ORIGINAL ARTICLE

Risk Factors for *Staphylococcus aureus* Acquisition in the Neonatal Intensive Care Unit: A Matched Case-Case-Control Study

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OBJECTIVE. To determine risk factors independent of length of stay (LOS) for *Staphylococcus aureus* acquisition in infants admitted to the neonatal intensive care unit (NICU).

DESIGN. Retrospective matched case–case-control study.

SETTING. Quaternary-care referral NICU at a large academic children's hospital.

METHODS. Infants admitted between January 2014 and March 2016 at a level IV NICU who acquired methicillin resistant (MRSA) or susceptible (MSSA) *S. aureus* were matched with controls by duration of exposure to determine risk factors for acquisition. A secondary post hoc analysis was performed on the entire cohort of at-risk infants for risk factors identified in the primary analysis to further quantify risk.

RESULTS. In total, 1,751 infants were admitted during the study period with 199 infants identified as having *S. aureus* prevalent on admission. There were 246 incident *S. aureus* acquisitions in the remaining at-risk infant cohort. On matched analysis, infants housed in a single-bed unit were associated with a significantly decreased risk of both MRSA ($P = .03$) and MSSA ($P = .01$) acquisition compared with infants housed in multibed pods. Across the entire cohort, pooled *S. aureus* acquisition was significantly lower in infants housed in single-bed units (hazard ratio, = 0.46; confidence interval, 0.34–0.62).

CONCLUSIONS. NICU bed design is significantly associated with *S. aureus* acquisition in hospitalized infants independent of LOS.

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Healthcare-acquired infections (HAIs) due to *Staphylococcus aureus* are an important complication among infants admitted to neonatal intensive care units (NICUs).[1–4] *Staphylococcus aureus* is the second leading cause of HAIs in NICUs, with an annual estimated incidence of 44.8 invasive infections per 10,000 infants nationally.[5] Colonization precedes the development of most infections with *S. aureus*.[6] Critically ill infants and children colonized with MRSA are at a >20-fold increased risk for developing an invasive infection.[7] Infants with a HAI caused by *S. aureus* frequently develop disseminated disease and require prolonged hospital length of stays (LOS) with increased associated healthcare costs.[8]

Controlling the transmission of *S. aureus* within the NICU environment has proven challenging given the high prevalence of asymptomatic carriage within the community and the ability of staphylococci to contaminate environmental surfaces.[9–14] Since its initial description in hospitalized neonates in 1980, the epidemiology of methicillin-resistant *S. aureus* (MRSA) within NICUs has been well studied with prematurity, low birth weight, and need for invasive medical procedures identified as risk factors for acquisition.[15–22] More recently, increased attention has been given to methicillin-susceptible *S. aureus* (MSSA) because infected infants have similar outcomes as infants infected with the methicillin-resistant phenotype.[23–27]

Antecedent LOS itself is a risk factor for acquiring HAIs in hospitalized patients, which can complicate the interpretation of risk factors.[28,29] Within the NICU, an infant's odds of MRSA colonization has been shown to increase 29% per 10 days in LOS.[30] Date regarding the impact of LOS on previously identified risk factors for *S. aureus* acquisition in the NICU are limited. The objective of our study was to determine risk factors for MRSA and MSSA acquisition in a level IV referral NICU independent of LOS.

METHODS

Study Setting

We performed a retrospective matched case–case-control investigation of risk factors for acquisition of *S. aureus* within

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the NICU at Cincinnati Children's Hospital Medical Center (CCHMC).[31] CCHMC houses a quaternary care NICU which consists of 59 beds divided into 6 multibed pods (6–7 beds per pod) and 2 single-bed units (10–11 beds per unit). An active surveillance screening program has been in place since 2012 to identify infants colonized with *S. aureus*. Nares cultures (chromID MRSA and chromID *S. aureus* agar, bioMérieux, Marcy l'Etoile, France) are obtained on admission and once weekly during an infant's hospitalization. Infants who acquire MRSA are placed in Contact Precautions for the remainder of their hospitalization. The NICU at CCHMC does not perform routine decolonization with intranasal mupirocin of infants colonized with MRSA. Chlorhexidine bathing is performed on infants with indwelling central venous catheters regardless of colonization status. This study was approved by the Institutional Review Board at CCHMC.

