*.

both children and adults; however, in our adjusted multilevel model, we did not see an association between *S. aureus* infections and areas with higher rates of foreign-born residents. Piper Jenks *et al* also reported that foreign-born individuals were at higher risk of MSSA than MRSA infections in their analyses of patients presenting with SSTIs in New York.[33] After

adjusting for foreign-born population, crowding and areas 'concentrated' with non-Hispanic, non-white populations, we saw increased risk of MRSA SSTIs among children only. Additional studies are needed to examine more closely the relevance of years in birthplace outside of the USA and the risks of developing either MRSA or MSSA infections.

Modifiable determinants of health and wellness include income and education, so that as income level increases, education levels usually also increase, and both correlate with better health outcomes. Thus, not surprisingly, we, like others, saw an increased risk of MRSA SSTIs in adults with lower education attainment.[34] Limited access to credible information resources (eg, internet, opportunities for preventive care or a medical home) in preventing MRSA SSTIs may contribute to this finding.

There were several limitations to this analysis, such as excluding laboratory sites due to incomplete SSTI-related data. Additionally, the data that could not be georeferenced may impact the generalisability of our findings. Children experienced far fewer invasive infections, particularly MRSA, limiting the reliability of associated estimates. Finally, surveillance conducted in metro Atlanta may not be representative of other areas in the USA. However, the major strength of this study is the use of a large georeferenced dataset of laboratory-confirmed MRSA or MSSA to identify individual and neighbourhood sociodemographic risk factors. Data are representative of all *S. aureus* in a diverse geographical catchment area and are not limited to a single health system or community. By using information on census tracts, we captured smaller clusters of socioenvironmental characteristics for individuals with confirmed infections. Furthermore, we evaluated the spatial relatedness between categories of *S. aureus* infections and computed covariates using reliable population estimates.

This large population-based analysis of *S. aureus* SSTIs and invasive infections in a large urban area revealed the importance of and contrast between place-based risks among children and adults for MRSA compared with MSSA infections. Understanding the relevance of geographical variations can lead to identifying those place-based differences in socioeconomic and socioecological variables which contribute to risk of both MRSA and MSSA infections. Our findings do not identify risks at the individual level, but rather, are based on population effects and ecological conditions at the census tract level which may contribute to risks of *S. aureus* infections. The findings can then serve as the basis for developing targeted interventions, such as efforts to reduce crowding or increase equity of healthcare resources, in areas with significant community-level risk factors for *S. aureus* infections, while adjusting the approach based on the age group and type of infection.

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Competing interests None declared.

Patient and public involvement Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

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Supplemental Table 1. Multiple imputation of demographics for incident *S. aureus* skin and soft tissue (n=7,800) and invasive (n=2,038) infections

|	All Case Analysis		Multiple Imputation 1		Multiple Imputation 2		Multiple Imputation 3		Multiple Imputation 4		Multiple Imputation 5	
	SSTI	Invasive	SSTI	Invasive	SSTI	Invasive	SSTI	Invasive	SSTI	Invasive	SSTI	Invasive
Race												
American Indian/Alaska Native	21	4										
Asian	158	32										
Black	3,446	1,012	3,864	1,045	3,838	1,057	3,825	1,049	3,882	1,054	3,862	1,054
Native Hawaiian/Pacific-Islander	13	8										
White	3,162	845	3,715	943	3,744	936	3,759	943	3,702	937	3,727	937
Unknown	1,000	137										
Other	-	-	221	50	218	45	216	46	216	47	211	47
Ethnicity												
Hispanic	488	124	577	130	573	128	562	130	567	127	565	129
Non-Hispanic	5,966	1,846	7,223	1,908	7,227	1,910	7,238	1,908	7,233	1,911	7,235	1,909
Unknown	1,346	68										
Sex												
Male	4,257	821	4,259	821	4,258	821	4,258	821	4,259	821	4,259	821
Female	3,541	1,217	3,541	1,217	3,542	1,217	3,542	1,217	3,541	1,217	3,541	1,217
Unknown	2	0										
Age Category												
0-2	344	78	344	78	344	78	344	78	344	78	344	78
>2-5	216	11	216	11	216	11	216	11	216	11	216	11
>5-13	468	34	468	34	468	34	468	34	468	34	468	34
>13-18	403	15	403	15	403	15	403	15	403	15	403	15
19-25	425	52	425	52	425	52	425	52	425	52	425	52
>25-45	1,941	362	1,942	362	1,942	362	1,942	362	1,942	362	1,941	362
>45-65	2,493	833	2,493	833	2,493	833	2,494	833	2,494	833	2,494	833
>65	1,508	653	1,509	653	1,509	653	1,508	653	1,508	653	1,509	653
Unknown	2	0										

