Trends in Invasive Methicillin-Resistant *Staphylococcus aureus* Infections

**AUTHORS:** Martha Iwamoto, MD, MPH,a Yi Mu, PhD,a Ruth Lynfield, MD,a Sandra N. Bulens, MPH,a Joelle Nadle, MPH,a Deborah Aragon, MSPH,a Susan Petit, MPH,a Susan M. Ray, MD,a Lee H. Harrison, MD,b Gihinwa Dumyati, MD,b John M. Townes, MD,b William Schaffner, MD,b Rachel J. Gorwitz, MD, MPH,a and Fernanda C. Lessa, MD, MPHa

aCenters for Disease Control and Prevention, Atlanta, Georgia; bMinnesota Department of Health, St Paul, Minnesota; cCalifornia Emerging Infections Program, Oakland, California; dColorado Department of Public Health and Environment, Denver, Colorado; eConnecticut Department of Health, Hartford, Connecticut; fGeorgia Emerging Infections Program, Atlanta, Georgia; gDivision of Infectious Diseases, Department of Medicine, Emory University School of Medicine, Atlanta, Georgia; hMaryland Emerging Infections Program, Baltimore, Maryland; iDepartment of International Health, Johns Hopkins Bloomberg School of Public Health, Baltimore, Maryland; jDepartment of Medicine, Infectious Diseases, University of Rochester, Rochester, New York; kDivision of Infectious Diseases, Oregon Health and Science University, Portland, Oregon; and lDepartment of Preventive Medicine, Vanderbilt University School of Medicine, Nashville, Tennessee

**KEY WORDS**

*Staphylococcus aureus* infection, methicillin resistance, children, infants, epidemiology

**ABBREVIATIONS**

ABCS—Active Bacterial Core Surveillance

BSI—bloodstream infection

CA—community-associated

CDC—Centers for Disease Control and Prevention

CI—confidence interval

CLABSI—central line–associated bloodstream infection

HACO—health care–associated community-onset

HO—hospital-onset

MRSA—methicillin-resistant *Staphylococcus aureus*

PFGE—pulsed-field gel electrophoresis

Dr Iwamoto conceptualized and designed the study and drafted the initial manuscript; Dr Mu carried out the statistical analyses and reviewed and revised the manuscript; Drs Lynfield and Townes critically interpreted the data, supervised data collection at one of the study sites, and reviewed and revised the manuscript; Ms Bulens coordinated and supervised data collection and reviewed and revised the manuscript; Ms Nadle, Ms Aragon, Ms Petit, and Drs Ray, Harrison, Dumyati, and Schaffner critically interpreted the data and reviewed and revised the manuscript; Dr Gorwitz and Townes critically interpreted the data and reviewed and revised the manuscript; Dr Lessa conceptualized and designed the study and critically reviewed and revised the manuscript; and all authors approved the final manuscript as submitted.

The findings and conclusions in this report are those of the authors and do not necessarily represent the official position of the Centers for Disease Control and Prevention.

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**WHAT’S KNOWN ON THIS SUBJECT:** Invasive methicillin-resistant *Staphylococcus aureus* (MRSA) in children is associated with high morbidity and mortality. Although reductions in health care–associated MRSA infection among adults are documented, it is unclear if a similar trend is occurring among children.

**WHAT THIS STUDY ADDS:** Data from population-based surveillance were analyzed to assess changes in invasive MRSA infection incidence over time. This analysis describes the epidemiology and trends of invasive MRSA infections among children in 9 US metropolitan areas and estimates national burden.


**METHODS:** We evaluated reports of invasive MRSA infections in pediatric patients identified from population-based surveillance during 2005–2010. Cases were defined as isolation of MRSA from a normally sterile site and classified on the basis of the setting of the positive culture and presence or absence of health care exposures. Estimated annual changes in incidence were determined by using regression models. National age- and race-specific incidences for 2010 were estimated by using US census data.

**RESULTS:** A total of 876 pediatric cases were reported; 340 (39%) were among infants. Overall, 35% of cases were hospital-onset, 23% were health care–associated community-onset, and 42% were community-associated (CA). The incidence of invasive CA-MRSA infection per 100 000 children increased from 1.1 in 2005 to 1.7 in 2010 (modeled yearly increase: 10.2%; 95% confidence interval: 2.7%–18.2%). No significant trends were observed for health care–associated community-onset and hospital-onset cases. Nationally, estimated invasive MRSA incidence in 2010 was higher among infants aged <90 days compared with older infants and children (43.9 vs 2.0 per 100 000) and among black children compared with other races (6.7 vs 1.6 per 100 000).

