Space Time Trends of Community Onset *Staphylococcus Aureus* Infections in Children Living in Southeastern United States: 2002-2010

Lilly Immergluck (✉ limmergluck@gmail.com)

Morehouse School of Medicine <https://orcid.org/0000-0001-8542-896X>

Ruijin Geng

Morehouse School of Medicine

Chaohua Li

Morehouse School of Medicine, National Center for Primary Care

Mike Edelson

InterDev LLC

Lance Waller

Emory University School of Public Health

George S. Rust

Florida State University College of Medicine

Junjun Xu

Ningbo Consulting Inc.

Traci Leong

Emory University School of Public Health

Peter Baltrus

Morehouse School of Medicine, Department of Community Health & Preventive Medicine

Research article

Keywords: Community onset methicillin-resistant *Staphylococcus aureus*, community onset methicillin susceptible *Staphylococcus aureus*, group-based trajectory modeling, hotspot mapping

Posted Date: September 8th, 2020

DOI: <https://doi.org/10.21203/rs.3.rs-59691/v1>

License: © ⓘ This work is licensed under a Creative Commons Attribution 4.0 International License. [Read Full License](#)

Abstract

Background

Staphylococcus aureus (*S. aureus*) remains a serious cause of infections in the U.S. and worldwide. Non antibiotic resistant *Staphylococcus aureus* (methicillin susceptible or MSSA) is the cause of half of all health care–associated *staphylococcal* infections, and methicillin resistant *Staphylococcus aureus* (MRSA) still is the leading cause of community onset skin and soft tissue infections in the U.S. This is the first study to spatially look at trends of both community onset MRSA and MSSA infections over nine years and determine ‘best’ to ‘worst’ infection trends over a nine year period (2002-2010), which spanned when community onset MRSA infections were occurring in epidemic proportions across the U.S.

Methods

Retrospective study from 2002-2010, using electronic health records of children living in the southeastern U.S. (Atlanta, Georgia) with *S. aureus* infections and relevant U.S. census data (at the census tract level). The Proc Traj for SAS was applied to generate community onset MRSA and MSSA trajectory infection groups (low, high, very high, or deviant trends), and then, mapping of these trajectory groups using census tract boundaries.

Results

From community onset MRSA infection trend patterns (low, high, very high), only 0.8% of the census tracts showed a dramatic increase from 2002-2007 and then a gradual decline from 2008 to 2010. From community onset MSSA infection trend patterns (low and high), 85.7% of ‘high infection’ group persisted throughout the nine year period, compared to 14.3% of ‘low infection’ group over this same period. Low community onset MRSA and MSSA trend patterns were seen throughout the 20 counties of Atlanta, Georgia’s metropolitan statistical area, but more often seen in those counties less densely populated. Census tracts reflecting Atlanta’s ‘innercity’ had the highest proportion of the worst infection trend pattern (community onset MRSA-Very High-CO-MSSA-High or community onset MRSA-High-CO-MSSA-High). The deviant trend of community onset MRSA Very High- CO-MSSA Low infection were in census tracts east of downtown Atlanta.

Conclusions

‘Trends’ of *S. aureus* infection patterns, stratified by antibiotic resistance, over geographic areas and time identify communities with higher risks for community onset MRSA infection compared to community onset MSSA infection.

Background

Staphylococcus aureus (*S. aureus*) is a major cause of community onset and health care–associated infections, ranging from superficial skin and soft tissue infections (SSTI) to invasive infections, sepsis, and death (1). In 2017, U.S. Centers for Disease Control and Prevention reported the antibiotic resistant bacteria, methicillin resistant *S. aureus* (MRSA) was the cause of more than 11,000 deaths per year in the U.S. and the cause of over 80,000 invasive forms of infection(2). The non-antibiotic resistant form, methicillin susceptible *S. aureus* (MSSA), also is a serious cause of infections and is estimated to be the cause of half of all health care–associated *S. aureus* infections(1). Hospital onset MSSA infection rates have remained at a steady rate since 2012, whereas community

onset MSSA (CO-MSSA) infection rates continue to increase (1). Given U.S. Department of Health and Human Services' goal for a fifty percent reduction of *S. aureus* invasive infections by 2020 (3, 4), community based primary and secondary prevention efforts to prevent spread of these infections seem more than ever important to put in place. Majority of efforts have focused on reducing infections within healthcare settings, rather than in community settings.

Risks associated with community onset staphylococcal infections have been widely reported over the last decade (5–10), but few studies have shown the relationship of 'place-based' or community level risks from a spatial or geographic lens (9, 11). Spatial analyses factoring geographic areas allow for visualization of how socio- and built environments might contribute to occurrence of *S. aureus* infections. Little has been published on how rates of infections may differ between different geographic areas over a longitudinal time period, especially during a period when community onset MRSA (CO-MRSA) infections were occurring in epidemic proportions (1, 12).

Analyses of trends in population health data have mostly been determined by comparing rate differences between two time points and changes in the linear or log linear rates over time (13). Another way to analyze trends of population is through group based trajectory models (GBTM), which incorporates information from all time points and examines non linear (quadratic, cubic, and other higher order) rate trends. In this manner, GBTM determine if groups of study units have similar trajectory patterns and can predict outcome trends of individual units which are grouped together into patterns (14–16). There are currently no studies to model or analyze multiyear trends of MRSA or MSSA rates over a longitudinal time period, identifying high or low infection trends based on location.

We sought to determine trends of CO-MRSA and CO-MSSA infections and specifically, to identify particular trends (trajectory patterns) of infections rates which reveal areas with continued low rates of infections over nine years, relatively high rates of infection throughout this period, or 'deviant' trends (high rate with one type of *S. aureus* infection and low rate with the other.) We also sought to determine areas where clusters of trajectory patterns occurred and specifically, to identify geographic deviants, where 'cluster' of census tracts had one type of trend, which differed significantly from the trajectory patterns of surrounding or neighboring census tracts. This is the first study to group *S. aureus* infection rates into community-onset MRSA and MSSA infection 'trajectory' group patterns at the community level and then, map spatially the trajectory patterns (ranging from 'best' to 'worst' trends of staphylococcal infections, stratified by their resistance to methicillin).

Methods

Overview. A retrospective study was conducted of children < 19 years who were treated for *S. aureus* infections from January 1, 2002 through December 31, 2010 at two pediatric hospitals in Atlanta, Georgia (Scottish Rite Children's Hospital and Egleston Children's Hospital are part of Children's Healthcare of Atlanta (CHOA), a large pediatric healthcare system in Atlanta, Georgia, which consistently provides more than 80% of the pediatric hospitalizations for the Atlanta metropolitan statistical area (MSA)) (12). Patients < 19 years of age diagnosed with *S. aureus* infection who had emergency department visit (ED) and/or inpatient admission with residential addresses within the 20 counties of the Atlanta MSA were included. All study participants had an International Classification of Diseases, Clinical Modification (ICD- 9-CM) code compatible with *S. aureus* infection and a positive *S. aureus* culture as previously described (12, 17). We included only those patients who met the definition for community-onset infection (patients with positive *S. aureus* culture within 48 hours from the time patient was initially evaluated or admitted) (18–20).