Supplemental Table 2. Demographics of pediatric and adult *S. aureus* incidents by methicillin sensitivity based on multiple imputation

|	Pediatric				Adult				
	All (n=1,569)	**MRSA (n=557)**	**MSSA (n=1,012)**	*P* value	**All (n=8,269)**	**MRSA (n=3,637)**	**MSSA (n=4,632)**	*P* value	**All *P* value**
Individual Level, No. (%)									
County				0.05				<0.001	<0.001
Clayton	147 (9.4)	62 (11.1)	85 (8.4)		664 (8.0)	326 (9.0)	338 (7.3)		
Cobb	408 (26.0)	135 (24.2)	273 (27.0)		1,864 (22.5)	810 (22.3)	1,054 (22.8)		
DeKalb	332 (21.2)	113 (20.3)	219 (21.6)		1,440 (17.4)	603 (16.6)	837 (18.1)		
Douglas	63 (4.0)	31 (5.6)	32 (3.2)		520 (6.3)	267 (7.3)	253 (5.5)		
Fulton	266 (17.0)	101 (18.1)	165 (16.3)		1,752 (21.2)	794 (21.8)	958 (20.7)		
Gwinnett	291 (18.5)	91 (16.3)	200 (19.8)		1,510 (18.3)	642 (17.7)	868 (18.7)		
Newton	37 (2.4)	12 (2.2)	25 (2.5)		278 (3.4)	94 (2.6)	184 (4.0)		
Rockdale	25 (1.6)	12 (2.2)	13 (1.3)		241 (2.9)	101 (2.8)	140 (3.0)		
Race				<0.001				<0.001	<0.001
White	595 (37.9)	176 (31.6)	419 (41.4)		4,107 (49.7)	1,733 (47.6)	2,374 (51.3)		
Black	891 (56.8)	360 (64.6)	531 (52.5)		3,983 (48.2)	1,844 (50.7)	2,139 (46.2)		
Other	83 (5.3)	21 (3.8)	62 (6.1)		179 (2.2)	60 (1.6)	119 (2.6)		
Ethnicity				<0.001				0.003	<0.001
Non-Hispanic	1,319 (84.1)	495 (88.9)	824 (81.4)		7,827 (94.7)	3,473 (95.5)	4,354 (94.0)		
Hispanic	250 (15.9)	62 (11.1)	188 (18.6)		442 (5.3)	164 (4.5)	278 (6.0)		
Gender				0.18				0.24	0.002
Female	753 (48.0)	280 (50.3)	473 (46.6)		3,610 (43.7)	1,614 (44.4)	1,996 (43.1)		
Male	816 (52.0)	277 (49.7)	539 (53.3)		4,659 (56.3)	2,023 (55.6)	2,636 (56.9)		
Census Tract Level, Mean (SD)									
Income Inequality Index	0.41 (0.05)	0.41 (0.06)	0.41 (0.05)	0.68	0.41 (0.05)	0.42 (0.05)	0.41 (0.05)	0.32	0.35
Crowding, No. (%)				0.01				<0.001	0.19
Yes	1,319 (84.1)	486 (87.3)	833 (82.3)		6,840 (82.7)	3,076 (84.6)	3,764 (81.3)		
Racial Ethnic Concentration, No. (%)				<0.001				0.64	0.86
> 47.8%	793 (50.5)	322 (57.8)	471 (46.5)		4,200 (50.8)	1,858 (51.1)	2,342 (50.6)		
Proportion No High School Diploma	0.13 (0.10)	0.14 (0.09)	0.13 (0.10)	0.23	0.12 (0.09)	0.13 (0.09)	0.12 (0.09)	0.06	<0.001
Poverty Concentration, No. (%)				0.12				0.35	0.46
> 40%	60 (3.8)	27 (4.9)	33 (3.3)		285 (3.5)	133 (3.7)	152 (3.3)		
Proportion No Health Insurance	0.18 (0.10)	0.18 (0.10)	0.18 (0.10)	0.10	0.16 (0.09)	0.17 (0.09)	0.16 (0.09)	0.09	<0.001
Proportion Under 18 years-old	0.26 (0.05)	0.26 (0.05)	0.26 (0.05)	0.24	0.25 (0.06)	0.25 (0.06)	0.25 (0.06)	0.85	<0.001
Proportion Foreign-Born	0.17 (0.12)	0.15 (0.12)	0.17 (0.13)	0.02	0.15 (0.11)	0.15 (0.11)	0.15 (0.11)	0.82	<0.001