Study Design

Infants who were admitted to CCHMC's NICU between January 1, 2014, and March 30, 2016, were eligible for inclusion in the study. Infants with a known history of *S. aureus* colonization or infection prior to transfer were excluded. Additionally, infants were excluded if their admission screening culture was positive for *S. aureus* or if a clinical culture was positive for *S. aureus* before hospital day 3. These excluded infants were included in colonization pressure calculations, however. The remaining infants were considered at-risk for acquisition and were included in the study. Infants who acquired *S. aureus* identified during a follow-up screening culture or a clinical culture obtained ≥ hospital day 3 were included as case patients. As infection prevention practices differed by resistance phenotype, cases were categorized as either MRSA or MSSA. Phenotypes for clinical isolates were determined using the Vitek 2 antimicrobial susceptibility testing system (bioMérieux, Marcy l'Etoile, France). Cases in infants who had cultures positive for both MRSA and MSSA during their admission were classified based on the first phenotype identified. The exposure time for each case was defined as the duration from admission to the date that the positive *S. aureus* culture was obtained. To control for LOS, matched controls were randomly selected from the at-risk population for each case using the exposure time as matching criteria in the primary analysis. Risk-set sampling was used to minimize bias associated with the retrospective design. Eligible controls for a case were the pool of infants who were hospitalized at least as long as the case patient's exposure time and who either (1) never acquired *S. aureus* or (2) acquired *S. aureus* and had a longer exposure time than the case patient. As the exposure time varied per case patient, the pool of eligible controls differed between cases.

Data Collection

Clinical data on potential risk factors were abstracted from the electronic medical records for the case patients and controls, including maternal and infant demographics, complications of pregnancy, and birth information. For the exposure time, NICU level data were also collected for each case and control including surgical operations, bed location, days intubated, central-line days, and antibiotic use. Antibiotics were classified as anti-Staphylococcal β-lactams (anti-staphylococcal penicillin, penicillin plus β-lactamase inhibitor combination, cephalosporins, carbapenems), non–anti-staphylococcal β-lactams (eg, penicillin, ampicillin, amoxicillin), systemic anti-MRSA (eg, vancomycin, clindamycin), aminoglycosides, or other. The CCHMC's Infection Prevention Program provided data on hand hygiene compliance within the NICU.

Statistical Analysis

In the primary analysis, MRSA cases were matched 3:1 and MSSA cases were matched 2:1 to detect an effect size of odds ratios ≥ 2.3 (MRSA) and ≥1.7 (MSSA) with 80% power and type I error of 5%. Average unit-wide hand hygiene compliance and colonization pressure (defined as the percentage of infants in the NICU who were either colonized or infected with MRSA or MSSA) were calculated for each case and control during the exposure time. Variables with an unadjusted $P < .10$ on bivariate conditional logistic regression along with variables determined a priori (ie, gestational age, birth weight, operation performed, colonizing pressure, and hand hygiene compliance) were included in the initial multivariate model. Stepwise conditional logistic regression was performed to determine the final adjusted effect sizes. Because LOS was controlled for as a matching variable in the primary analysis, a secondary post hoc analysis was performed on statistically significant variables identified in the final multivariate model, defined as $P < .05$, using Cox regression with the entire cohort of at-risk infants. As *S. aureus* transmission increases with colonization pressure >10%, clinical significance was defined as a 10% difference in hazard curves for the secondary analysis.[32] All analyses were performed using STATA version 14.1 software (StataCorp, College Station, TX).

RESULTS

The distribution of infants admitted to the NICU at CCHMC during the study period is displayed in Figure 1. Across the entire cohort, LOS was associated with increased *S. aureus* acquisition (odds ratio [OR], 1.15 per weekly screening interval; 95% confidence interval [95% CI], 1.11 − 1.20). Of the 1,751 infants admitted during the study period, 1,552 (89%) were neither colonized nor infected with *S. aureus* at admission and were eligible for inclusion. Overall, 246 infants (15.9%) acquired incident *S. aureus* during their hospitalization at CCHMC's NICU, including 67 (4.3%) with MRSA and 174 (11.2%) with MSSA alone. An additional 5 (0.3%) infants acquired both MRSA and MSSA; these infants were

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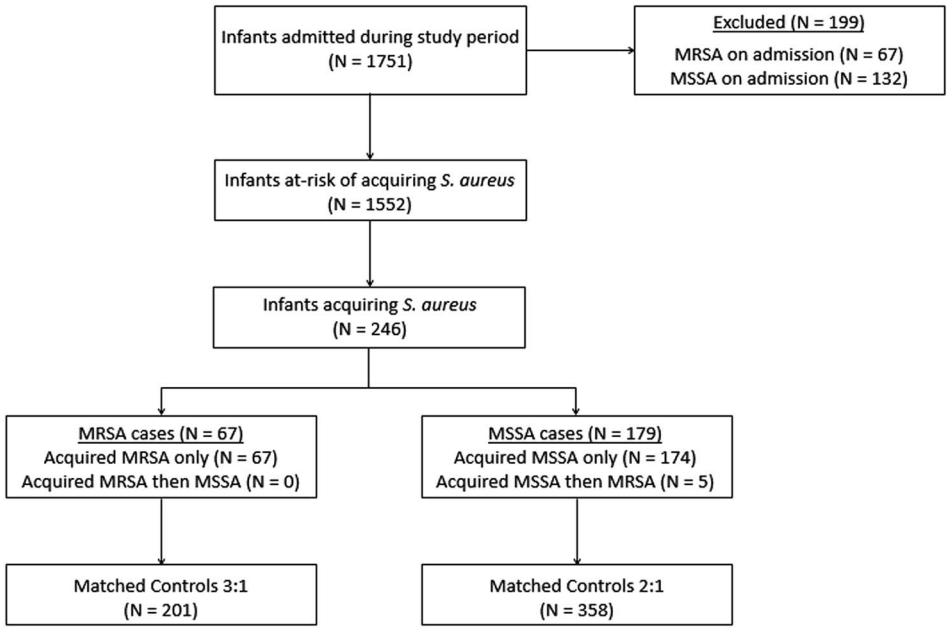