Individual Level Patient Data from Electronic Health Records. Demographic data (race/ethnicity, gender, type of health insurance, and place of residence); relevant laboratory information (*S. aureus* culture site(s), antibiotic susceptibility phenotype patterns); and relevant clinical information (clinical diagnoses, prior hospitalizations or ED visits within 12 months of the date of admission, number and source of cultures positive for *S. aureus*, recorded past medical history of chronic illnesses) were abstracted from patients' electronic health records (EHR). Georeferencing of the patients' U.S. postal addresses was performed after excluding addresses which were confirmed to be out-of-state or U.S. post office box numbers. All georeferencing was performed using ArcGIS 10.6 (ESRI, Redlands CA). See **Fig. 1. Enrollment Scheme**.

Table 1. Area-based Characteristics of Population		
Variable	Definition	Data Source
Median Household Income	Median distribution of the total number of households and families including those with no income**	ACS*
Education Attainment	Percent of people above 25 years of age with high school degree, bachelor's degree and professional degree	ACS
Kindergarten to 12th Grades Enrollment	Percent of people above 3 years of age who attended kindergarten to 12th grades	ACS
Employment Status	Percent of people above 16 years of age in labor force	ACS
Population under 18 years old	Percent of youth under 18 years of age***	ACS
Median House Value	Median housing value in USD	ACS
Race	Percent Black in Population, Percent White in Population	ACS
Ethnicity	Percent Hispanic and Non-Hispanic in Population	ACS
Household Crowding	Percent of occupied households with > 1 person/room	ACS
Poverty	Percent of population living below poverty level in past 12 months as defined by the U.S. Census Bureau	ACS
Income inequality index	Gini Coefficient measures inequality among values of a frequency distribution of income, where a coefficient of zero expresses perfect equality	ACS
*ACS: American Community Survey (2000, and 2010)		
**For Median Household Income, and Median House Value, data obtained from US Census 2000 and US Census 2010 (ACS) were used. Values from US 2000 were adjusted to 2010 dollar values, using inflation calculator. (21)		
***No ACS or Census data for 2000 or 2010 available for '<19 years of age'		

Area Level Variables from US Census Tracts. Demographic, socio-economic and socio-environmental characteristics at the census tract level were obtained from U.S. Census 2000 and 2010, American Community Survey (ACS) 2000 and 2010 as outlined in **Table 1**. Variables were selected if previously reported as determinants of health or risk factors associated with community associated MRSA (12, 22). Based on the inclusion criteria for

selecting patients, area variables included: race, ethnicity, median household income, education attainment, population enrolled in grades K-12, proportion of population < 18 years of age, proportion of population employed, median housing value, household crowding, Gini coefficient index for income inequality, and proportion of population living below poverty. Median household income and median house values for 2000 were adjusted to 2010 values using an inflation calculator(21). Area level data was limited to census tracts associated with CO-MRSA and/or CO-MSSA patients. Difference of means in 2000 and 2010 were calculated.

U.S. 2000 Census Data Adjusted to U.S. 2010 Census Tract Boundaries. Census tracts are fundamental enumeration units for the U.S. decennial censuses and their boundaries change over time. Area data obtained from U.S. Census 2000 and U.S. Census 2010 were adjusted through longitudinal tract data base (LTDB) in the same way as previously described by Logan JR et al (23), which used 2010 census tract geographic boundaries. Estimates of < 19 years of age population were then made for each census tract per year from 2002 to 2009 via linear extrapolation and actual population size for 2010 were then used in the trajectory model as a time varying covariate.

Statistical analyses.

Group-based trajectory modeling: We included all children with *S. aureus* infections (2002–2010), stratified by antibiotic resistant cases (CO-MRSA) and non-antibiotic resistant controls (CO-MSSA) per year across all census tracts located within Atlanta's MSA 20 counties boundaries. The yearly case counts of CO-MRSA and CO-MSSA infected patients < 19 years of age in each census tract from 2002 to 2010 were converted to rate of infection per 1,000 children. The yearly CO-MRSA or CO-MSSA infection rate was the outcome measure used to generate rate trajectories using Proc Traj for SAS, version 9.4 (SAS Institute, Inc). In group-based trajectory modeling, discrete underlying groups within the population are assumed to have their own case intercept, slope and possibly higher order terms. Proc Traj requires specification of the number of groups the model will fit. We used a process of evaluating model fit while simultaneously identifying informative similar trajectory groups as previously described by Baltrus et al(16). We estimated a zero-inflated Poisson model with a first order, quadratic term for each outcome, and an independent variable of time (years) for each group. We continued adding groups and assessed the change in the Bayesian information criterion (BIC) as an evaluation of model fit. Since Proc Traj has the limitation that does not allow for an offset variable in order to generate rates, we adjusted for each census tract's < 19 years of age population as a time varying covariate. (The CO-MSSA and CO-MRSA overall model fit did not improve with the addition of more than two groups. The CO-MRSA model produced a small "very high infection" group of census tracts with the addition of a third group into the model with only a slight decline in the fit of overall model.) We next added or removed second and higher-order terms from each group's model based on significance ($p < 0.05$).

Descriptive analyses by individual-level and area-level variables across the trajectory groups: Characteristics from individual level data were stratified by group-based trajectory patterns for CO-MRSA and CO-MSSA. We grouped the individual level data into two periods, designated as early period (2002–2005) and late period (2006–2010). The early period individual level data was linked to area data from U.S. Census 2000, and the late period individual level data was linked to U.S. Census 2010. Since spatial factors, including the ecological conditions and neighborhood spatial boundaries differed during the 10-year time span between U.S. Census 2000 and 2010, we used information from both time periods in order to best characterize the neighborhoods at the time of CO-MRSA or CO-MSSA infection occurrence. Chi-square test was applied to compare CO-MRSA and CO-MSSA population characteristics, stratified by the CO-MRSA trajectory groups and CO-MSSA trajectory groups, respectively. For area

level variables, normality of distribution was determined using Shapiro-Wilk test. For normally distributed population, ANOVA was used when comparing three trend groups and T-test when comparing two trend groups. Kruskal-Wallis test was used for three groups, and Mann-Whitney test for two groups when population was not normally distributed. All statistical analyses were done by SAS version 9.4 (SAS Institute, Inc).

Spatial Patterns for Community Onset MRSA and MSSA Trajectory Trends. Thematic mapping of different CO-MRSA and CO-MSSA infection trajectories was performed and assessed for spatial autocorrelation, which confirmed whether adjacent observations were related (and not independent occurrences). The degree of spatial autocorrelation was measured using the Global Moran's I statistic (ESRI ArcGIS Pro, Redlands CA). Census tracts that had CO-MRSA or CO-MSSA were grouped into six group based trajectories: 1) Very High MRSA–High MSSA clusters representing all census tracts with very high CO-MRSA and high CO-MSSA infection rates, the worst trajectory group across the nine years of the study period; 2) Very High CO-MRSA–Low CO-MSSA clusters representing census tracts in the worst trajectory CO-MRSA group near census tracts in the most favorable trajectory CO-MSSA group (deviant trend); 3) High CO-MRSA–High CO-MSSA clusters representing census tracts in the second worst trajectory CO-MRSA group near census tracts in the worst trajectory CO-MSSA group; 4) High CO-MRSA–Low CO-MSSA clusters of census tracts in the second worst trajectory CO-MRSA group near census tracts in the most favorable trajectory CO-MSSA group (deviant trend); 5) Low CO-MRSA-High CO-MSSA clusters representing census tracts in the most favorable trajectory CO-MRSA group near census tracts in the worst trajectory CO-MSSA group (deviant trend); and 6) Low CO-MRSA-Low CO-MSSA clusters representing all census tracts with low infection rates, the most favorable trajectory group.

