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Burden of Invasive *Staphylococcus aureus* Infections in Hospitalized Infants

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Abstract

Importance—*Staphylococcus aureus* is a frequent cause of infection in hospitalized infants. These infections are associated with increased mortality and morbidity, and longer hospital stays, but data on the burden of *S. aureus* disease in hospitalized infants are limited.

Objective—To compare demographics and mortality of infants with invasive methicillin-resistant *S. aureus* (MRSA) and methicillin-susceptible *S. aureus* (MSSA), determine the annual proportion of *S. aureus* infections that were MRSA, and compare the risk of death following an invasive MRSA infection to the risk following an invasive MSSA infection.

Design—Multicenter retrospective study of a large, nationally representative cohort.

Setting—348 neonatal intensive care units managed by the Pediatrix Medical Group.

Participants—3888 infants with an invasive *S. aureus* infection who were discharged between 1997 and 2012.

Exposure—Invasive *S. aureus* infection.

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Authors' Contributions: Drs. Ericson and Benjamin had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

Study concept and design: Drs. Milstone, Popoola, Smith, and Ericson.

Drafting of the manuscript: Dr Ericson.

Critical revision of the manuscript for important intellectual content: Drs Smith, Popoola, Benjamin, Benjamin Jr., and Milstone.

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Main Outcomes and Measures—Incidence of invasive *S. aureus* infections. Infant characteristics and mortality following MRSA or MSSA infection.

Results—The 3888 infants had 3978 invasive *S. aureus* infections (2868 MSSA, 1110 MRSA). The incidence of invasive *S. aureus* infection was 44.8 infections/10,000 infants. The yearly proportion of invasive infections caused by MRSA increased from 1997 to 2006 and has remained relatively stable since then. Infants with invasive MRSA or MSSA infections had similar gestational ages and birth weights. Invasive MRSA infections occurred more often at a younger postnatal age. For infants with available mortality data, more infants with invasive MSSA infections died at hospital discharge (N=237) than those with invasive MRSA infections (N=110). The proportion of infants who died following invasive MSSA or MRSA infection were similar: 237/2474 (9.6%) and 110/926 (11.9%), $P=.05$, respectively. Adjusted risk of death at hospital discharge was similar after invasive MSSA and MRSA infections overall (risk ratio, 1.19; 95% CI, 0.96-1.49). Risks of death at 7 and 30 days after invasive infection were similar between infants with invasive MSSA and MRSA infection.

Conclusion—Infant mortality following invasive MRSA and MSSA infections is similar. MSSA causes more infections and more deaths in infants than MRSA. Measures to prevent *S. aureus* infection should include MSSA in addition to MRSA.

INTRODUCTION

Staphylococcus aureus (*S. aureus*) is a frequent cause of infection in hospitalized infants.¹ Infections due to *S. aureus* are associated with increased mortality², morbidity,³ and length of hospital stay.⁴ *S. aureus* is the second most frequent cause of late-onset sepsis in very low birth weight (<1500 g; VLBW) infants¹ and is resistant to methicillin in 8-28% of cases.⁵⁻⁷

Antibiotic-resistant *S. aureus* strains, specifically methicillin-resistant *S. aureus* (MRSA), have emerged and become prevalent in neonatal intensive care units (NICUs). Because MRSA-colonized infants often serve as a reservoir for spread to other infants, many NICUs have developed procedures to detect and isolate colonized infants.^{8,9} Identification of colonization is often followed by efforts to eradicate MRSA.^{8,10} Although infection due to methicillin-susceptible *S. aureus* (MSSA) also occurs, few centers have screening protocols for MSSA.¹¹

The proportion of nosocomial *S. aureus* infections caused by MRSA has decreased in some settings, including NICUs.^{12,13} However, most studies evaluating *S. aureus* and MRSA in NICU patients have included small numbers of patients or culture sites, and have been conducted in single institutions, at tertiary care centers, or in outbreak settings.^{5,6,14} Our objective was to describe the epidemiology of *S. aureus* invasive infections using a large, nationally representative cohort of hospitalized infants.