Supplemental material

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Supplemental Table 3. Multilevel model for SSTI MRSA compared to MSSA by pediatric and adult incidents

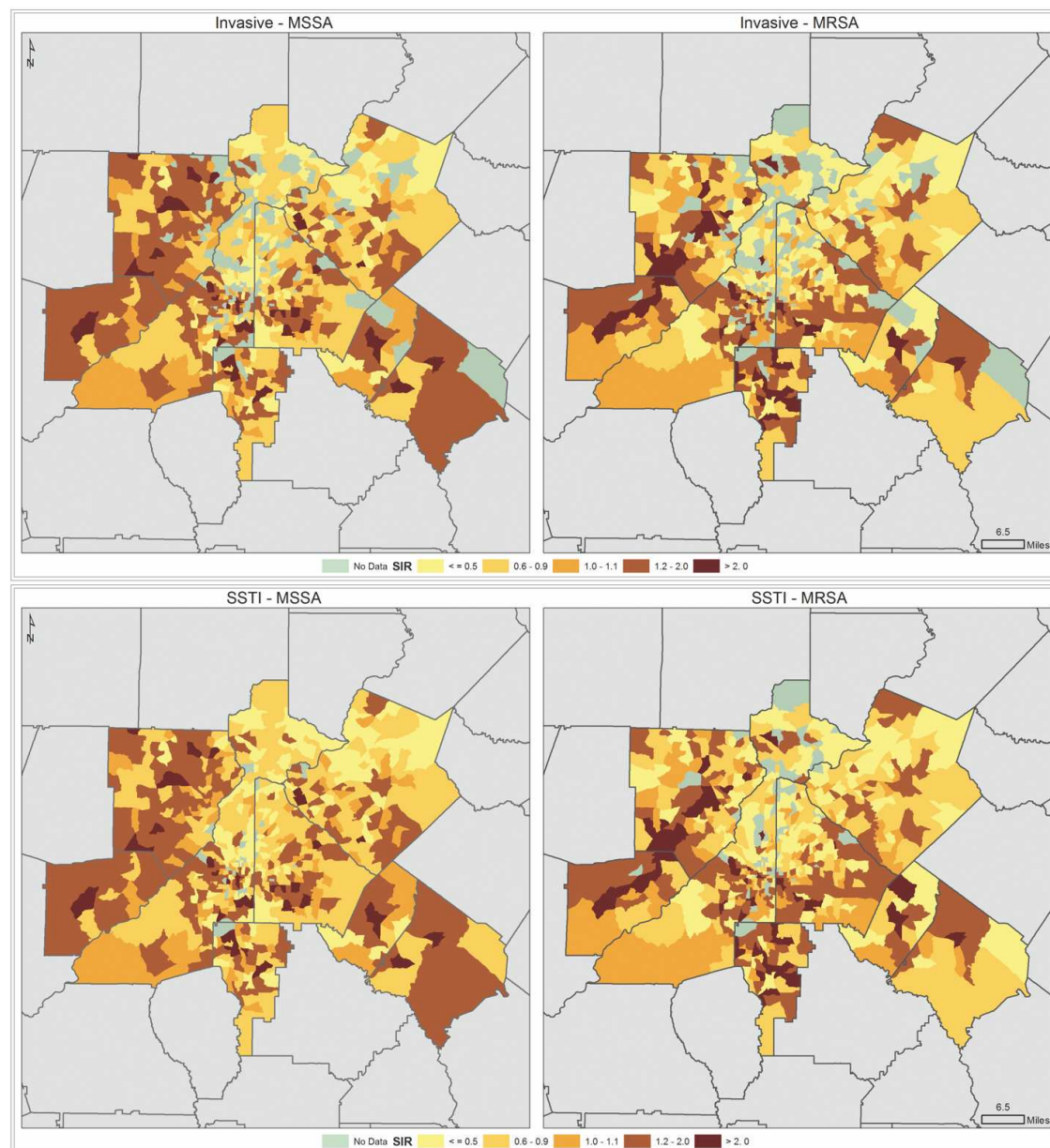| Variable	Pediatric		Adult	
	Adjusted OR (95% CI)	***P* value**	**Adjusted OR (95% CI)**	***P* value**
Age[a]				
Level 1	Referent		Referent	
Level 2	1.00 (0.69, 1.45)	0.99	1.24 (0.97, 1.60)	0.08
Level 3	0.53 (0.39, 0.73)	<0.001	0.96 (0.75, 1.23)	0.75
Level 4	0.63 (0.45, 0.87)	0.005	1.33 (1.03, 1.73)	0.03
Gender				
Female	Referent		Referent	
Male	0.93 (0.73, 1.17)	0.53	1.03 (0.92, 1.16)	0.61
Race				
White	Referent		Referent	
Black	1.09 (0.77, 1.54)	0.62	1.09 (0.95, 1.24)	0.22
Other	0.61 (0.30, 1.23)	0.16	0.63 (0.40, 0.98)	0.04
Ethnicity				
Non-Hispanic	Referent		Referent	
Hispanic	0.63 (0.43, 0.94)	0.02	0.75 (0.56, 0.99)	0.05
Crowding				
No	Referent		Referent	
Yes	1.44 (1.02, 2.04)	0.04	1.35 (1.14, 1.59)	<0.001
Racial Ethnic Concentration				
$\leq$ 47.8%	Referent			
> 47.8%	1.19 (0.90, 1.58)	0.22		
Proportion No HS Diploma			2.98 (1.35, 6.56)	0.007
Proportion Foreign-Born	0.55 (0.18, 1.63)	0.28	0.63 (0.34, 1.18)	0.15