Local 'clusters' of aggregated patients' point data were determined by applying the local indicators of spatial association (LISA) technique as previously described (16, 24, 25). From this, hot and cold spot analyses were performed using GetisOrd Gi* statistic. The output is a surface raster layer depicting the different degrees of 'hot spots' and 'cold spots' of CO-MRSA or CO-MSSA occurrences. Significant clusters were those areas, where an occurrence of infection (CO-MRSA or CO-MSSA) and its neighboring points all had high Getis-Ord Gi* values (hot spots). Geographic deviants were defined as clusters that had much higher or much lower values than neighboring occurrence points (cold spots).

Spatial Analyses. Optimized Hot Spot Analysis (OHPA) tool (Esri ArcGIS Pro, Redlands, CA) was performed to assess spatial patterns in our data. This allowed us to visualize statistically significant patterns, where clustering of cases (CO-MRSA) or controls (CO-MSSA) exist, which are not likely due to random occurrence. The results of the applying this tool showed us areas within the 20 counties where 'hot spots' occur within a 'cluster' in a non random way. (A simple 'hot spot' analysis will not tell necessarily inform "why" a particular event is occurring in a statistically significant cluster, only that it is occurring in a non random manner). We ran the analysis using all unique patients' point locations from 2002 to 2010, < 19 years, with CO-MRSA and then repeated these steps for CO-MSSA patients within the same time period and for the same ages. With the OHPA tool, we set our 'Study Area' to the boundaries of Atlanta's MSA 20 counties. We then assigned 'neighborhood' variables as 1-mile hexagon patterns. We chose the 1-mile hexagon neighborhood size based on Tobler's First Law of Geography, which follows the spatial diffusion theory for infectious pathogens, whereby the risk for infection increases with closer distance to source of infection. In our model, we postulate that the closer an individual's neighborhood is geographically near to an occurrence of CO-MRSA or CO-MSSA, the more likely the persons within the neighborhood are likely to contract CO-MRSA or CO-MSSA. In this model, we accounted for various sizes of neighborhoods, apartment complexes, and other living or housing units. We estimated that a neighborhood is within approximately a mile of

the residence of any CO-MRSA or CO-MSSA occurrence. This study was approved by Institutional Review Boards of hospitals and affiliated academic institutions.

Results

There were 12,120 children with *S. aureus* infections from 1,969 census tracts during 2002-2010 who were seen at Children’s Healthcare of Atlanta’s two pediatric hospitals. For Atlanta’s 20 counties’ MSA, there were 9,095 patients, < 19 years of age, from 901 census tracts. Overall, the number of infections increased steadily from 2002 to 2010, with the highest rates occurring in 2009 for CO-MRSA and 2008 for CO-MSSA; CO-MRSA rates increased at a higher rate compared to CO-MSSA. Of six possible combinations for trends of CO-MRSA and CO-MSSA infections, there were five group-based trajectory patterns for CO-MRSA (3) and CO-MSSA (2) with overlapping U.S. census tracts as shown in **Table 2**; no census tracts fell into the group-based trajectory pattern of Very High CO-MRSA - High CO-MSSA infections. **Figure 2** shows the three CO-MRSA group-based trajectory trends and the two CO-MSSA group-based trajectory trends over this nine-year period: Of the three CO-MRSA group-based trajectory trends, only 0.8% of the census tracts showed a dramatic increase over the first six years followed by a gradual decline in the last three years; over two thirds (67.2%) remained in the low infection trend across all years. In contrast, for CO-MSSA, 85.7% of census tracts fell into the high infection group-based trajectory pattern which lasted throughout the nine-year period, compared to 14.3% of census tracts which belonged to a low infection trend over this same period. (**Supplemental Section: Table A** shows the coefficients for the terms used in the three group-based CO-MRSA trajectory models and the two group-based CO-MSSA trajectory models. For the three CO-MRSA group-based models, the equations all contained a quadratic term. For the two CO-MSSA group-based models, the equations contained a quadratic term, and a slope term that was relatively flat.)

Table 2. US Census Tracts with Community onset MRSA- / MSSA- Infection Group-Based Trajectory Patterns, 2002-2010

CO-MRSA Infection Category	CO-MSSA Infection Category	Total N	
Low	High		
N (%)	N (%)		
Low	682 (75.7%)	29 (3.1%)	711
High	170 (18.9%)	14 (1.6%)	184
Very High	6 (0.7%)	0	6
Total	858	43	901

From 901 census tracts with *S. aureus* infections, 682 (75.7%) were in the low infection group-based trajectory for both CO-MRSA and CO-MSSA (this is the ‘best’ trend category); deviant trajectory census tracts included 6 (0.7%) with Low CO-MSSA infection rate but Very High CO-MRSA infection rate, 170 (18.9%) Low CO-MSSA and High CO-MRSA infection rates and 29 (3.2%) High CO-MSSA and Low CO-MRSA infection rates. High CO- MSSA- High CO-MRSA (worst group-based trajectory) were seen in 14 (1.6%) census tracts. In 2002, there were 38 cases (0.03 infection per 1,000 children) in the Low CO-MRSA infection trajectory group, but this trend over time increased

steadily to peak at 334 cases (0.48 infection per 1,000 children) in 2008, before declining to 257 cases (0.43 infection per 1,000 children) in 2010. Similarly, CO-MSSA low infection trajectory group had a baseline of 192 cases (0.18 infection per 1,000 children) in 2002, but this trend peaked later in 2009 with 560 cases (0.51 infection per 1,000 children) before dipping slightly to 482 cases (0.47 infection per 1,000 children) in 2010. Census tracts that started with High CO-MRSA infection trajectory followed a similar pattern of increasing with each year, beginning with 29 cases (0.15 infection per 1,000 children) in 2002, peaking to 454 cases (1.25 infection per 1,000 children) in 2008, before dropping to 422 cases (0.99 infection per 1,000 children) in 2010. Comparatively, High CO-MSSA infection trajectory more than tripled in infections over six years from 32 cases (0.46 infections per 1,000 children) to 102 cases (1.26 infections per 1,000 children). Like other trajectories, its rates also dropped after 2008 with 88 cases (1.02 infection per 1,000 children) in 2010. **(Table 3)**

Table 3. Counts of Community Onset MRSA and MSSA And Average Infection Rates by Group-Based Trajectory Patterns

Year	Type of Trajectory Pattern									
CO-MSSA-Low	CO-MSSA-High	CO-MRSA-Low	CO-MRSA-High	CO-MRSA-Very High						
Count (Rate)	Count (Rate)	Count (Rate)	Count (Rate)	Count (Rate)						
2002	192	0.18	32	0.47	38	0.03	29	0.15	0	0.00
2003	362	0.36	58	0.79	74	0.10	69	0.34	1	0.14
2004	332	0.32	50	0.63	122	0.24	165	0.49	3	0.40
2005	382	0.35	61	0.76	219	0.30	274	0.80	6	0.71
2006	476	0.43	83	1.07	269	0.49	386	0.99	19	2.24
2007	419	0.38	89	1.14	312	0.47	416	1.16	24	2.91
2008	525	0.47	102	1.27	334	0.48	454	1.26	27	3.24
2009	560	0.51	87	1.09	312	0.48	445	1.15	25	2.54
2010	482	0.47	88	1.02	257	0.43	422	0.99	13	1.71

For each census tract with *S. aureus* occurrence, we determined the number of CO-MSSA or CO-MRSA infections per 1,000 children <19 yearst. The actual number of CO-MSSA or CO-MRSA by year is provided along with the rate (infections per 1,000).