**CONCLUSIONS:** Invasive MRSA infection in children disproportionately affects young infants and black children. In contrast to reports of declining incidence among adults, there were no significant reductions in health care–associated MRSA infections in children. Concurrently, the incidence of CA-MRSA infections has increased, underscoring the need for defining optimal strategies to prevent MRSA infections among children with and without health care exposures. *Pediatrics* 2013;132:e817–e824
Methicillin-resistant *Staphylococcus aureus* (MRSA) causes a wide spectrum of disease ranging from skin and soft tissue infections to life-threatening systemic infections. MRSA is an important cause of infections in health care and community settings, and its epidemiology has been changing rapidly. Recent studies, predominantly in adult populations, have revealed reductions in both health care–associated and community-onset invasive MRSA infections. Meanwhile, the epidemiology of infections among children is less established and likely distinct from that in adults. The incidence of invasive infections is high in infants and young children. Studies in single centers have shown increases in invasive and noninvasive community-associated (CA) MRSA infections in children, and a national study showed an increase in the number of hospitalized children with MRSA infection. Similarly, numerous outbreaks in NICUs have been attributed to strains of both health care and community origins, and increasing trends in late-onset infections in US NICUs caused by MRSA have been reported. The prevention of MRSA infections both in health care and community settings remains a priority. Identifying the unique epidemiologic characteristics, burden, and trends in incidence of MRSA infections in children is needed to develop strategies to further decrease risks of infection. We describe the results of laboratory-, population-based surveillance for invasive MRSA infections in children during 2005–2010.

**METHODS**

**Surveillance Population**

The Active Bacterial Core Surveillance (ABCs) for invasive MRSA infections is an active, population-based surveillance system for laboratory-confirmed MRSA that started in July 2004 in selected counties in 9 geographically diverse metropolitan areas with a population of ~4.4 million persons younger than 18 years, including California (Alameda, Contra Costa, and San Francisco Counties), the state of Connecticut, Colorado (Arapahoe County), Georgia (Clayton, Cobb, DeKalb, Douglas, Fulton, Gwinnett, Newton, and Rockdale Counties), Maryland (Baltimore City), Minnesota (Ramsey County), New York (Monroe County), Oregon (Clackamas, Multnomah, and Washington Counties), and Tennessee (Davidson County). During 2005–2010, the following changes occurred in the surveillance catchment area: in 2007, Colorado added Adams, Denver, Douglas, and Jefferson Counties; and in 2008, Maryland and Minnesota added Baltimore County and Hennepin County, respectively. The ABCs population and surveillance methods have been described.

**Definitions**

A case of invasive MRSA infection was defined by the isolation of MRSA from a normally sterile body site (eg, blood, cerebrospinal fluid, pleural fluid) in a surveillance area resident younger than 18 years at least 30 days apart of an initial invasive MRSA culture. Surveillance personnel routinely receive all positive MRSA clinical microbiology reports from laboratories serving residents of surveillance areas. Demographic characteristics, clinical characteristics, disease outcomes, and information on established health care risk factors (ie, history of hospitalization [not including admission to a level I, well-newborn nursery], surgery, dialysis, or residence in a long-term care facility in the previous year; or presence of a central venous catheter within 2 days before culture) were abstracted from medical records.

Cases were classified into mutually exclusive epidemiologic categories on the basis of health care risk factors and timing of MRSA culture collection. Cases were considered hospital-onset (HO) if the MRSA clinical culture was obtained on or after the fourth calendar day of hospitalization, where admission was hospital day 1; as health care–associated community-onset (HACO) if the culture was obtained in an outpatient setting or before the fourth calendar day of hospitalization in a patient with an established health care risk factor; and as CA if the culture was obtained in an outpatient setting or before the fourth calendar day of hospitalization in a patient without documentation of a health care risk factor. Among young infants, cases were categorized as early-onset infection if MRSA was isolated from infants younger than 3 days or late-onset infection if infants were 3 to 89 days of age. Early-onset infections and other cases in which health care exposures could not be determined were not classified into an epidemiologic category. Cases were categorized into infection syndromes on the basis of physicians’ diagnoses present in the medical record and source of isolate. All syndromes were associated with the presence of MRSA in a normally sterile site. Cases were categorized as bloodstream infections (BSIs) if MRSA was isolated from blood. Syndromes were not mutually exclusive; for example, a case could have pneumonia with a BSI.