METHODS

We identified all infants with an invasive *S. aureus* infection who were discharged between 1997 and 2012 from 348 NICUs managed by the Pediatrix Medical Group. The Pediatrix Medical Group cares for >20% of infants admitted to NICUs in the US and is composed of

both academic and community sites in 34 states. Data were obtained from the electronic medical record generated prospectively by clinicians on all infants. Data were extracted, de-identified, and stored in the Pediatrix Clinical Data Warehouse.¹³ Information stored for infants includes maternal history, birth information, and demographics. Medications, laboratory results, microbiology results, diagnoses, and procedures are recorded on a daily basis. Microbiology results are reported as documented by the treating physician in the medical record.

Definitions

Positive *S. aureus* cultures obtained within 21 days of each other were considered to be a single infection.¹⁵ Infections in which any positive culture was obtained from cerebrospinal fluid (CSF), blood, sterile fluid, or an abscess were considered to be invasive. Infections in which all positive cultures were obtained from the trachea, urine, conjunctiva, or a wound were considered to be non-invasive. Abscess cultures included all cultures labeled “abscess” and may have included both cutaneous and deep tissue abscesses. Because the method of collection was missing for most urine samples, positive urine cultures were considered to be non-invasive. Cultures obtained from the skin surface, umbilicus, rectum, nasopharynx, or gastric aspirate were considered to represent surveillance cultures. Non-invasive and surveillance cultures were excluded from the analysis. Cultures for which the specimen type was “unknown” or “other” were also excluded. Infections that had growth of both MSSA and MRSA were considered to be MRSA infections.

Inotropic support was defined as exposure to dopamine, dobutamine, epinephrine, norepinephrine, or milrinone. Mechanical ventilation was defined as exposure to any invasive mechanical ventilation. Oxygen supplementation was defined as the administration of any fraction of inspired oxygen >21%. Antibiotic exposure was defined as exposure to any antibiotic. Anti-MRSA antibiotic exposure was defined as exposure to vancomycin, rifampin, linezolid, daptomycin, clindamycin, trimethoprim-sulfamethoxazole, or mupirocin. Small-for-gestational-age (SGA) status was defined as previously described.¹⁶

Statistical Analysis

We determined the proportion of *S. aureus* infections that were methicillin-resistant by year of discharge and by NICU site. We calculated the incidence of positive MSSA and MRSA infections per 10,000 admitted infants for each year.

Infant demographics were assigned to *S. aureus* type (MRSA vs MSSA) by the type of first invasive infection and were compared using Wilcoxon rank sum tests for continuous variables and chi-square tests for categorical variables. We compared the median number of days of exposure to inotropic support, oxygen support, ventilator support, antibiotic use, and MRSA-active antibiotic use prior to the first positive invasive culture for infants with MRSA to those parameters for infants with MSSA using Wilcoxon rank sum tests.

We determined the number of deaths that occurred before hospital discharge and within 7 and 30 days after the first positive culture of an invasive infection, both overall and separately for infants <1500 g birth weight and for infants ≥1500 g birth weight. For infants

with more than one invasive infection, we considered the risk of death following the last infection. We compared the risk of death following an invasive MRSA infection to the risk of death following an invasive MSSA infection using modified Poisson regression adjusted for gestational age, SGA status, male sex, and race/ethnicity with random effects for site.

Statistical analyses were performed using Stata 13 (College Station, TX). Statistical significance was set at $P < .05$. This study was approved by the Duke University Institutional Review Board.

RESULTS

Burden of Invasive MSSA and MRSA Disease

We identified 3888/887,910 (0.4%) infants with 3978 invasive *S. aureus* infections. Infections were caused more commonly by MSSA (2868/3978, 72%) than MRSA (1110/3978, 28%).

Overall, invasive *S. aureus* infections occurred at an incidence of 44.8 infections/10,000 infants. The annual incidence of invasive *S. aureus* infection increased from 1997 to 2007 and declined from 2007 to 2012 (Figure 1). Invasive *S. aureus* infections were more common in infants born at <1500 g than those ≥1500 g (3061/136,797 [223.8/10,000 infants] vs 917/751,113 [12.2/10,000 infants], respectively, $P < .01$) (Table 1). MSSA was more common than MRSA for all birth weight categories.

