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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.

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. Hospital-associated MRSA (HA-MRSA) and community-associated MRSA (CA-MRSA) infections have been well described in previous literature, highlighting the risks associated with invasive HA-MRSA infections (hospitalisation, extreme age groups, males, black race and haemodialysis patients) 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)). 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. 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, 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. This area is shown on a map of the USA in online supplemental figure 1.

**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). 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 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.

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. 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.

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 χ² 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, 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
Geocoding of all data was previously done 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 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 |  |  |  |  |  |  |  |  |
| Paediatric               |  |  |  |  |  |  |  |  |  |
| Adult                    |  |  |  |  |  |  |  |  |  |
| County                   | <0.001 |  |  |  |  |  |  |  |  |
| Clayton                  |  |  |  |  |  |  |  |  |  |
| Cobb                     |  |  |  |  |  |  |  |  |  |
| DeKalb                   |  |  |  |  |  |  |  |  |  |
| Douglas                  |  |  |  |  |  |  |  |  |  |
| Fulton                   |  |  |  |  |  |  |  |  |  |
| Gwinnett                 |  |  |  |  |  |  |  |  |  |
| Newton                   |  |  |  |  |  |  |  |  |  |
| Rockdale                 |  |  |  |  |  |  |  |  |  |
| Race                     | <0.001 |  |  |  |  |  |  |  |  |
| White                    |  |  |  |  |  |  |  |  |  |
| Black                    |  |  |  |  |  |  |  |  |  |
| Other                    |  |  |  |  |  |  |  |  |  |
| Ethnicity                | <0.001 |  |  |  |  |  |  |  |  |
| Non-Hispanic             |  |  |  |  |  |  |  |  |  |
| Hispanic                 |  |  |  |  |  |  |  |  |  |
| Gender                   |  |  |  |  |  |  |  |  |  |
| Female                   | 0.065 |  |  |  |  |  |  |  |  |
| Male                     | 0.088 |  |  |  |  |  |  |  |  |
| 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) | 1088 (83.2) | 0.49 | 0.36 |
| Racial-ethnic concentration, no (%) | 0.04 |  |  |  |  |  |  |  |  |
| >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 |  |  |  |  |  |  |  |  |
| >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 | 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 | 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 | 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 | 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        |  |  |  |  |  |  |  |  |
| 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 | 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 |  |
| Poverty concentration |  |  |  |  |  |  |  |  |
| ≤40%            | Referent | Referent | Referent | Referent | 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, 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 | 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 | 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 | 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 | 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) | 0.001 | 4.34 (0.86 to 21.98) | 0.08 |
| Crowding | | | | | | | | |
| No | Referent | Referent | Referent | Referent | Referent | Referent | 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 | Referent | Referent | Referent | Referent | 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 | Referent | Referent | Referent | Referent | 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.
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%, 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. 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. 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. 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). Cultural practices in communities where the majority of residents are of similar ethnicity may lower risk of developing MRSA-related infections. 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. 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

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**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.
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. Limited access to credible information resources (e.g., 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 Staphylococcus 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 Staphylococcus aureus infections and computed covariates using reliable population estimates.

This large population-based analysis of Staphylococcus 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 Staphylococcus 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 Staphylococcus aureus infections, while adjusting the approach based on the age group and type of infection.