**Isolate Collection and Testing**

As part of surveillance, a convenience sample of MRSA isolates is sent to the Centers for Disease Control and Prevention (CDC) for further testing as described elsewhere. Briefly, isolates undergo confirmation of *S aureus* identification, antimicrobial susceptibility testing, and molecular characterization, including pulsed-field gel electrophoresis (PFGE). Beginning in 2008, all submitted isolates were...
characterized either by PFGE or by inference of PFGE patterns on the basis of microbiological characteristics, including staphylococcal cassette chromosome, presence of Panton-Valentine leukocidin, and antimicrobial susceptibility results.15

**Statistical Analysis**

Incidence rates were calculated by using US Bureau of the Census bridged-race vintage postcensus population estimates.14-16 For cases in patients with unknown race, race was imputed on the basis of the distribution of known race and gender for each surveillance area. Because there are no population estimates for infants by month of age, we estimated that the population of infants younger than 90 days was approximately one-quarter of the population of infants younger than 1 year. Annual MRSA infection incidence was determined by pooling data by year across surveillance areas. To ensure comparability over time, analyses comparing incidence over time were restricted to surveillance areas that reported continuously during the study period. All other analyses used all available data during 2005–2010.

Trends in incidence were assessed by using a Poisson regression model or negative binomial distribution, if there was evidence of overdispersion. For cases in patients aged 3 to 89 days, annual incidences of all late-onset invasive MRSA infections and of HO infections were used to calculate trends. For cases in patients aged 90 days to 17 years, trends in incidences were calculated by epidemiologic category. The outcome variable was number of invasive MRSA infections, and time (year) as a continuous variable was the predictor. All models for trend analysis were adjusted by age, gender, and race; and P values <.05 were considered statistically significant.

Point estimates and 95% confidence intervals (CIs) for the yearly percentage change were determined by using each model. The final models were used to determine the adjusted incidence for each year. For national estimates of cases in 2010, age- and race-specific incidence of infection across surveillance sites were applied to the age and racial distribution of the US population. CIs were estimated by using a method based on the gamma distribution.17

**RESULTS**

**Characteristics of Cases**

During 2005 through 2010, 876 cases of invasive MRSA infections were reported among 834 pediatric patients. The median age at time of infection was 2.1 years (range: 0 days to 17 years), and 39% of cases occurred among infants younger than 1 year. Most (799 of 876; 91%) were hospitalized, and there were 53 (6%) fatal cases (Table 1). Males accounted for 59% (490 of 834) of patients. Among patients with reported race (n = 682), 59% were black, 36% were white, and 5% were children of other races. Overall, 68% (565 of 834) of children with invasive MRSA infection had an underlying medical condition, including prematurity (19%), dermatologic condition (eg, eczema, abscesses) (18%), asthma (8%), congenital disorder (4%), renal disease (2%), and malignancy (2%).

Of the 876 cases, 857 were classified into an epidemiologic category; 363 (42%) were CA-MRSA infections, 298 (35%) were HO-MRSA infections, and 196 (23%) were HACO-MRSA infections. Ten cases were early-onset neonatal infections, and epidemiologic category was unknown for 9 cases. Eighty percent (151 of 190) of infections in infants aged 3–89 days were HO-MRSA infections, with almost half occurring in premature infants. The most common health care risk factors among cases with HO- and HACO-MRSA infections were previous hospitalization (55% and 86%, respectively), presence of a central venous catheter (32% and 28%, respectively), and history of surgery (22% and 26%, respectively). The distribution of epidemiologic categories varied with age and with underlying medical condition. More than 80% of HO- and HACO-MRSA cases were in patients with a reported underlying medical condition, compared with half of CA-MRSA cases. The proportion of CA-MRSA infections was highest in children aged 5 to 10 years old (92 of 130; 71%).

MRSA was isolated from blood in 692 cases (79%), and 364 cases (41.6%) were BSIs only without another infection syndrome (Table 1). However, of these 364 cases, 248 (68%) had a central venous catheter within the 2 days before the positive MRSA blood culture. Other common types of invasive infections included bone and joint infections (179 of 876; 20%), skin and soft tissue infections (152 of 876; 17%), pneumonia or empyema (129 of 876; 15%), and meningitis or cerebrospinal fluid shunt infection (35 of 876; 4%). Infection syndromes varied by epidemiologic category (Table 1).