FIGURE 1. Flow diagram of infants admitted during the study period.

categorized as cases based on the first isolate identified (all 5 were MSSA cases). The 67 MRSA cases were matched with 201 controls. The 179 total MSSA cases were matched with 358 controls.

The results of the matched case-control analyses are displayed in Table 1 for MRSA and Table 2 for MSSA. After matching for exposure length, infants who were housed in the single-bed unit had lower odds of acquiring both MRSA (OR, 0.44; 95% CI, 0.21–0.92) and MSSA (OR, 0.43; 95% CI, 0.23–0.81) on multivariate analysis. Infants admitted to single-bed units had older postnatal ages compared to infants admitted to multibed pods (26 days vs 13 days; $P < .01$); however, the inclusion of postnatal age at admission in the multivariate analyses did not change the effect size noted for either MRSA or MSSA acquisition.

Infants who acquired MRSA had a nonsignificant increased exposure to systemic anti-MRSA antibiotics compared with controls (3.6 vs 2.7 days of therapy; $P = .31$). There were no significant differences between antibiotic exposure for infants acquiring MSSA and controls ($P = .21$). In addition, there were no significant differences between cases and controls in gestational age or birth weight for either MRSA ($P = .52$; $P = .40$) or MSSA ($P = .60$; $P = .49$). Furthermore, there was no difference in operations performed or central venous access utilization for infants who acquired MRSA ($P = .96$; $P = .79$) or MSSA ($P = .92$; $P = .92$).

Because LOS was controlled in the primary analysis, a post hoc secondary analysis was performed on at-risk infants to determine rates of *S. aureus* acquisition stratified by room type across time. There was a significantly lower acquisition of both MRSA (hazard ratio [HR], 0.39; 95% CI, 0.21–0.70) and MSSA (HR, 0.49; 95% CI, 0.35–0.69) in infants housed in the single-bed units compared with the multibed pods for the cohort, which were similar to the effect sizes observed on matched analysis (Figure 2a and 2b). Pooling all *S. aureus* acquisition yielded a combined HR of 0.46 with a 95% CI of 0.34–0.62 (Figure 2c). A 10% area under the curve difference in *S. aureus* acquisition occurred between the 2 room types at hospital day 14, with a 10% point difference occurring at hospital day 41. Statistical deviation of the hazard curves occurred at hospital day 42.

DISCUSSION

Infants admitted to the NICU are highly vulnerable to developing HAIs due to *S. aureus*.[2,33] Prolonged LOS in the NICU increases the risk of acquiring *S. aureus* in hospitalized infants.[30] Effect modification by LOS may alter the true effect size of many previously identified risk factors for *S. aureus* acquisition in the NICU, including lower gestational age and birth weight, central-venous catheterization, and endotracheal tube intubation.[28]

A moderate incidence of *S. aureus* acquisition occurred in our quaternary-care referral NICU during the study period of approximately 15%. Controlling for LOS on both the matched case-control and cohort analyses identified infants housed in single-bed units as significantly less likely to acquire either MRSA or MSSA compared with infants housed in multibed pods. Clinically significant deviation occurred as early as 2 weeks of hospitalization with statistical deviation at 6 weeks of hospitalization. Colonization pressure did not differ between pod and single-bed units to account for this

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TABLE 1. Potential Risk Factors Investigated for Methicillin-Resistant *Staphylococcus aureus* (MRSA)