[a] Pediatric: Level 1= 0-2 years, Level 2 = >2-5 years, Level 3 = >5-13 years, Level 4 = >13-18 years (inclusive); Adult: Level 1 = 19-25 years (inclusive), Level 2 = >25-45 years, Level 3 = >45-65 years, Level 4 = 65+ years (non-inclusive)
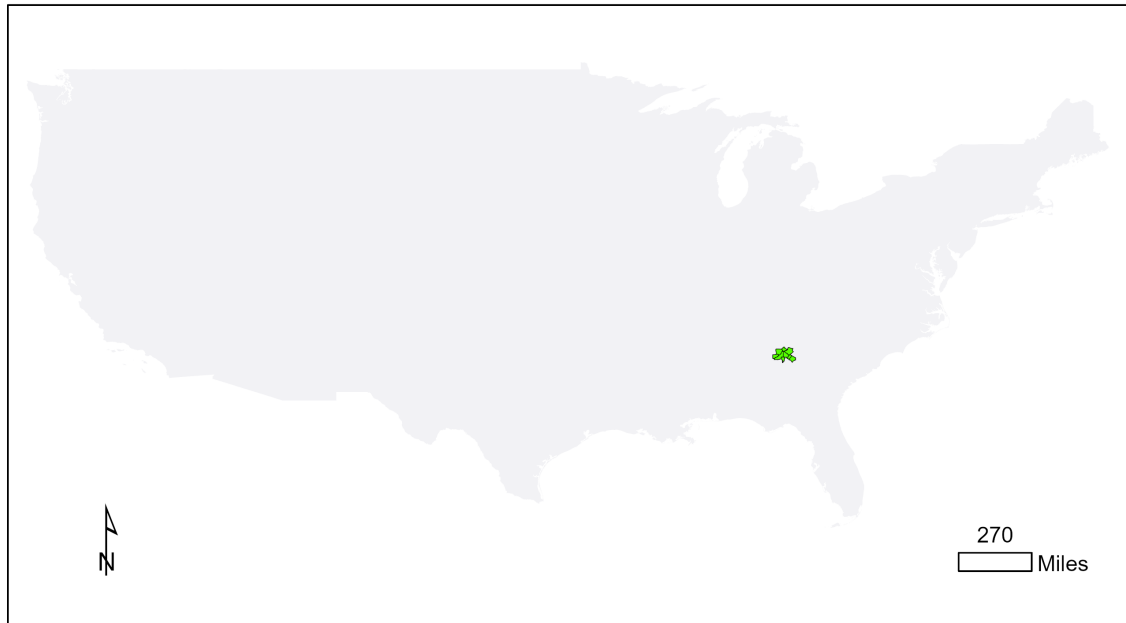
