BMJ Open

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

Gerard Thomas Portela ,[1] Traci Leong,[2] Andrew Webster,[3] Anthony Giarrusso,[4] Scott Fridkin,[1] Susan M Ray,[5] David Swerdlow,[6] Lilly Cheng Immergluck [7]

To cite: Portela GT, Leong T, Webster A, *et al*. 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. *BMJ Open* 2022;**12**:e059327. doi:10.1136/bmjopen-2021-059327

► Prepublication history and additional supplemental material for this paper are available online. To view these files, please visit the journal online (http://dx.doi.org/10.1136/bmjopen-2021-059327).

Received 18 November 2021
Accepted 20 July 2022

For numbered affiliations see end of article.

Correspondence to
Gerard Thomas Portela ; gtp14@pitt.edu and
Dr Lilly Cheng Immergluck ; limmergluck@msm.edu

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 georeferenced 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 south-eastern 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.

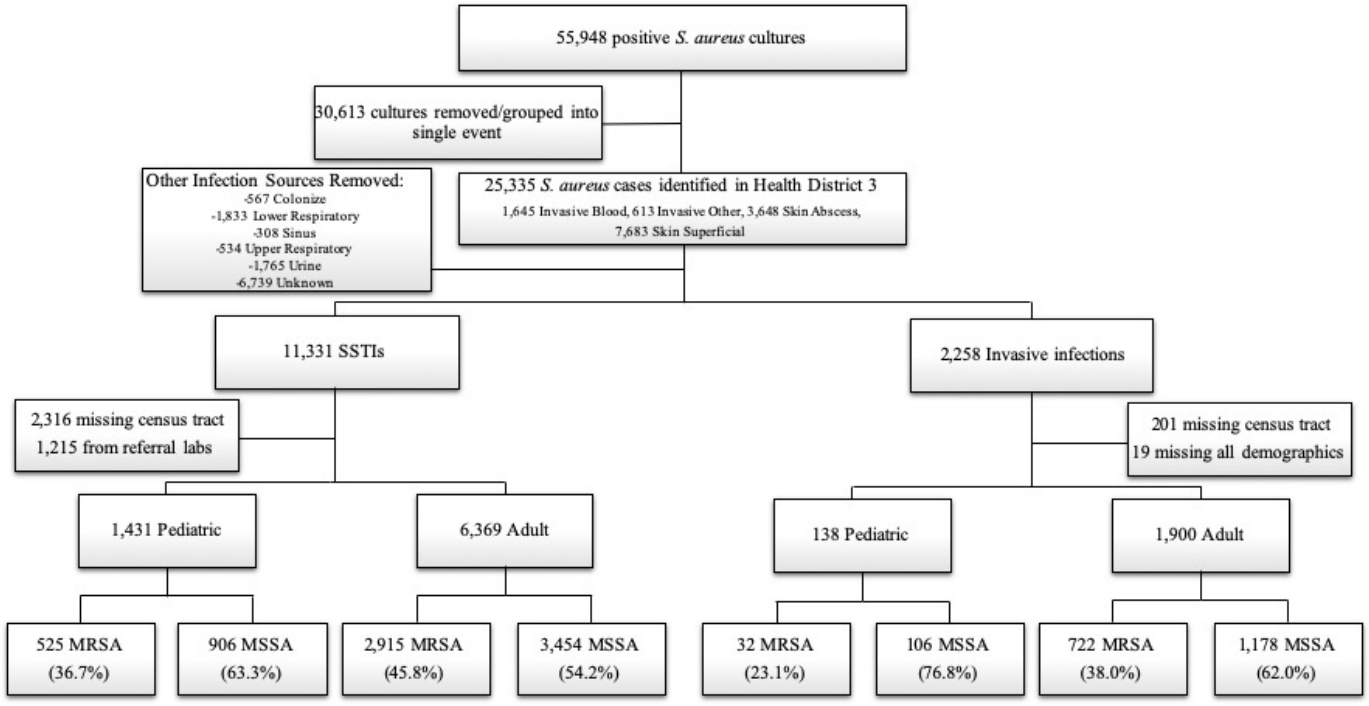

Figure 1 Enrolment scheme for all *Staphylococcus aureus* cultures in adults and children, based on distribution of type of infection (invasive vs non-invasive) and resistance to methicillin, 2017. MRSA, methicillin-resistant *S. aureus*; MSSA, methicillin-sensitive *S. aureus*; SSTIs, skin and soft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