From aggregated individual level data of early and late time periods (2002-2005 and 2006-2010), we identified significant differences in both time periods, across the all three CO-MRSA infection group-based trajectories and also differences between the high and low CO-MSSA infection group-based trajectories **(Table 4)**: Rates of blacks increased for CO-MRSA group-based trajectories as the CO-MRSA group-based trajectory moved from low to very high infection trend patterns, and overall, were relatively higher than rates of whites with MRSA infections. This finding remained consistent for both early and late time periods. Health insurance status also was significantly

different across the three CO-MRSA infection trajectories with public health insurance ranking highest ($p=0.0002$) in CO-MRSA-High and CO-MRSA-Very High groups. Having prior hospitalization was significantly different among the three CO-MRSA infection trend patterns ($p < 0.05$) in 2002-2005 but not significant in 2006-2010. Having a skin and soft tissue infection (SSTI), the most common clinical presentation for *S. aureus* in the community or outpatient setting, was not significant among the three CO-MRSA infection trend patterns in 2002-2005 or 2006-2010. In contrast, rates of whites increased for CO-MSSA group-based trajectories from low to high infection trend patterns, and overall, were relatively higher than rates of blacks with CO-MSSA infections. Rates among females were much higher in CO-MSSA High infection trend group, and the difference was statistically significant in the early period, 2002-2005 ($p=0.0076$). Rates of private health insurance was significantly higher than public health insurance in CO-MSSA low and high infection trajectory groups for both 2002-2005 ($p=0.04140$, and 2006-2010 ($p=0.0057$) periods. History of prior hospitalization was increased with CO-MSSA trajectory groups moving from low to high, in both 2002-2005 ($p<0.001$) and 2006-2010 ($p<0.001$). Rates of skin and soft tissues infections decreased in CO-MSSA trajectory groups moving from low to high, for both 2002-2005 ($p=0.004$) and 2006-2010 ($p<0.001$).

Table 4. Patient-level Characteristics of Group-Based Trajectory Patterns of MRSA and MSSA for 2002-2005/2006-2010

Patient Characteristic	MRSA-low (N= 2660)	MRSA-High (N=1937)	MRSA-VeryHigh (N= 118)		MSSA-low (N= 3730)	MSSA-high (N=650)	
	2002-2005, N= 537	2002-2005, N=453	2002-2005, N= 10	p-value	2002-2005, N= 1268	2002-2005, N= 201	p-value
	2006-2010, N= 2123	2006-2010, N= 1484	2006-2010, N= 108		2006-2010, N= 2462	2006-2010, N= 449	
Race**							
2002-2005				<.0001*			0.0003*
Black	163(31.17%)	215(48.53%)	7(70%)		286 (22.95%)	25 (12.63%)	
White	46(8.8%)	51(11.51%)	2(20%)		797 (63.96%)	155 (78.28%)	
Other	314(60.04%)	177(39.95%)	1(10%)		163 (13.08%)	18 (9.09%)	
2006-2010				<.0001*			<.0001*
Black	758(36.32%)	878(60.05%)	87(80.56%)		816 (34.1%)	94 (21.76%)	
White	1113(53.33%)	455(31.12%)	14(12.96%)		1287 (53.78%)	286 (66.2%)	
Other	216(10.35%)	129(8.82%)	7(6.48%)		290 (12.12%)	52 (12.04%)	
Ethnicity (Hispanic)***							
2002-2005	7(2.18%)	11(5.85%)	0(0)	0.078	n/a	n/a	n/a
2006-2010	175(13.09%)	118(17.05%)	7(19.44%)	0.0392	251 (16%)	51 (17.47%)	0.5321
Gender (Female)							
2002-2005	262(48.79%)	245(54.08%)	3(30%)	0.0972	535 (42.19%)	105 (52.24%)	0.0076*
2006-2010	1073(50.54%)	782(52.7%)	68(62.96%)	0.0272*	1137 (46.18%)	220 (49%)	0.2714
Health Insurance							
2002-2005				0.0002*			0.0414*
Private	269(50.09%)	179(39.51%)	0(0)		776 (61.2%)	140 (69.65%)	
Public	250(46.55%)	258(56.95%)	10(100%)		456	54	

					(35.96%)	(26.87%)	
Other****	18(3.35%)	16(3.53%)	0(0)		36 (2.84%)	7 (3.48%)	
2006-2010				<.0001*			0.0057*
Private	935(44.04%)	464(31.27%)	17(15.74%)		1163 (47.24%)	246 (54.79%)	
Public	1080(50.87%)	906(61.05%)	86(79.63%)		1163 (47.24%)	188 (41.87%)	
Other****	108(5.09%)	114(7.68%)	5(4.63%)		136 (5.52%)	15 (3.34%)	
SSTI Diagnosis							
2002-2005	336 (62.57%)	252 (55.63%)	7 (70%)	0.0632	352 (27.76%)	32 (15.92%)	0.0004*
2006-2010	1495 (70.42%)	1077(72.57%)	79 (73.15%)	0.3389	1082 (43.95%)	141 (31.4%)	<.0001*
History of Hospitalizations							
2002-2005	29 (5.4%)	55 (12.14%)	0	0.0005	210 (16.56%)	70 (34.83%)	<.0001
2006-2010	100 (4.71%)	63 (4.25%)	2 (1.85%)	0.373	214 (8.69%)	100 (22.27%)	<.0001*

*p-value <0.05, means statistically significant.

** Other races include: Asian, Native Hawaii, Alaskan, and Multiple-races (self identified by patients as more than one race).

***Other health insurance types include: Self-pay, no insurance, and those with both private and public.

Patient level data aggregated into two periods, 2002-2005 and 2006-2010, and then stratified by MRSA and MSSA population characteristics respectively based on MRSA and MSSA trajectory groups. (There are 9095 patients that accounted for the five different group-based trajectory patterns who resided within the 20 counties of Atlanta MSA across all years, <19 years.)

Comparing population data from US Census 2000 and 2010, we found significant differences among socio-economic and demographic variables, stratified by CO-MRSA- and CO-MSSA- group-based trajectory patterns (**Table 5**): Similar to what was seen with individual level data, we also found rates of whites decreased as the CO-MRSA group-based trajectories moved from low infection to very high infection in both US Census 2000 and 2010. In contrast, the rates of blacks increased as the CO-MRSA infection trajectories moved from low to very high for both U.S. Census 2000 and 2010. For CO-MSSA group-based trajectories, a similar pattern was also seen whereby, rates of whites increased as CO-MSSA moved from low to high both in U.S. Census 2000 (p=0.054) and U.S. Census 2010 (p=0.0096). In CO-MSSA group-based trajectories, proportions of blacks decreased as infection trends increased; these trends were significant for both U.S. Census 2000 (p=0.0158) and 2010 areas (p=0.001). Although the proportion of census tracts with children <19 years of age increased as infection trends increased for both CO-MRSA and CO-MSSA group-based trajectories, and relatively higher in U.S. Census 2010 compared to

2000, none of the CO-MRSA or CO-MSSA infection trend patterns were significant except for U.S. Census 2010 census tracts representing the CO-MSSA-High infection trend pattern.