Characteristics of Infants With MSSA and MRSA Disease

Most characteristics of infants with invasive MSSA and MRSA infections were similar, including gestational age, birth weight, and the proportion that were male, small for gestational age or born by Cesarean-section (Table 2). MSSA was more common than MRSA for all races except for African American infants. MRSA infections occurred at a younger median postnatal age than MSSA infections (15 days [25th, 75th percentiles: 9, 26] vs 18 days [10, 32], respectively, $P < .001$). When considering exposure to potential risk factors before the first invasive *S. aureus* infection, infants whose first invasive *S. aureus* infection was MRSA had a shorter median duration of oxygen support before the infection than those with MSSA (5 days [1, 15] vs 8 days [1, 20], $P < .001$). Previous exposure to a surgical procedure and the number of days of antibiotic exposure, MRSA-active antibiotic exposure, ventilator support, and inotropic support before the first invasive *S. aureus* infection were similar for infants with MSSA and those with MRSA.

Mortality of Infants With MSSA and MRSA Disease

Among the 2474 infants with invasive MSSA infections for whom mortality information was available, 237 (9.6%) had died at hospital discharge. Mortality was higher among infants with invasive MRSA infection (110/926 [11.9%], $P = .049$). Infants < 1500 g birth weight with invasive *S. aureus* infection died at hospital discharge more often than infants ≥1500 g (302/2596 [11.6%] vs 45/804 [5.6%], $P < .01$). When the risk of death was adjusted for birth weight, gender, and race with random effects for site, there was no statistically significant difference in the risk of death following an invasive MSSA infection compared to

an invasive MRSA infection overall, or separately for infants < 1500 g and ≥ 1500 g (Table 3). The risk of death was also similar at 7 and 30 days after the start day of the invasive infection.

Trends in Methicillin Resistance Over Time

The proportion of *S. aureus* infections resistant to methicillin increased from 1999 to 2006 (Figure 2). A slight decrease in the proportion of *S. aureus* cultures that were MRSA occurred in 2007, but the annual proportion of MRSA cultures has overall remained increased. For the 100 sites with ≥ 10 episodes of invasive *S. aureus* infection, the proportion of invasive *S. aureus* infections caused by MRSA varied widely by site (median 26.3% [16.7, 36.8]). The proportion of invasive infections caused by MRSA ranged from 0 at 5 sites to 86.7% at 1 site.

DISCUSSION

In this large representative cohort of hospitalized infants, invasive *S. aureus* infections occurred in 0.4% of all infants and in 2.2% of VLBW infants. Overall, MSSA caused 2.5 times more invasive *S. aureus* infections than MRSA. The adjusted risk of death was similar for MSSA and MRSA invasive infections overall and for VLBW infants.

Our findings confirm results of earlier studies demonstrating that infections due to MSSA are more common than MRSA infections. A single-center retrospective study of 172 *S. aureus* infections found that 72% of *S. aureus* infections were caused by MSSA, with most of the infections occurring in infants <1000 g birth weight.⁶ A study of VLBW infants in the National Institute of Child Health and Human Development's Neonatal Research Network study similarly found that 72% of bacteremia and meningitis cases due to *S. aureus* were caused by MSSA.⁵ Infection prevention strategies should broadly target both MSSA and MRSA in this population.

In our cohort, invasive *S. aureus* infections occurred at an incidence of 2.2% in VLBW infants. Previous studies found that the incidence of *S. aureus* infections in this population was approximately 3%.^{5,6} Our observed disease incidence of 2.2% may better reflect the national burden of disease but may not be applicable to all high-acuity centers. If current birth trends continue, an incidence of invasive *S. aureus* disease of 2.2% in VLBW infants and 0.1% in non-VLBW infants will result in more than 5000 invasive *S. aureus* infections each year.¹⁷

Studies of older patients have found that prolonged hospital stay, presence of a central line, recent surgical procedures and recent antibiotic therapy may predispose patients to infection with MRSA.¹⁸⁻²⁰ In infants, some studies have noted that a low birth weight and gestational age, as well as recent surgical procedure and prior treatment with systemic antibiotics, are associated with a higher incidence of MRSA colonization and subsequent infection.^{6,21,22} We found that infants with invasive MRSA infection were more often of African American race, outborn status, and younger postnatal age. Other studies have also noted that infants with MRSA infection are younger in postnatal age than those with MSSA.^{6,23,24} This is intuitively unexpected because, as a hospital-associated infection, it would be expected that

more days in the hospital and more days of antibiotic exposure would increase risk of MRSA infections. MRSA infections have been noted to be more common in African American patients.²⁵⁻²⁷ The reasons for this difference are not clear but may be due to differences in immune function, maternal colonization rates or other unknown factors.²⁸