	SSTIs				Invasive infections				
Individual level, no (%)	**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

	Paediatric skin and soft tissue infections				Adult skin and soft tissue infections			
Individual level	**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			
>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			
>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	
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*.

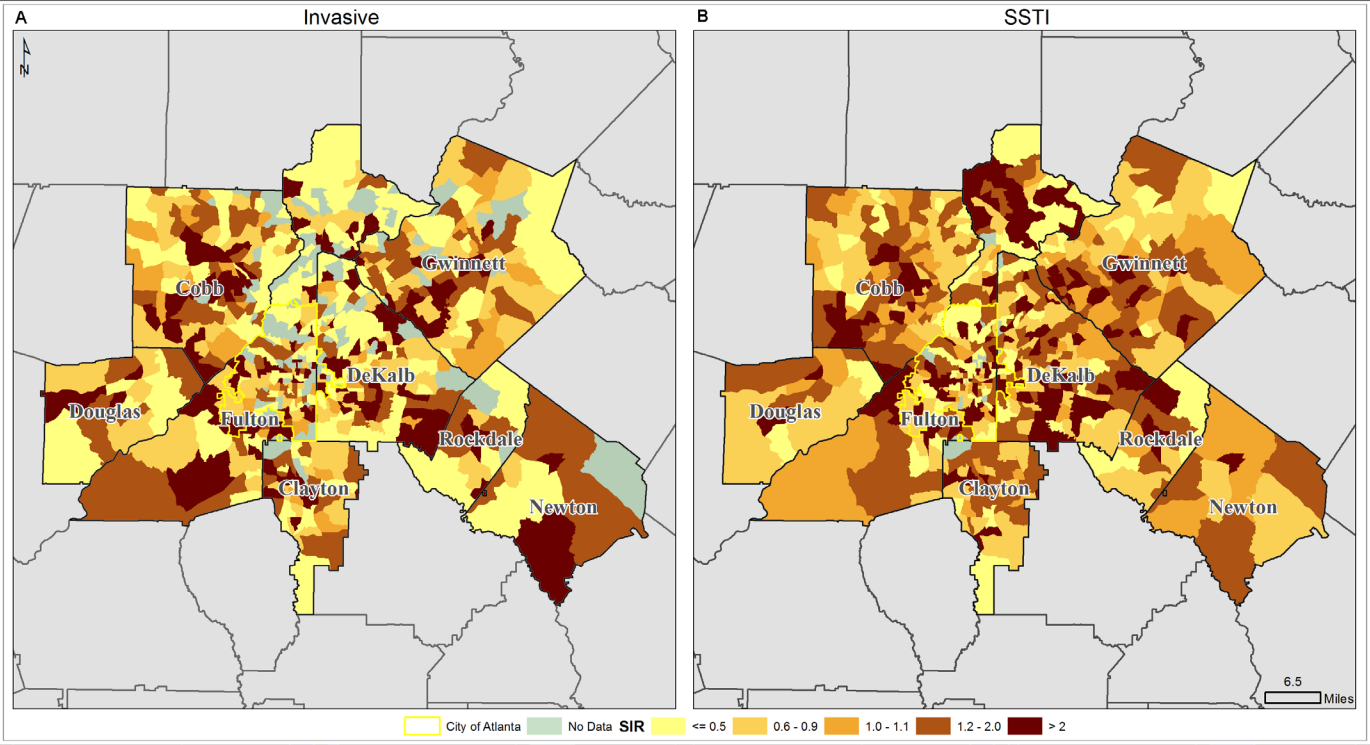

Figure 2 Standardised incidence ratio (SIR) for *Staphylococcus aureus* infections, stratified by type of infection (invasive (A) and skin and soft tissue, (B)). SSTI, skin and soft tissue infection.