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References
1 Antibiotic Resistance Threats in the United States, 2019. In: CDC, ed. CDC Threat Report. Atlanta, GA 2019.
2 David MZ, Daum RS. Community-associated methicillin-resistant Staphylococcus aureus: epidemiology and clinical consequences of an emerging epidemic. Clin Microbiol Rev 2010;23:616–87.
3 Fridkin SK, Hageman JC, Morrison M, et al. Methicillin-resistant Staphylococcus aureus disease in three communities. N Engl J Med 2005;352:1436–44.
4 Dantes R, Mu Y, Belflower R, et al. National burden of invasive methicillin-resistant Staphylococcus aureus infections, United States, 2011. JAMA Intern Med 2013;173:1970–8.
5 Kleven RS, Morrison MA, Nadle J, et al. Invasive methicillin-resistant staphylococcus aureus infections in the United States. JAMA 2007;298:1763–71.
6 Popovich KJ, Snitkin ES, Hota B, et al. Genomic and epidemiological evidence for community origins of hospital-onset methicillin-resistant staphylococcus aureus bloodstream infections. J Infect Dis 2017;215:1640–7.
7 Tong SYC, Davis JS, Eichenberger E, et al. Multiple imputation with large data sets: a case study of the children's mental health Initiative. Am J Epidemiol 2009;169:1133–9.
8 Bukharie HA. A review of community-acquired methicillin-resistant Staphylococcus aureus infections: epidemiology, pathophysiology, clinical manifestations, and management. Clin Microbiol Rev 2015;28:603–61.
9 See I, Wesson P, Gualandi N, et al. Socioeconomic factors explain racial disparities in invasive community-associated methicillin-resistant Staphylococcus aureus disease rates. Clin Infect Dis 2017;64:597–604.
10 Breyer A, Frazea PW. Skin and soft tissue infections in the emergency department. Emerg Med Clin North Am 2018;36:723–50.
11 Kollef MH, Micek ST. Methicillin-resistant Staphylococcus aureus: a new community-acquired pathogen? Curr Opin Infect Dis 2006;19:161–8.
12 Naimi TS, LeDell KH, Como-Sabetti K, et al. Comparison of community- and health care-associated methicillin-resistant Staphylococcus aureus infection. JAMA 2003;290:2976–84.
13 Olaniyi R, Pozzi C, Grimaldi L. Staphylococcus aureus-associated skin and soft tissue infections: anatomical localization, epidemiology, therapy and prevention. In: Bagnoli F, Rappuoli R, Grandi G, eds. Staphylococcus aureus: microbiology, pathology, immunology, therapy and prophylaxis. Cham: Springer International Publishing, 2017: 199–227.
14 Otto M. Community-associated MRSA: what makes them special? Int J Med Microbiol 2013;303:324–30.
15 Strzyzewski ME, Chambers HF. Skin and soft-tissue infections caused by community-acquired methicillin-resistant Staphylococcus aureus. Clin Infect Dis 2008;46:S368–77.
16 Jackson KA, Gokhale RH, Nadle J, et al. Public health importance of invasive methicillin-sensitive Staphylococcus aureus infections: surveillance in 8 US counties, 2016. Clin Infect Dis 2020;70:1021–8.
17 Emerging Infections Program USA.gov: centers for disease control and prevention 2020.
18 Stuart EA, Azur M, Frangakis C, et al. Multiple imputation with large data sets: a case study of the children’s mental health Initiative. Am J Epidemiol 2009;169:1133–9.
19 Blake K, Kellerson RL, Simic A. Measuring overcrowding in housing. Washington, DC: US Dept of Housing and Urban Development, Office of Policy Development and Research, 2007.
20 State of Arizona Consolidated Plan 2010-2014. In: Housing ADo, ed 2010.
21 Jargowsky PA. Stunning progress, hidden problems: the dramatic decline of concentrated poverty in the 1990s. The living cities census series. The Brookings Institution, 2003.
22 Immergluck LC, Leong T, Malhotra K, et al. Geographic surveillance of community-associated MRSA infections in children using electronic health record data. BMC Infect Dis 2019;19:170.
23 Lindberg E, Adlerberth I, Hesselmar B, et al. High rate of transfer of Staphylococcus aureus from parental skin to infant gut flora. J Clin Microbiol 2004;42:530–4.
24 Lebon A, Labout JAM, Verbrugh HA, et al. Dynamics and determinants of Staphylococcus aureus carriage in infancy: the generation R study. J Clin Microbiol 2008;46:3517–21.
25 Fritz SA, Hogan PG, Hayek G, et al. Staphylococcus aureus colonization in children with community-associated Staphylococcus aureus skin infections and their household contacts. Arch Pediatr Adolesc Med 2012;166:551–7.
26 Jimenez-Truque N, Tedeschi S, Saye EJ, et al. Relationship between maternal and neonatal Staphylococcus aureus colonization. Pediatrics 2012;129:e1252–9.
27 Fritz SA, Epplin EK, Garbutt J, et al. Skin infection in children colonized with community-associated methicillin-resistant Staphylococcus aureus. J Infect 2009;59:394–401.
28 Shapiro A, Raman S, Johnson M, et al. Community-acquired MRSA infections in North Carolina children: prevalence, antibiotic sensitivities, and risk factors. N C Med J 2009;70:102–7.
29 Ali F, Immergluck LC, Leong T, et al. A spatial analysis of health disparities associated with antibiotic resistant infections in children living in Atlanta (2002–2010). EGEMS 2019;7:308.
30 Gonzalez de Gispert J. Hispanic paradox: why immigrants have a high life expectancy. BBC 2015.
31 Tobin JN, Hower S, D’Orazio BM, et al. Comparative effectiveness study of home-based interventions to prevent CA-MRSA infection recurrence. Antibiotics 2021;10:1105.
32 Gotter A. Home remedies for boils: healthline, 2020. Available: https://www.healthline.com/health/home-remedies-for-boils [Accessed 21 Feb 2022].
33 Piper Jenks N, Pardos de la Gandara M, D’Orazio BM, et al. Differences in prevalence of community-associated MRSA and MSSA among U.S. and non-U.S. born populations in six New York community health centers. Travel Med Infect Dis 2016;14:551–60.
34 Maree CL, Eels SJ, Tan J, et al. Risk factors for infection and colonization with community-associated methicillin-resistant Staphylococcus aureus in the Los Angeles County jail: a case-control study. Clin Infect Dis 2010;51:1248–57.