Table 5. Population Area-level Characteristics of Group-Based Trajectory Patterns of MRSA and MSSA in Atlanta

Population Characteristic	MRSA–Low	MRSA-High	MRSA-Very High	p-value	MSSA-Low	MSSA-High	p-value
	N (%)	N (%)	N (%)		N (%)	N (%)	
Census tracts N=901 (%)	711 (67.2%)	184 (32%)	6 (0.8%)		858 (85.7%)	43 (14.3%)	
Race/Ethnicity, %							
White, %							
2000	68.4	46.5	31.4	<.0001*	63.4	69.5	0.054
2010	59.4	39.8	21.5	<.0001*	54.6	65.3	0.0096*
Difference in Periods, %	-8.7	-6.2	-9.1	0.1188	-8.4	-4.2	0.0349*
Black, %							
2000	24.3	44.9	63.3	<.0001*	29.1	21.8	0.0158*
2010	29.2	49.9	71.9	<.0001*	34.2	22.3	0.001*
Difference in Periods, %	4.8	4.1	8.2	0.981	4.9	0.8	0.0293*
Hispanic, %							
2000	5.77	7.48	4.44	0.2315	6.02	8.04	0.6623
2010	9.8	10.8	5.7	0.3007	9.8	13.4	0.6361
Difference in Periods, %	3.8	3.6	1.7	0.8551	3.6	5.6	0.4351
<18 years, %							
2000	26.4	27.1	29.5	0.4065	26.5	27.9	0.2359
2010	28.6	29.2	29.8	0.7528	28.6	30.8	0.0253
Difference in Periods, %	2.4	2.3	-0.9	0.3644	2.3	2.9	0.4148
K-12th Grades, %							
2000	71.3	72.6	76.1	0.2774	71.4	73.9	0.6034
2010	67.9	69.0	69.6	0.8499	67.9	73.9	0.0042*
Difference in Periods, %	-2.9	-3.0	-6.8	0.6411	-3.1	-0.2	0.0415
Nursery to preschool, %							

2000	8.9	8.5	7.2	0.177	8.8	9.3	0.2455
2010	7.9	7.6	5.6	0.401	7.7	8.6	0.115
Difference in Periods, %	-1.0	-1.0	-2.0	0.9299	-1.0	-0.6	0.2138
High School, %							
2000	24.6	25.8	26	0.3111	25.0	21.4	0.0295*
2010	24.7	28.3	29.7	0.0002*	25.7	22.1	0.0431*
Difference in Periods %	0.2	2.4	3.8	0.0002*	0.7	1.0	0.5
Bachelor, %							
2000	21.7	18.5	14.5	0.0085*	20.8	25.6	0.0255*
2010	23.7	19.1	16.2	<.0001*	22.5	26.9	0.0327*
Difference in Periods, %	1.91	0.45	1.7	0.0022*	1.6	1.0	0.8262
Graduate or professional, %							
2000	10.4	9.0	8.8	0.0839	9.9	12.6	0.0801
2010	12.4	10.3	9.8	0.01*	11.8	14.1	0.208
Difference in Periods, %	2.0	1.4	-0.7	0.1914	1.9	1.0	0.2307
Labor Force, %							
2000	70.6	69.35	69.35	0.2486	70.3	70.9	0.7147
2010	70.0	70.65	70.68	0.6528	70.2	70.2	0.7211
Difference in Periods, %	-0.6	1.2	0.3	0.0464*	-0.2	-0.7	0.7159
Median Annual Household Income^, \$							
2000	71,537.44	64,354.33	60,191.23	0.0048*	69,118.34	87,486.73	0.0043*
2010	63,983.19	54,450.01	45,369.67	<.0001*	61,026.01	79,598.74	0.0090*
Difference in Periods, \$	-7,554.25	-9,904.32	-14,821.6	0.1179	-8,092.33	-7,887.98	0.4704
Median House Value^, \$							
2000	193,740.38	170,922.67	145,859.5	0.023*	186,692.81	230,044.26	0.0178*
2010	217,349.72	197,003.26	155,783.33	0.0365*	210,287.79	262,673.81	0.0158*
Difference in Periods, \$	25,719.34	26,080.59	9,923.83	0.8035	24,761.96	44,466.64	0.0262*

Household Crowding**, %							
2000	1.3	1.1	1.0	<.0001*	1.2	0.8	0.1311
2010	3.9	5.6	7.3	0.9937	4.3	4.1	0.0823
Difference in Periods, %	-2.7	-4.5	-6.1	<.0001*	-3.1	-3.3	0.6453
Poverty*** %							
2000	9.1	10.7	10.1	<.0001*	9.5	7.40	0.0727
2010	18.3	19	17.0	0.0236*	18.6	14.1	0.0202*
Difference in Periods, %	8.8	7.6	6.1	0.7673	8.6	6.8	0.5399
Gini Index-2010	0.40	0.4	0.40	0.1912	0.4	0.4	0.858

A total of 901 census tracts from 20 counties in Atlanta (2000 and 2010) represent the patients with *S. aureus* infections who were included in the study.

*p-value <0.05, means statistically significant.

**Occupied households with >1 person/room.

***People living under poverty level in past 12 months.

^Median Annual Household Income and Median House Value for 2000 were adjusted to 2010, using an inflation calculator.

Socio-economic conditions of the neighborhoods where CO-MRSA infection trends were higher differed from CO-MSSA infection trends over the same time period. For example, median household income and housing values decreased as CO-MRSA infection group-based trajectories moved from low to very high infection trends. Proportion of the population living below the federal poverty level also increased significantly in areas where CO-MRSA infection trends moved from low to very high infection rates. This trend was not seen with CO-MSSA group-based trajectories, where the median household income and housing values increased, and the proportion of the population living below the federal poverty level decreased in areas where it was clearly a CO-MSSA high infection trend pattern.

Since crowding is a known risk associated with community-associated MRSA infections, we calculated the percentage of U.S. 2000 census tracts with evidence of household crowding and found crowding increased significantly as trends of CO-MRSA infection moved from low infection to very high infection pattern ($p < 0.0001$). However, rates of crowding in U.S. 2010 census tracts were not significantly different in those areas where CO-MRSA infection trends moved from low to very high ($p = 0.9937$). In contrast, for CO-MSSA group-based trajectories, household crowding was not significantly increased over the different categories of CO-MSSA infection trends, nor was the change in rates between the two time periods significantly different ($p = 0.6453$).