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

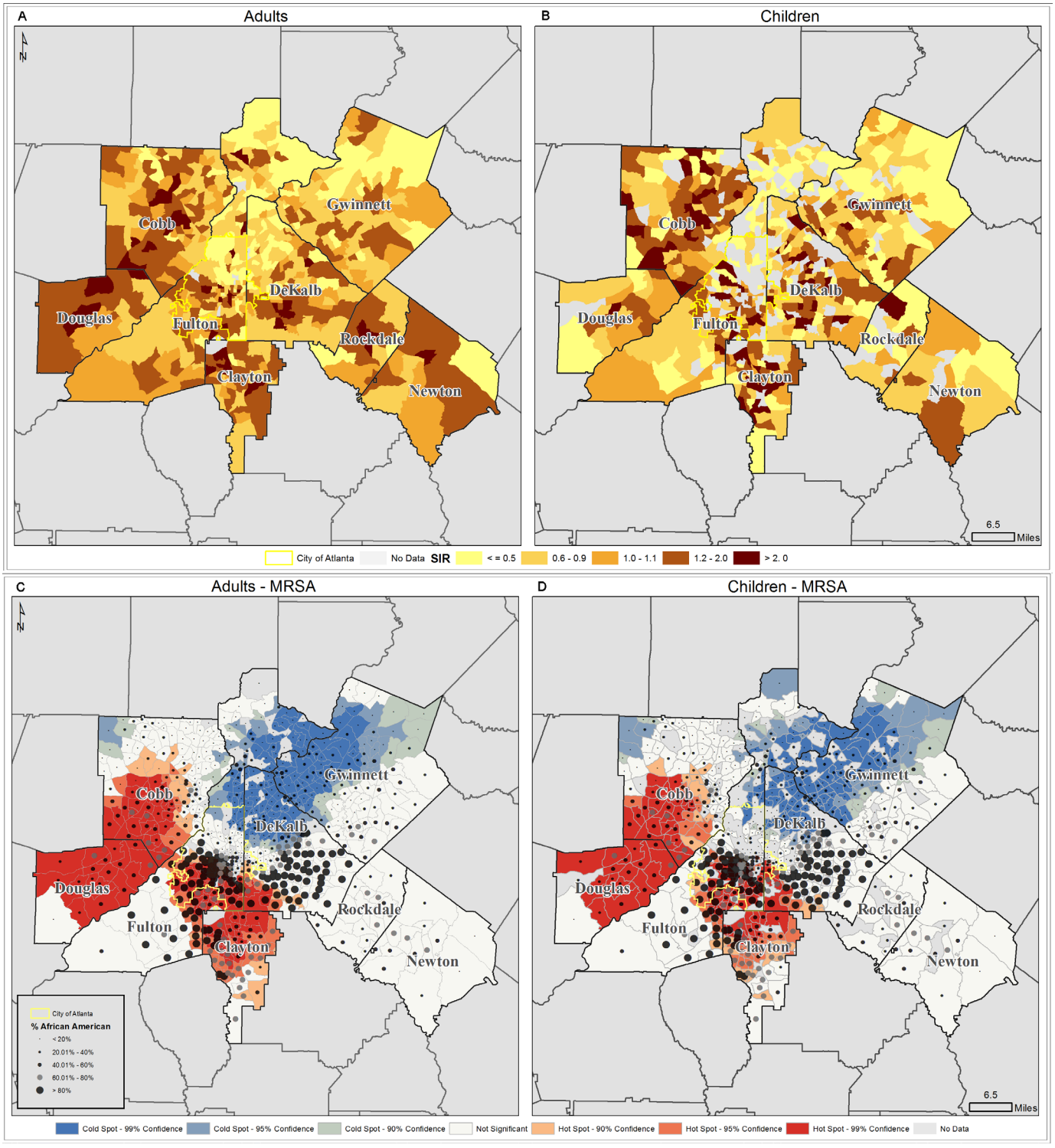

Figure 3 Standardised incidence ratio (SIR) for *Staphylococcus aureus* infections, stratified by adults and children (A,B) and hot and cold spots of MRSA infections in Health District 3, comparing adults and children (C,D). MRSA, methicillin-resistant *S. aureus*.