**Characteristics of Invasive MRSA Isolates**

Among the 876 cases, 257 (29%) had an MRSA isolate submitted to the CDC. Isolates were obtained from blood (189 cases; 74%), pleural fluid (16 cases; 6%), cerebrospinal fluid (11 cases; 4%), joint (10 cases; 4%), peritoneal fluid (6 cases; 2%), bone (5 cases; 2%), and other sites (20 cases; 8%). Overall, the predominant strain patterns were USA300 (184 cases; 72%) and USA100 (47 cases; 18%); other pulsed-field types were less common, each accounting for <2% of isolates. USA300 strains were identified among 107 (84%) isolates from CA-MRSA infections,
Invasive infection, c
year (95% CI: adjusted for race, declined 9.8% per ing continuous surveillance during the
Fatal cases,
IWAMOTO et al
n = 257.
Epidemiologic Categories of Invasive MRSA Isolates by PFGE Type
Overall, 178 late-onset invasive MRSA infections among children older than 18 years in 2010. Adjusted national incidence was higher among infants aged 3–98 days and among black children, whereas children aged 11 to 17 years had the lowest incidence (Table 3).

**DISCUSSION**
Our results distinguish the epidemiology of invasive MRSA infections among children compared with adults, emphasizing the need for pediatric-specific prevention strategies. In contrast to recent published reports of declines in invasive health care–associated MRSA infections and community-onset BSIs in study populations composed mostly of adults,5–5 in children older than 3 months we observed no significant trends in HO- or HACO-invasive MRSA infections and an increase in rates of invasive CA-MRSA infections. Additionally, we found that invasive MRSA infections disproportionately affect young infants and blacks. Taken together, these findings reveal that multiple factors may impact risk and complicate efforts to control MRSA transmission and infections in children.

<table>
<thead>
<tr>
<th>Patient age at time of infection, n (%)</th>
<th>HO (n = 288)</th>
<th>HACO (n = 196)</th>
<th>CA (n = 363)</th>
<th>Total* (N = 878)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;3 days</td>
<td>10 (1.1)</td>
<td>10 (1.1)</td>
<td>10 (1.1)</td>
<td>30 (3.4)</td>
</tr>
<tr>
<td>3–89 days</td>
<td>190 (21.7)</td>
<td>190 (21.7)</td>
<td>190 (21.7)</td>
<td>570 (64.2)</td>
</tr>
<tr>
<td>3–11 months</td>
<td>141 (16.1)</td>
<td>141 (16.1)</td>
<td>141 (16.1)</td>
<td>423 (47.7)</td>
</tr>
<tr>
<td>1–4 years</td>
<td>209 (23.9)</td>
<td>209 (23.9)</td>
<td>209 (23.9)</td>
<td>627 (71.3)</td>
</tr>
<tr>
<td>5–10 years</td>
<td>130 (14.8)</td>
<td>130 (14.8)</td>
<td>130 (14.8)</td>
<td>390 (44.5)</td>
</tr>
<tr>
<td>11–17 years</td>
<td>216 (24.4)</td>
<td>216 (24.4)</td>
<td>216 (24.4)</td>
<td>648 (74.3)</td>
</tr>
</tbody>
</table>

Invasive infection, n (%) | BSI | BSI only | Pneumonia or empyema | Soft tissue/skin infection | Bone or joint infection | Other infection | Fatal cases, n (%) | Hospitalization, n (%) | Median stay, d (interquartile range) |
--------------------------|------|--------|---------------------|--------------------------|----------------------|----------------|-------------------|------------------------|--------------------------|
| HO (n = 288) | 252 (86.4) | 195 (65.4) | 42 (14.1) | 27 (9.1) | 11 (3.7) | 28 (9.4) | 43 (14.4) | 298 (100) | 60 (24–95) |
| HACO (n = 196) | 147 (75.0) | 84 (42.8) | 30 (15.3) | 31 (15.8) | 27 (13.8) | 33 (16.8) | 4 (2.0) | 175 (89.3) | 10 (6–19) |
| CA (n = 363) | 277 (76.3) | 76 (20.9) | 55 (15.2) | 93 (25.6) | 138 (38.0) | 39 (10.7) | 6 (1.7) | 311 (85.7) | 9 (5–15) |
| Total* (N = 878) | 692 (79.0) | 364 (41.6) | 129 (14.7) | 152 (17.3) | 179 (20.4) | 104 (11.9) | 53 (8.1) | 789 (81.2) | 15 (7–43) |

* Includes cases occurring in patients younger than 3 days and cases in which epidemiologic classification could not be determined.
** P-values were determined by χ² statistic and indicated significant differences in proportion of infections by epidemiologic category.
A case could represent >1 infection syndrome.
Associated with an MRSA culture from a normally sterile site (eg, blood, cerebrospinal fluid, pleural fluid).
Infants younger than 3 days are categorized as early-onset infections that are not classified in an epidemiologic category.