Spatial analyses of census tract group-based trajectories for MRSA and MSSA. Spatial variations of the different community onset MRSA-MSSA infection group-based trajectories were identified (Figure 3): The most favorable group-based trajectory (CO-MRSA Low infection and CO-MSSA Low infection) and second most favorable trajectory (CO-MRSA High-CO-MSSA Low) were scattered with higher proportion of census tracts in counties where the population is less dense relative to inner city Atlanta. There were also ‘pockets’ within Gwinnett, Henry and Douglas counties, where there were census tracts with CO-MRSA-Very High or CO-MRSA-High, even though most of the county fell into a more ‘favorable’ or lower infection group-based trajectory pattern. In contrast, counties representing the inner city (areas within DeKalb County and Fulton County) had the highest proportion of the worst trajectories (CO-MRSA-Very High-CO-MSSA-High or CO-MRSA-High-CO-MSSA-High). Seven of these census tracts, representing CO-MRSA Very High-CO-MSSA Low or worst group-based trajectory combination, were from areas located east of downtown Atlanta (DeKalb County) and a single census tract southeast of downtown Atlanta (Henry County). To identify areas where infections intensified with each year in a particular census tract and also in neighboring census tracts (‘hot spots’) compared to areas where the infections were much lower than neighboring census tracts across each year (‘cold spots’), we found CO-MRSA and CO-MSSA ‘hot’ and ‘cold’ spots overlapped in a number of areas over the 2002-2010 period. ‘Hot spots’ for CO-MRSA and CO-MSSA overlapped for a large number of census tracts located primarily in the most heavily populated counties (DeKalb, Fulton and Gwinnett), but CO-MRSA ‘hot spots’ extended much further down into the southern counties of Rockdale, Henry and Clayton compared to CO-MSSA ‘hot spots’. ‘Cold spots’ followed the perimeter of the ‘hot spots’ for both CO-MRSA and CO-MSSA. Interestingly, ‘cold spots’ were seen southeast of Fulton county, where there were CO-MRSA ‘hot spots’. There was a large band of cold spots, located in the northwestern portion of 20 counties boundaries, which ran along the perimeter of hot spots seen in Cobb and Cherokee counties (northwest of the most densely populated counties) (Figure 4). In order to discern what group-based trajectory patterns might fall within ‘hot spots’, we overlaid the group-based trajectory map with hot spots and found that the ‘worst’ group-based trajectory was located in areas found to be ‘hot spots’ for CO-MRSA and CO-MSSA, and the best trajectory groups tended to occur where there were neither cold nor hot spots. Interestingly, Bartow county (northwest of Atlanta’s downtown area) had a number of census tracts which had a CO-MRSA-high – CO-MSSA- low designation, yet no CO-MSSA or CO-MRSA ‘hot’ or ‘cold’ spots.

Discussion

We applied group-based trajectory modeling to identify Atlanta MSA census tracts with ‘worst’ and ‘best’ temporal trends of community onset MRSA and MSSA infection rates over nine years. We identified three distinct CO-MRSA group-based trajectory infection patterns and two CO-MSSA group-based trajectory infection patterns over this period, which included the time when community associated MRSA infections were occurring in epidemic proportions around the U.S. We found ~ 94% of all the census tracts with *S. aureus* occurrence during this time period belonged to the best trend categories of low infection rates for both CO-MRSA and CO-MSSA. With group-based trajectory models, we used all the rates generated over the nine year span instead of relying on change between just two rates at the beginning and end of this period. This allowed us to detect and examine the trajectory shape over the entire time period, including non-linear shapes which are common for the epidemic curves associated with communicable diseases. Given how this bacteria, *S. aureus*, can have many strains with various virulent factors that may contribute to infection, understanding these epidemic curves within any community is important. It provides some insight as to which communities may have higher proportion of its population, with risks for infection. A recent worldwide review of *S. aureus* nasal carriage estimated that the average prevalence of nasal colonization in the general population is 24%(26) but the possible place based risks which contribute to

movement from colonized to infected population have not been elucidated. We have clearly delineated population level crowding is associated with worst trajectory trends for CO-MRSA infection in specific communities at the census tract level. Furthermore, we also identified the groups which make up the trajectory patterns from both individual and area level data instead of defining group categories *a priori*. This study highlights not only individual and area level risks which may contribute to why certain census tracts over time have either a high or low rate of infection, but also the location-based relationships which may be explanatory of these staphylococcal trend patterns of infection.

Our main findings demonstrated that variations in spatial trend patterns of CO-MRSA infection and CO-MSSA infection rates across these 20 counties include both rural and urban communities. We mapped out the geographic clustering of the group-based trajectory patterns, with 'worst' trajectories clustering mainly in Dekalb and northwest counties of Bartow, Cherokee, Paulding and Cobb, and 'best' trajectories clustering in the northeast, southeast, and southwest of the inner-city area. Identification of these clusters of census tracts with similar rate trajectories over time will direct us to better understand what 'place based' conditions or factors might contribute to these findings that are location specific. For example, population density of the 'worst' trajectories, along with demographic factors including race and age distribution have been demonstrated to partially explain the unfavorable trajectory seen in DeKalb County. However, the southwest section of Bartow County has a significant group of census tracts which are geographically deviant from the surrounding 'low infection' census tracts. Socioeconomic factors (e.g., poverty, inequality index, employment status, etc.) may be more of a 'driver' than population density or household crowding in these rural communities.

When considering demographic characteristics of the 901 census tracts and the distribution based on five distinct *S. aureus* infection group-based trajectories, we found that race differences were seen in census tracts where infection trends were high for both MRSA and MSSA infection trend patterns. Areas with low *S. aureus* infection trends had higher proportion of whites compared to blacks, whereas high infection trend patterns occurred in areas where there were higher proportion of blacks. (In Gwinnett county, 29.3% of the population are black and 54.5% are white, but the pockets with much higher trends of CO-MRSA correspond to census tracts with higher proportion of blacks.)

Many of the census tracts found to have the 'worst' CO-MRSA infection trajectories were in areas with lower housing value, lower household income, and higher poverty rates. These findings are consistent with findings published from CDC researchers in their two year population surveillance study of 33 counties across nine states, which also demonstrated higher incidence of MRSA infection from census tracts with low-household income, persons living under the poverty level, and low education (27). They also found that 'crowding' was associated with increased MRSA rates. Our analyses, which focused on 'trend' patterns of MRSA infections over a nine-year period and not incidence rates, did not find crowding to persist over this nine-year time period. This may be related to the fact that our data compared a longer time interval (nine years compared to two years) and was based on analyses of multi-level data, including individual patient level data. Another explanation maybe related to communities in our catchment area may have improved housing conditions between the early and late time periods, e.g., higher percentage of people living in less crowded housing situations over almost a decade of time.

Profiles of socioeconomic conditions in areas where CO-MSSA trajectories were high differed from the profiles where CO-MRSA trajectories were high: In areas where CO-MSSA infections trended high, the proportion of whites was higher than proportion of blacks. This relationship was reversed in areas of high or very high CO-MRSA group-based infection trajectories, where proportions of blacks were higher than whites.

Higher household income and housing values and lower individual poverty levels were seen in areas with high CO-MSSA- infection trend patterns, compared to low CO-MSSA infection trend patterns. Whether or not this is a temporal effect related in part by the fact that some of these CO-MSSA-high infection census tracts crossover with CO-MRSA-low infection, is unclear.

Overall, multi-level factors contribute to the explanation of geographically 'deviant' communities whose trajectory group is surrounded by very different types of infection trend patterns. Our study did not look at the changes of demographic composition as a dependent variable or other factors, e.g., changes in socioeconomic conditions, housing conditions, etc. which may potentially contribute to the geographic deviation found. Interestingly, we did not see a 'Hispanic paradox'(28), where census tracts with higher proportion of Hispanics were in areas with the best infection trajectories. In our analyses, we did not see significant differences among Hispanics for any of the CO-MRSA group based trajectories and in fact, found worsening infection trend rates among Hispanics in the low and high CO-MSSA group based trajectories over the nine-year period.