Worse outcomes following MRSA infection compared to MSSA infections have been noted in older patients with bloodstream infections,^{29,30} endocarditis,³¹ and osteomyelitis.³² Differences in outcomes following MRSA infection compared to MSSA infection in infants, however, have been less clear, and our findings are consistent with several previous studies. We found no difference in adjusted mortality following MRSA or MSSA invasive infection at 7 days, 30 days, or hospital discharge. A single-center study of 172 *S. aureus* infections in hospitalized infants found that mortality was similar between infants with MRSA and MSSA (16% vs 17%, respectively, $P=1.00$).⁶ Hospital length of stay was also similar (64 days for MRSA and 64 days for MSSA, $P=.80$).⁶ Another single-center study found no differences in the duration of hospital length of stay ($P=.70$), death ($P=.20$), or the incidence of neurodevelopmental impairment at 12-36 months of age ($P=.28$) for 53 infants with *S. aureus* bacteremia.²⁴ A multicenter retrospective study of 316 infants found no difference in survival for infants < 1500 g with MRSA versus MSSA bacteremia or meningitis.⁵

Given similar outcomes in infants with MRSA and MSSA disease, prevention strategies should focus broadly on *S. aureus* prevention and not focus solely on prevention of MRSA. Single-center studies have suggested that MRSA screening and decolonization may reduce MRSA infection. However, a lack of controlled trials has led to a large variation in approaches in MRSA identification and treatment in the NICU.⁸ Even though MSSA causes more infections and more deaths per year in infants, most centers only consider MRSA in their screening and decolonization protocols.⁸ As we have previously described, a broader approach to *S. aureus* prevention should go beyond MRSA to also include MSSA.¹⁰ When MSSA has been included in screening and decolonization efforts, subsequent MSSA infections have decreased.^{33,34} One NICU was able to dramatically reduce both MRSA and MSSA infections with a universal *S. aureus* screening and decolonization program.³³ Screening and decolonization protocols have been demonstrated to reduce infections due to both MRSA and MSSA in adult orthopedic and cardiac surgery patients.^{35,36}

The annual proportion of MRSA cultures in our population increased from 1996 to 2006 when an initial decrease occurred followed by a plateau. The early increase has been seen in other studies. A study including data from 40 freestanding children's hospitals found that the incidence of MRSA increased from 2002 to 2007 with MSSA incidence remaining stable.³⁷ A 10-year single-center study that included 156 infants with *S. aureus* bloodstream infections found a peak in the incidence of infections due to MRSA in 2005 with a steadily decreasing incidence from 2006-2009.²³ Further studies are needed to identify differences between centers with high and low proportions of isolates with methicillin-resistance.

The stabilization in MRSA incidence that we observed starting in 2007 is also consistent with the findings of other investigators. A study including 1751 infants found that surveillance cultures positive for MRSA peaked in 2006 at 5.8% and then plateaued with approximately 3% of cultures being positive.¹² Using national surveillance data, the Centers

for Disease Control found that the incidence of MRSA decreased nearly 10% per year from 2005-2010 in infants <90 days postnatal age.³⁸ A large study that included infants, children, and adults found that *S. aureus* bacteremia decreased by 41% from 2006-2010.¹³ This stabilization in MRSA rates may be due to improved infection control practices leading to fewer hospital-acquired infections.³⁸

We opted to exclude surveillance and non-invasive cultures from analysis because of varying surveillance practices (i.e., centers with no surveillance, surveillance for MRSA only, varying surveillance frequency and methods). Specimens from invasive infections may have been classified as surveillance cultures or non-invasive infections, but this number was likely small and should have been similar for MRSA and MSSA. Our analysis evaluated all-cause mortality not *S. aureus*-attributable mortality; however, the relative risk of death following invasive MRSA compared to invasive MSSA is not likely to be influenced by this distinction.

CONCLUSIONS

The absolute numbers of infections and deaths due to MSSA exceed those due to MRSA. Consideration should be given to expanding hospital infection control efforts targeting MRSA to include MSSA as well.^{10,39,40} Future studies to better define the relationship between MSSA colonization and subsequent infection will help to clarify the importance of such interventions for preventing MSSA disease.