36 (54%) from HO-MRSA infections, and 35 (62%) from HACO-MRSA infections (Table 2). USA100 was most commonly associated with HO-MRSA infections (22 of 47 USA100 isolates; 47%). Although 10 (21%) USA100 isolates were from CA-MRSA infections, they represented only 8% of isolates from CA-MRSA infections overall.

**Invasive MRSA Infection Incidence and Trends**
Overall, 178 late-onset invasive MRSA infections among infants aged 3 to 89 days were identified in areas conducting continuous surveillance during the study period. The modeled incidence, adjusted for race, declined 9.8% per year (95% CI: −17.5% to −1.4%). When analysis was restricted to late-onset HO-MRSA infections, a more pronounced decrease was detected (modeled yearly change: −11.3%; 95% CI: −19.6% to −2.0%) (Fig 1). Incidence among black infants was consistently higher than incidence among infants of other races, which was not driven by any particular surveillance site. Stratified by race, there was no statistically significant trend observed in incidence in black infants (modeled yearly change: −7.8%; 95% CI: −17.7% to 3.2%), whereas the decline in incidence among nonblack infants approached significance (modeled yearly change: −12.8%; 95% CI: −24.4% to 0.6%). A total of 617 invasive MRSA infections were identified among children older than 3 months. Incidence and trends of invasive infections differed by epidemiologic category (Fig 2). The modeled incidence of CA-MRSA infections, adjusted for age and race, increased 10.2% per year (95% CI: 2.7%–18.3%). Increases in incidence of CA-MRSA infections were observed across 7 of the 9 surveillance sites. Overall, no sustained change over time was observed in the incidence of HACO-MRSA infections, nor were significant changes observed among HO-MRSA infections. Across all epidemiologic categories, black children and children younger than 5 years were at increased risk of infection, compared with nonblack children and older children, respectively.

An estimated 1895 invasive MRSA infections and 140 (7.4%) deaths occurred in the United States among children younger than 18 years in 2010. Adjusted national incidence was higher among infants aged 3–89 days and among black children, whereas children aged 11 to 17 years had the lowest incidence (Table 3).

**TABLE 2** Epidemiologic Categories of Invasive MRSA Isolates by PFGE Type

<table>
<thead>
<tr>
<th>Epidemiologic Category</th>
<th>USA100, n (%)</th>
<th>USA300, n (%)</th>
<th>Other PFGE Type, n (%)</th>
<th>Total, n</th>
</tr>
</thead>
<tbody>
<tr>
<td>HO</td>
<td>22 (33.3)</td>
<td>36 (54.5)</td>
<td>8 (12.1)</td>
<td>66</td>
</tr>
<tr>
<td>HACO</td>
<td>13 (23.2)</td>
<td>35 (62.5)</td>
<td>8 (14.3)</td>
<td>56</td>
</tr>
<tr>
<td>CA</td>
<td>10 (7.9)</td>
<td>107 (84.3)</td>
<td>10 (7.8)</td>
<td>127</td>
</tr>
<tr>
<td>Early-onset infection</td>
<td>1 (20.0)</td>
<td>4 (80.0)</td>
<td>0 (0)</td>
<td>5</td>
</tr>
<tr>
<td>Unknown epidemiologic category</td>
<td>1 (33.3)</td>
<td>2 (66.7)</td>
<td>0 (0)</td>
<td>3</td>
</tr>
</tbody>
</table>

n = 257.
within and outside of health care settings.

In our pediatric population, CA-MRSA infections represent the largest proportion of cases, which is different from what has been reported among adults in whom ~60% of cases are HACO.4,6 Although invasive infections are likely only a small fraction of all CA-MRSA infections, the increase in incidence of CA-MRSA invasive infections we observed nationally supports findings from single-center studies where both invasive and noninvasive CA-MRSA infections in children were reported to be increasing.8,9,18,19 Additionally, findings from a large national study examining administrative data from children’s hospitals found an increase in MRSA hospitalizations, largely driven by skin and soft tissue infections in primarily healthy children.7 However, a direct comparison cannot be made with these studies because we report on invasive infections only. The increase in rates of CA-MRSA in children is concerning. Current prevention strategies for CA-MRSA focus on education and behavior change aimed at improving hygiene, and it is unknown whether these strategies are effective or have been widely adopted.