eFigure 1. Counties in Georgia Health District 3 contextualized in contiguous United States map.
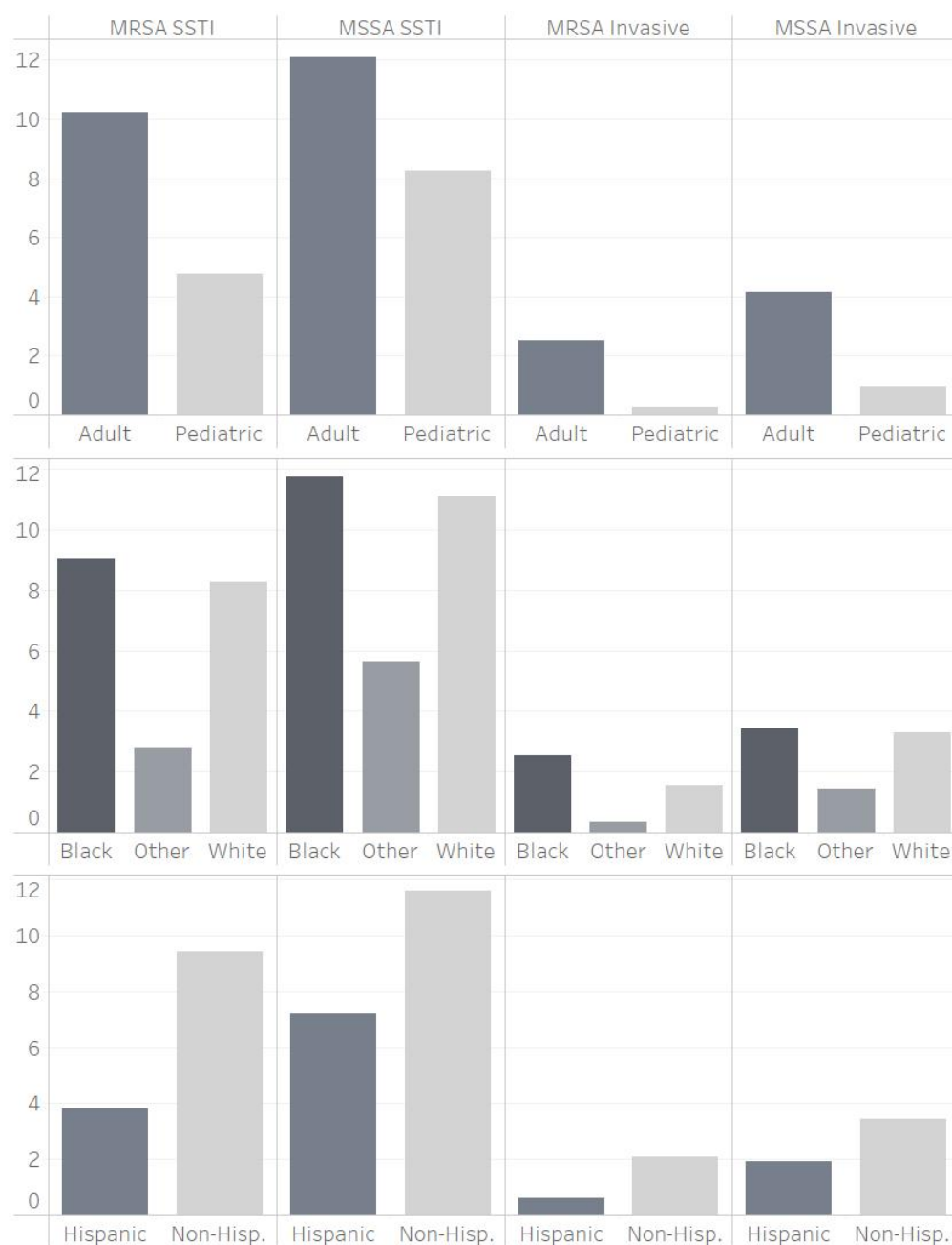
eFigure 2. Crude incidence rates (per population of 100,000) of invasive and skin and soft tissue *S. aureus* infections by resistance to methicillin, stratified by age group, race, and ethnicity. Created with Tableau (version 9.1).