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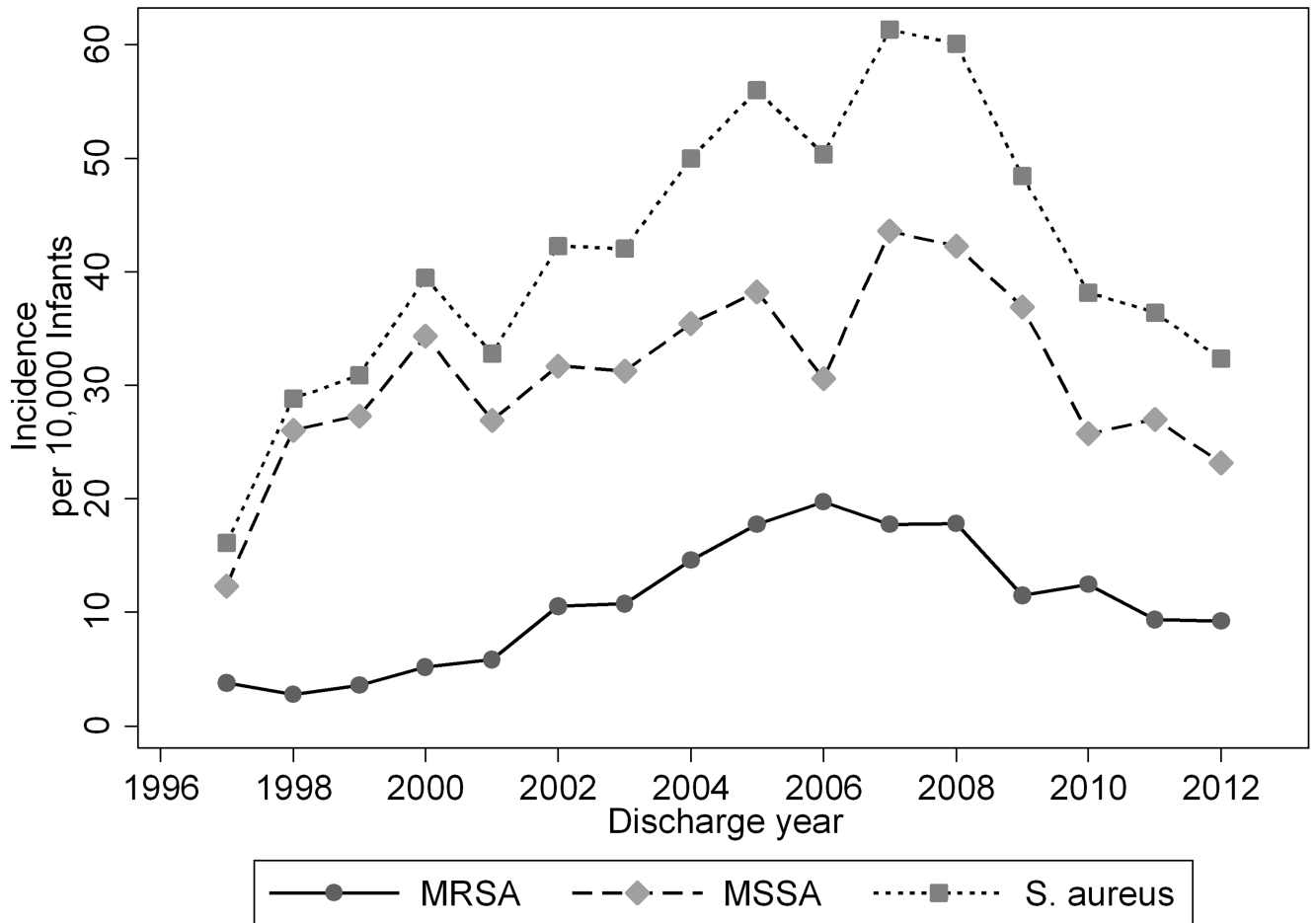


Figure 1.
Annual Incidence of Invasive *Staphylococcus aureus*, Methicillin-Resistant *Staphylococcus aureus*, and Methicillin-Sensitive *Staphylococcus aureus* Infections per 10,000 Discharged Infants