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.

Author affiliations
[1]Department of Epidemiology, Emory University School of Public Health, Atlanta, Georgia, USA
[2]Department of Biostatistics and Bioinformatics, Emory University, Atlanta, Georgia, USA
[3]Department of Medicine, Emory University, Atlanta, Georgia, USA
[4]College of Design, Georgia Institute of Technology, Atlanta, Georgia, USA
[5]Department of Medicine, Emory University Woodruff Health Sciences Center, Atlanta, Georgia, USA
[6]Pfizer Vaccines, Pfizer, Collegeville, PA, USA
[7]Department of Microbiology, Biochemistry, Immunology, Morehouse School of Medicine, Atlanta, Georgia, USA

Twitter Lilly Cheng Immergluck @limmergluck

Acknowledgements The authors would like to acknowledge the following individuals from Georgia EIP: Minerva Mendez and Amber Britton for the collection of non-invasive *Staphylococcus aureus* data; Shanita Shack for her work on geocoding all patients; Amy Tunali, Rahsaan Overton, and Stepy Thomas for their assistance with study design and data collection for invasive *S. aureus*.

Contributors Guarantor - LCI. Study conception and design—LCI, SF, DS, SMR. Data acquisition—SF. Analysis and interpretation of results—AW, GTP, TL, AG, LCI, SF, SMR, DS. Draft manuscript preparation—GTP, LCI, SF. All authors reviewed the results and revised/approved the final version of the manuscript.

Funding Georgia Emerging Infections Program surveillance of invasive *S. aureus* was funded though the Centers for Disease Control and Prevention (CDC) Emerging Infections Program (grant number U50CK000485). Surveillance of non-invasive *S. aureus* was funded through an agreement between Pfizer and Emory University (grant number CP154653). Research reported in this publication was supported in part by funds received (PHS Grant UL1TR002378) from the Clinical and Translational Science Award Program, National Institutes of Health, as part of the Georgia Clinical & Translational Science Alliance (Georgia CTSA) (formerly, UL1RR025008, Atlanta Clinical and Translational Science Institute (ACTSI)); Grant Number G12-RR03034, a component of the National Institute of Health; Grant Number HS024338-01; K-08 Mentored Clinical Scientist Award, Agency for Healthcare Research & Quality; and Grant Number G08LM013190-0, National Library of Medicine.

Disclaimer The content is solely the responsibility of the authors and does not necessarily represent the official views (or position) of either the National Institutes of Health or the CDC. The funding organisations (other than Pfizer) had no role in the design and conduct of the study, collection, management, analysis of the data, interpretation of the results, review of the manuscript or approval of the study. Pfizer was involved, as co-investigator contributing to the interpretation, review, and approval of the study; but not in the design and conduct of the study, collection, management, or analysis of the data.

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.

Patient consent for publication Not required.

Ethics approval This research has been approved by the Institutional Review Boards at the Atlanta VA Medical Center (data collection) and Emory University (data analysis) (Institutional Review Board Number: MOD003-IRB00094202).

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement No data are available.

ORCID iDs
Gerard Thomas Portela http://orcid.org/0000-0002-1871-6117
Lilly Cheng Immergluck http://orcid.org/0000-0001-8542-896X

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 Klevens RM, 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*. Staphylococcus aureus infections: epidemiology, pathophysiology, clinical manifestations, and management. *Clin Microbiol Rev* 2015;28:603–61.
8 Bukharie HA. A review of community-acquired methicillin-resistant Staphylococcus aureus for primary care physicians. *J Family Community Med* 2010;17:117–20.
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 Breyre A, Frazee BW. 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 potential prophylaxis. 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 Stryjewski 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, Eells 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.