The use of this novel method of group-based trajectory analysis (GBTA) of communicable disease trends holds some advantages over traditional hot-spot analysis. Hot spot analysis is good for spotting where concentrations of cases have occurred over time. However, hot spot analyses may not always identify geographic areas where residents are at highest risk, since the analyses does not take into account the population size where cases are actually occurring. For instance, a tract that has 5 cases arising over the nine year period may not show up in a hot spot analysis; however, if that tract has a relatively low population it may show up as a high infection rate trajectory tract in GBTA. This may be why some tracts in the more suburban areas in our study were found to be high infection rate trajectory tracts, yet did not show up as 'hot spots'. The practical clinical application of using GBTA can be demonstrated, when estimating whether or not a patient who presents with a skin or soft tissue infection has CO-MRSA or CO-MSSA, based on the patient's assigned group based trajectory infection category. In this scenario, the treating healthcare provider could factor location based CO-MRSA or CO-MSSA infection trends as part of the management strategy. Another advantage is that with GBTA, we can ascertain a general idea of the rate pattern experienced over the study period by tracts without having to examine the hot spot maps for each year.

Limitations. There are several limitations to this analyses: First we were not able to determine causal association (relationship) between the population characteristics of an area and CO-MRSA and CO-MSSA infections, since the study draws from area level data which were collected in two different time periods (2000 and 2010). Although we have included children seen for all staphylococcal infections within one healthcare system, our findings may not necessarily be generalizable to children who did not access care from this single pediatric healthcare system or applicable to other geographically distinct locations where the place based factors are different from this catchment area.

Future Directions. We plan to look at geographic influences from changes which are place based, using particular 'neighborhoods' as boundaries, and not census tracts. These 'neighborhood' boundaries tend to outline areas where the sociocultural influences are similar among the residents of the neighborhood, e.g., types of healthcare access, density and types of daycare centers, mode and availability of transportation, and racial and ethnic groups including various immigrant populations or cultural influences.

Our study clearly outlines which census tracts have the greatest disparities in temporal *S. aureus* infection trends, and specifically, which census tracts are located in the 'worst' or 'best' group-based *S. aureus* infection trajectory areas. It is these 'geographic deviants' that deserve more attention. Identifying the potential remediable factors

may pave the path towards eliminating spread of these types of infections or at least, mitigate contributing factors to the spread. Similarly, looking at why certain census tracts perform consistently better than their surrounding areas will provide insights on how to prevent the spread of this bacterial infection, and thereby, improve outcomes for other census tracts which have failed to have a positive infection trajectory trends over time. Deciphering the primary multi-level factors, driven by place and time elements, for both antibiotic resistant and non-antibiotic resistant *S. aureus* infections is paramount in the effort to develop effective prevention models that effectively and efficiently decrease transmission and infections at the neighborhood or community level.

Conclusions. We demonstrated *S. aureus* infection trends over a nine-year period, factoring in time and space for both community onset MRSA and MSSA. We identified specific areas which are unique or overlapping at the census tract level for these staphylococcal infections, and specifically, identified unique areas which consistently proved to have high infection rates and performed the ‘worst’ over the nine year period. Group-based trajectory modelling allows us to not only identify areas which perform better, worse, or remain essentially, unchanged, but also identify the spatial relatedness of these areas. There is a continued need to develop strategies aimed at primary and secondary prevention, especially at the community level. Therefore understanding ‘trends’ of infection patterns, stratified by antibiotic resistance, over geographic areas and time can provide evidence-based information, necessary for community-specific prevention guidelines.

Abbreviations

S. aureus

Staphylococcus aureus

MRSA

Methicillin Resistant *S. aureus*

MSSA

Methicillin Susceptible *S. aureus*

CO-MRSA

Community Onset Methicillin Resistant *S. aureus*

CO-MSSA

Community Onset Methicillin Susceptible *S. aureus*

SSTI

Skin and Soft Tissue Infection

ED

Emergency Department

CHOA

Children’s Healthcare Of Atlanta

MSA

Metropolitan Statistical Area

EHR

Electronic Health Record

GBTA

Group Based Trajectory Analysis

Declarations

- Ethics approval and consent to participate

This study is approved by Children's Healthcare of Atlanta Institutional Review Board (IRB), Morehouse School of Medicine and Emory University. The individual data was from Electronic Health Record, so there was no consent needed to conduct this study.

- Consent for publication

All authors listed have consented to the publication of this manuscript.

- Availability of data and materials

This study used datasets from Children's Healthcare of Atlanta- Electronic Health Record, which is governed by HIPPA guidelines. There is no link to access patient level information.

- Competing interests

All authors declare that they have no competing interests of BMC Public Health.

- Funding

LCI receives funding from the following sources: National Library Medicine, Grant #1G08LM013190-01; K-08 AHRQ-Mentored Clinical Scientist Career Research Development Award- HS024338-01. LCI, RG supported by the National Center for Advancing Translational Sciences of the National Institutes of Health under Award Number UL1TR002378. The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health."

- Authors' contributions

Lilly Immergluck contributed to the hypothesis, study design, data analyses and interpretation and preparation of the manuscript. Ruijin Geng contributed to the data analysis, data interpretation and preparation of the manuscript; Peter Blatrus contributed to the study design, and oversaw the statistical analysis, data interpretation of the manuscript; Choahua Li contributed to the statistical analysis and data interpretation of the manuscript; Junjun Xu contributed to the overall statistical analysis; Mike Edelson contributed the spatial analysis methodology design and GIS mapping. Lance Waller, Traci Leong, and George Rust contributed to the interpretation of data analyses and preparation of the manuscript. All authors reviewed the final manuscript prior to submission. All authors read and approved the final manuscript.

- Acknowledgements

1. Children's Healthcare of Atlanta - IS&T Department, especially Mr. Tal Senior, Mr. Robert Massey.
2. Director of Clinical Microbiology Scottish Rite and Egleston Children's Healthcare of Atlanta—Dr. Robert C. Jerris, and Clinical Microbiology Laboratory
3. Morehouse School of Medicine, Clinical Research Center, Ms. Jacquelyn Ali.

- Authors information

1. Morehouse School of Medicine, Department of Microbiology/Biochemistry/Immunology; Clinical Research Center -Pediatric Clinical & Translational Research Unit, Atlanta, GA, USA.
2. Morehouse School of Medicine, National Center for Primary Care; Department of Community Health & Preventive Medicine, Atlanta, GA USA
3. Emory University, Department of Biostatistics and Bioinformatics, Rollins School of Public Health, Atlanta, GA, USA.
4. Florida State University, Center for Medicine and Public Health, College of Medicine, Tallahassee, FL, USA
5. InterDev, Roswell, GA, USA.
6. Ningbo Consulting Inc., Atlanta, GA, USA.