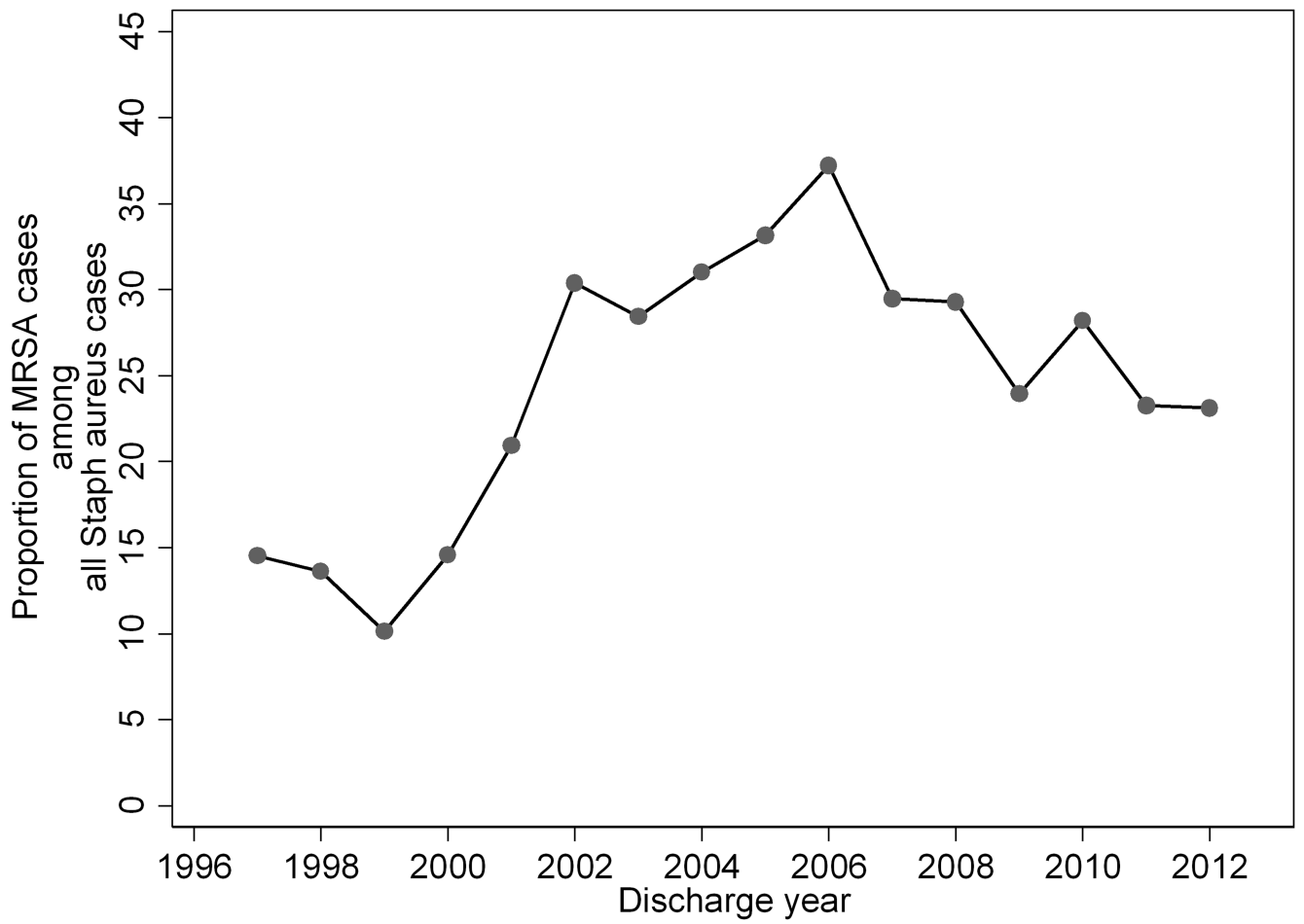


Figure 2.
Proportion of *Staphylococcus aureus* Positive Cultures That Were Methicillin-Resistant by Year of Discharge

Table 1
Incidence of Invasive *Staphylococcus aureus* Infections for Hospitalized Infants, Number of Infections/10,000 Infants

Culture Type	MSSA		MRSA		<i>S. aureus</i>	
	N	Infections/10,000	N	Infections/10,000	N	Infections/10,000
<1500 g birth weight (N=136,797)						
All sites	2208	161.4	853	62.4	3061	223.8
1500 g birth weight (N=751,113)						
All sites	660	8.8	257	3.4	917	12.2

Abbreviations: MRSA, methicillin-resistant *S. aureus*; MSSA, methicillin-susceptible *S. aureus*.