In our sample of isolates, USA300 strains were associated with 54% of HO-MRSA infections and with 63% of HACO-MRSA infections, which is much higher than what has been reported in adult population (25% and 33%, respectively).20 This finding is consistent with what was recently reported from 30 hospitals in California where pediatric and adult MRSA strains were compared.21 USA300 has emerged as a cause of health care–associated infections causing NICU outbreaks, and in at least 1 region of the country USA300 has been reported as the most prevalent strain causing health care–associated BSIs.21–24 It is still unclear, however, whether USA300 is adding to the current disease burden or replacing USA100 as the main cause of MRSA infections in the children.

We examined our data to describe infections in pediatric subpopulations, including infants in the NICU. In our study, the highest incidence of infection was among infants younger than 3 months old. Infections seemed to occur among infants in the NICU; most were HO BSIs in neonates who were premature and had been hospitalized since birth. This finding is not surprising given that established risk factors for MRSA infection in infants include prematurity, young gestational age, longer length of hospitalization, and colonization with MRSA.25–31 Promisingly, our study showed that the rate of late-onset (ie, 3 to 89 days of age) invasive MRSA infection in hospitalized infants is decreasing. The observed decline is likely due in part to progress in infection prevention practices in NICUs, especially improvements in central line insertion and maintenance practices. This interpretation is supported by results of studies from NICU collaboratives that have implemented programs designed to improve central line practices leading to substantial reductions in central line–associated BSIs (CLABSSIs) caused by all pathogens.32–35
Although the declining rate of late-onset infection among neonates is encouraging, we did not observe decreases in HO- or HACO-MRSA invasive infections, mostly BSIs, in children older than 3 months. This finding directly contrasts with declines in MRSA CLABSI rates reported in adult ICUs. The reasons for this discrepancy in MRSA trends among children compared with adults are unknown. However, there are relatively few studies assessing the preventability of MRSA infections in children, and evidence-based prevention guidelines are largely based on adult data. Additionally, some interventions recommended for adults may not be recommended in children because of the lack of data about risks versus benefits for young children. This situation has led to heterogeneity of practices to prevent CLABSiS and MRSA infections in children, with examples including variability in screening policies for MRSA, isolation precautions, MRSA decolonization, and central line care.

We found differences in incidence of invasive MRSA infections by race among all age groups in all epidemiologic categories. Previous studies have described disparities in invasive MRSA infections between blacks and whites; however, our understanding of factors that sustain these disparities remains poor. The higher rates in black children may suggest differences in behavioral or host factors. Socioeconomic factors may play a role in a health care–seeking behavior and MRSA transmission (eg, household crowding), and additional studies are needed to better understand the reasons for racial disparities.

Our analysis was subject to several limitations. First, our data represent surveillance in 9 US metropolitan areas. Although it is unknown whether incidence rates in the surveillance populations are representative nationally, they represent one of the largest populations evaluated for changes in incidence. Second, the sample of MRSA isolates received at the CDC was a sample of less than one-third of the pediatric cases reported and should not be interpreted as representative of all pediatric cases. Third, the population denominators used for infants younger than 90 days were extrapolated from census estimates; however, no US census estimates for infants by age-in-months are available and using a denominator for all infants younger than 1 year would underestimate incidence. Fourth, we were not able to assess trends in early-onset MRSA infections because of the small number of neonates in this category. Last, patient data were collected by medical record review, which could result in misclassification of epidemiologic category if health care risk factors were not well documented.

Despite these limitations, our findings represent those from a large, population-based surveillance system with thorough collection of data on epidemiologic and clinical characteristics of cases. Our study extends the existing literature by estimating the national burden of invasive infections in children and by showing trends in incidence of invasive MRSA infections acquired from both health care and community settings. Evaluating these trends helps us measure progress toward MRSA prevention, identify populations at risk, and set priorities for future studies.

CONCLUSIONS

In summary, invasive MRSA infection in children appears to disproportionately affect young infants and black children. In contrast to declining incidence among adults and NICU patients, there were no significant reductions in invasive health care–associated MRSA infections in children older than 3 months during 2005–2010. Concurrently, the incidence of invasive CA-MRSA infections increased. These findings underscore the need for defining optimal strategies to prevent MRSA infections among children, especially children without health care risk factors, hospitalized children outside of the ICU, and children with recent exposure to health care.

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