References

1. Kourtis AP, Hatfield K, Baggs J, Mu Y, See I, Epton E, et al. Vital Signs: Epidemiology and Recent Trends in Methicillin-Resistant and in Methicillin-Susceptible *Staphylococcus aureus* bloodstream infections - United States. MMWR Morb Mortal Wkly Rep. 2019;68(9):214-9.
2. Calfee DP. Trends in Community Versus Healthcare-acquired methicillin-resistant *Staphylococcus aureus* infections. Curr Infect Dis Rep. 2017;19(12):48.
3. Kavanagh KT, Abusalem S, Calderon LE. The incidence of MRSA infections in the United States: is a more comprehensive tracking system needed? Antimicrob Resist Infect Control. 2017;6:34.
4. U.S. Department of Health & Human Services. National Action Plan to Prevent Health Care-Associated Infections: Road Map to Elimination: Office of Disease Prevention and Health Promotion; 2017 [updated Mar. 30]. Available from: <https://health.gov/hcq/prevent-hai-action-plan.asp>.
5. Klevens RM, Morrison MA, Nadle J, Petit S, Gershman K, Ray S, et al. Invasive methicillin-resistant *Staphylococcus aureus* infections in the United States. JAMA. 2007;298(15):1763-71.
6. Suaya JA, Mera RM, Cassidy A, O'Hara P, Amrine-Madsen H, Burstin S, et al. Incidence and cost of hospitalizations associated with *Staphylococcus aureus* skin and soft tissue infections in the United States from 2001 through 2009. BMC Infect Dis. 2014;14:296.
7. Knox J, Uhlemann AC, Lowy FD. *Staphylococcus aureus* infections: transmission within households and the community. Trends Microbiol. 2015;23(7):437-44.
8. Tong SY, Davis JS, Eichenberger E, Holland TL, Fowler VG, Jr. *Staphylococcus aureus* infections: epidemiology, pathophysiology, clinical manifestations, and management. Clin Microbiol Rev. 2015;28(3):603-61.
9. Baker P, Cohen B, Liu J, Larson E. Incidence and risk factors for community-associated methicillin-resistant *Staphylococcus aureus* in New York City, 2006-2012. Epidemiol Infect. 2016;144(5):1014-7.
10. Sattler CA, Mason EO, Jr., Kaplan SL. Prospective comparison of risk factors and demographic and clinical characteristics of community-acquired, methicillin-resistant versus methicillin-susceptible *Staphylococcus aureus* infection in children. Pediatr Infect Dis J. 2002;21(10):910-7.
11. Tirabassi MV, Wadie G, Moriarty KP, Garb J, Konefal SH, Courtney RA, et al. Geographic information system localization of community-acquired MRSA soft tissue abscesses. J Pediatr Surg. 2005;40(6):962-5.

12. Immergluck LC, Leong T, Malhotra K, Parker TC, Ali F, Jerris RC, et al. Geographic surveillance of community associated MRSA infections in children using electronic health record data. *BMC Infect Dis.* 2019;19(1):170.
13. Vaughan AS, Kramer MR, Waller LA, Schieb LJ, Greer S, Casper M. Comparing methods of measuring geographic patterns in temporal trends: an application to county-level heart disease mortality in the United States, 1973 to 2010. *Ann Epidemiol.* 2015;25(5):329-35 e3.
14. Ben-Assuli O, Padman R, Bowman M, Leshno M, Shabtai I. On analyzing readmissions using a trajectory model: evidence from Israel. *Studies Health Tech & Informat.* 2015;216:1063.
15. Hybels CF, Bennett JM, Landerman LR, Liang J, Plassman BL, Wu B. Trajectories of depressive symptoms and oral health outcomes in a community sample of older adults. *Int J Geriatr Psychiatry.* 2016;31(1):83-91.
16. Baltrus P, Malhotra K, Rust G, Levine R, Li C, Gaglioti AH. Identifying county-level all-cause mortality rate trajectories and their spatial distribution across the United States. *Prev Chronic Dis.* 2019;16:E55.
17. ICD9Data.com. 2012 ICD-9-CM Diagnosis Code 041.10, *Staphylococcus* infection in conditions classified elsewhere and of unspecified site, *Staphylococcus*, unspecified 2012 [Available from: <http://www.icd9data.com/2012/Volume1/001-139/030-041/041/041.10.htm>].
18. Morrison MA, Hageman JC, Klevens RM. Case definition for community-associated methicillin-resistant *Staphylococcus aureus*. *J Hosp Infect.* 2006;62(2):241.
19. David MZ, Daum RS. Community-associated methicillin-resistant *Staphylococcus aureus*: epidemiology and clinical consequences of an emerging epidemic. *Clin Microbiol Rev.* 2010;23(3):616-87.
20. Ali F, Immergluck LC, Leong T, Waller L, Malhotra K, Jerris RJ, Parker TC, Edelson M, and Rust GS. A spatial analyses of health disparities associated with antibiotic resistant infections in children living in Atlanta (2002-2010). *Healthcare J Deliv Sci Innov* 2019;7(1):1-14.
21. US Bureau of Labor Statistics. Databases, Tables & Calculators by Subject– CPI Inflation Calculator: United States Department of Labor; [Available from: https://www.bls.gov/data/inflation_calculator.htm].
22. Braveman P, Gottlieb L. The social determinants of health: it's time to consider the causes of the causes. *Public Health Rep.* 2014;129 Suppl 2:19-31.
23. Logan J, Stults B, Xu Z. Census geography: Bridging data for census tracts across time [Available from: <https://s4.ad.brown.edu/projects/diversity/Researcher/Bridging.htm>].
24. Getis A. A Geographic Approach to Identifying Disease Clusters. *WorldMinds: Geographical Perspectives on 100 Problems : Commemorating the 100th anniversary of the Association of American Geographers 1904–2004* 2004:5.
25. Zhou Y, Hallisey EJ, Freymann GR. Identifying perinatal risk factors for infant maltreatment: an ecological approach. *Int J Health Geogr.* 2006;5:53.
26. Kim MW, Greenfield BK, Snyder RE, Steinmaus CM, Riley LW. The association between community-associated *Staphylococcus aureus* colonization and disease: a meta-analysis. *BMC Infect Dis.* 2018;18(1):86.
27. See I, Wesson P, Gualandi N, Dumyati G, Harrison LH, Leshner L, et al. Socioeconomic factors explain racial disparities in invasive community-associated methicillin-resistant *Staphylococcus aureus* disease rates. *Clin Infect Dis.* 2017;64(5):597-604.
28. The Hispanic paradox. *Lancet.* 2015;385(9981):1918.

Figures

Figure 1

Enrollment Scheme – Unique Patients with Community Onset MRSA and MSSA Infections

Figure 2

Trends of Community-Onset Staphylococcus aureus Infection Rates Based on Group-based Trajectory Models

Figure 3

Geographic Locations of Community Onset MRSA and MSSA Infection Group-Based Trajectory Patterns, 2002-2010 Note: The designations employed and the presentation of the material on this map do not imply the expression of any opinion whatsoever on the part of Research Square concerning the legal status of any country, territory, city or area or of its authorities, or concerning the delimitation of its frontiers or boundaries. This map has been provided by the authors.

Figure 4

Hot Spot Analyses for Community Onset MRSA and MSSA Infection Group-Based Trajectory Patterns Figure Legend. Optimized hot spot analyses of community onset MRSA (Left Panel) and community onset MSSA (Right Panel) for the 20 counties within Atlanta's MSA, 2002-2010. Hot spots are depicted in red or orange pixels with varying shades representing confidence intervals, ranging 90-99%. All pixels in white represent areas where there were no significant hot spots detected. The maps are created by co-author (M Edelson) using data from Atlanta Regional Commission and U.S. Census (both data sources are open access and available online). Software used to create maps include: ArcPro, 2.5.0; URL link: <https://www.esri.com/>. Note: The designations employed and the presentation of the material on this map do not imply the expression of any opinion whatsoever on the part of Research Square concerning the legal status of any country, territory, city or area or of its authorities, or concerning the delimitation of its frontiers or boundaries. This map has been provided by the authors.