Table 2Characteristics of All Infants and Infants With An Invasive Culture for *Staphylococcus aureus*^a

Characteristic	MSSA (N=2825)	MRSA (N=1063)	P Value
Gestational age, weeks			.72
<25	723 (26)	270 (25)	
26–28	966 (34)	345 (32)	
29–32	660 (23)	2659 (24)	
33–36	253 (9)	107 (10)	
37	219 (8)	82 (8)	
Birth weight, g			.42
<1000	1480 (52)	528 (50)	
1000–1499	689 (24)	284 (27)	
1500–2499	387 (14)	145 (14)	
2500–3499	194 (7)	82 (8)	
>3500	73 (3)	24 (2)	
Apgar score			.24
0-3	147 (5)	49 (5)	
4-6	512 (19)	215 (21)	
7-10	2087 (76)	762 (74)	
Race/ethnicity			<.001
White	1329 (49)	467 (45)	
African American	681 (25)	330 (32)	
Hispanic	564 (21)	201 (19)	
Other	151 (6)	37 (4)	
Male	1555 (55)	575 (54)	.60
Inborn	2236 (80)	783 (74)	<.001
Cesarean section	2033 (73)	741 (71)	.16
Small for gestational age	541 (19)	207 (20)	.84
Congenital anomaly	363 (13)	150 (14)	.30
Age at 1 st positive culture, days			.01
<7	324 (11)	123 (12)	
7–14	659 (23)	292 (27)	
15–28	905 (32)	348 (33)	
>28	937 (33)	300 (28)	
Previous surgical procedure	476 (17)	186 (18)	.63
Inotropic support ^b	0 (0, 2)	0 (0, 2)	.61
Oxygen support ^b	8 (1, 20)	5 (1, 15)	<.001
Ventilator support ^b	5 (0, 16)	5 (1, 13)	.06
Antibiotic exposure ^b	4 (1, 11)	4 (1, 10)	.62

Characteristic	MSSA (N=2825)	MRSA (N=1063)	P Value
Anti-MRSA antibiotic exposure ^b	0 (0, 4)	0 (0, 3)	.52

Abbreviations: MRSA, methicillin-resistant *S. aureus*; MSSA, methicillin-susceptible *S. aureus*.

^aExcept where indicated, data are presented as no. (%). Invasive cultures = blood, cerebrospinal fluid, abscess and sterile sites. For infants with more than one infection, only the first invasive infection was evaluated.

^bMedian (25th, 75th percentiles) number of days with exposure prior to first invasive *Staphylococcus aureus* infection.

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Table 3Mortality Following Invasive *Staphylococcus aureus* Disease by Last Infection

Death	No./No. (%)		Adjusted Risk Ratio, ^a MRSA vs MSSA (95% CI)
	MSSA	MRSA	
By hospital discharge			
All infants	237/2474 (10)	110/926 (12)	1.19 (0.96-1.49)
<1000 g birth weight	180/1262 (14)	82/457 (18)	1.23 (0.93, 1.62)
<1500 g birth weight	205/1883 (11)	97/713 (14)	1.24 (0.98-1.57)
1500 g birth weight	32/591 (5)	13/213 (6)	0.98 (0.60-1.61)
Within 7 days of culture			
All infants	95/2474 (4)	35/926 (4)	0.90 (0.65-1.24)
<1000 g birth weight	64/1262 (5)	23/457 (5)	0.91 (0.55, 1.51)
<1500 g birth weight	78/1883 (4)	30/713 (4)	0.96 (0.66-1.41)
1500 g birth weight	17/591 (3)	5/213 (2)	0.58 (0.18-1.82) ^b
Within 30 days of culture			
All infants	178/2474 (7)	81/926 (9)	1.15 (0.90-1.46)
<1000 g birth weight	129/1262 (10)	59/457 (13)	1.20 (0.87, 1.65)
<1500 g birth weight	151/1883 (8)	70/713 (10)	1.18 (0.91-1.54)
1500 g birth weight	27/591 (5)	11/213 (5)	0.97 (0.56-1.68)

Abbreviations: MRSA, methicillin-resistant *S. aureus*; MSSA, methicillin-susceptible *S. aureus*.^aRisk ratio calculated using Poisson regression adjusted for gestational age, small for gestational age status, gender, and race with random effects for site.^bPoisson regression will not converge, so results are reported from random effects logistic regression model controlling for the same covariates.