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eFigure 3. Standardized incidence ratios of invasive and skin and soft tissue infections caused by *S. aureus* by methicillin-resistance standardized to overall HD3 infection-specific rate
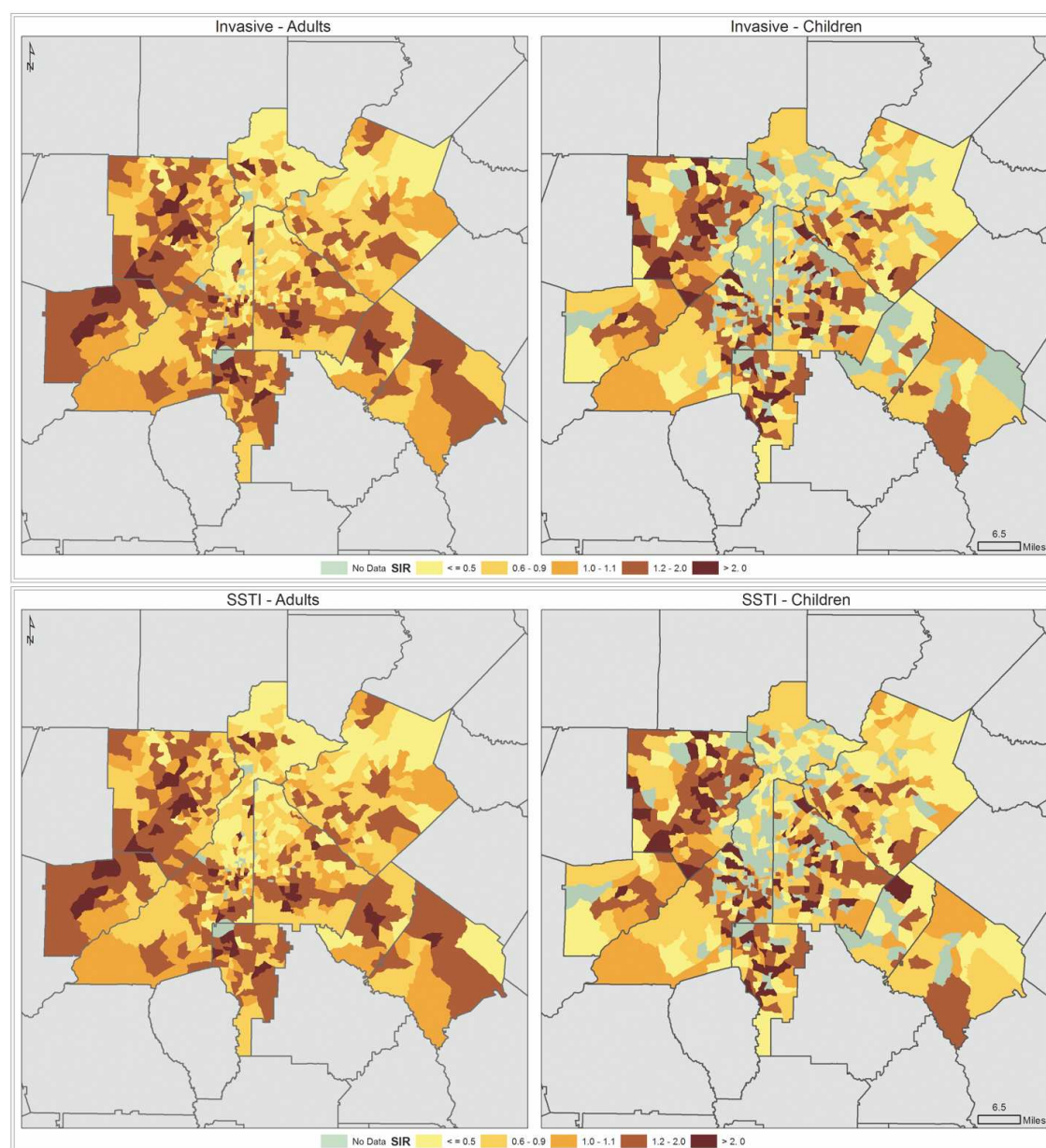
eFigure 4. Standardized incidence ratios of pediatric and adult *S. aureus* (MRSA or MSSA) infections by infection type standardized to overall incidence of age group rate for infection type