	MRSA Cases (N = 67), No. (%)[a]	MRSA Controls (N = 201), No. (%)[a]	Unadjusted *P* Value	Multivariate Odds Ratio	Multivariate *P* Value
Male Gender	40 (60)	106 (53)	.21		
Race			.98		
White	44 (66)	141 (70)			
African American	11 (16)	35 (17)			
Other	12 (18)	25 (12)			
Hispanic ethnicity	2 (3)	5 (2)	.82		
Birth weight, g (± SD)	2,190 (1,007)	2,124 (997)	.68	0.97 (0.91–1.04)[b]	.40
Gestational age, weeks (± SD)	34.1 (4.8)	33.4 (4.9)	.23	1.02 (0.96–1.09)	.52
Age at admission, d (± SD)	15 (30)	16 (29)	.77		
Operation performed	30 (45)	77 (38)	.17	1.03 (0.27–3.94)	.96
Type of operation			.27		
ENT	4 (6)	16 (8)			
Gastrointestinal	23 (34)	48 (24)			
Neurosurgery	3 (4)	6 (3)			
Urology	0 (0)	7 (3)			
Maternal age, y (± SD)	28 (8.2)	28 (5.4)	.77		
Multiple gestation	2 (3)	20 (10)	.09	0.36 (0.07–1.81)	.99
Birth via cesarean-section	44 (66)	123 (61)	.65		
Prolonged ROM	7 (10)	22 (11)	.73		
Mortality	7 (10)	16 (8)	.52		
Intubated, d (± SD)	12 (21)	11 (17)	.47		
Central venous access, d (± SD)	19 (26)	19 (28)	.79		
Infants with bed transfers	43 (64)	103 (51)	.04	1.83 (0.97–3.49)	.06
Housed in single bed	13 (19)	67 (33)	.03	**0.44 (0.21–0.92)**	**.03**[c]
Antibiotic exposure, DOT (± SD)	15.2 (27.3)	13.3 (19.1)	.33		
Anti-*Staphylococcal* β-lactams, DOT (± SD)	3.3 (6.6)	3.7 (6.8)	.93		
Non-anti-*Staphylococcal* β-lactams, DOT (± SD)	4.1 (9.3)	3.0 (6.5)	.22		
Systemic anti-MRSA antibiotic, DOT (± SD)	3.6 (8.8)	2.7 (7.3)	.31		
Aminoglycosides, DOT (± SD)	4.2 (8.6)	4.0 (7.1)	.67		
Colonization pressure, % (± SD)	17 (7.4)	17 (6.7)	.58	1.02 (0.96–1.08)	.55
Hand hygiene compliance, % (± SD)	89 (6.8)	91 (6.7)	.12	0.96 (0.91–1.02)	.18

NOTE. MRSA, methicillin-resistant *Staphylococcus aureus*; ENT, ear, nose, and throat; ROM, rupture of membranes; DOT, days-of-therapy.
[a]Unless otherwise specified. Controls matched by exposure time to cases 3:1 from the at-risk population.
[b]Per 100 grams.
[c]$P < .05$ was considered statistically significant.

association. No other maternal or infant demographic, pregnancy or birth, or NICU level exposure risk factors differed among infants who acquired MRSA or MSSA.

As no outbreaks of *S. aureus* were identified during the study period, our data suggest that LOS and NICU bed design are key factors in the endemic transmission among infants. Previous data have shown no association with MRSA colonization incidence rates and bed configuration within a mixed bed NICU.[34] Potential reasons for our discordant findings include both an increased burden of MRSA (4.3% vs 2.7% incidence rate) and an increased proportion of multibed pods within our NICU (64% vs 51%). Additionally, LOS distributions may have differed across studies.

Single-bed units may facilitate infection-prevention interventions designed to reduce transmission, such as increasing adherence with appropriate hand hygiene and use of contact precautions. As overall hand hygiene compliance was high at 90%, our results suggest that there may be additional reasons for the reduced transmission in single-bed units as well. These reasons potentially include differing total numbers of direct and indirect encounters with healthcare workers for infants within single-bed rooms compared with infants in multibed pods as well as differing common areas within the NICU that may facilitate transmission by families and other nonhealthcare workers.

In NICUs with mixed bed types and high *S. aureus* prevalence, infants with anticipated prolonged hospitalizations longer than 2–4 weeks may benefit from room placement into single-bed units to reduce both the infant's risk of *S. aureus* acquisition and unit-wide transmission risk. Broader strategies to reduce transmission should start in the architectural design phase of NICUs with increased emphasis on single-bed units

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TABLE 2. Potential Risk Factors Investigated for Methicillin-Susceptible *Staphylococcus aureus* (MSSA)

	MSSA Cases (N = 179), No. (%)[a]	MSSA Controls (N = 358), No. (%)[a]	Unadjusted *P* Value	Multivariate Odds Ratio	Multivariate *P* value
Male gender	108 (60)	187 (52)	.06	1.19 (0.76–1.87)	.44
Race			.23		
White	128 (72)	229 (64)			
African American	31 (17)	90 (25)			
Other	20 (11)	39 (11)			
Hispanic ethnicity	6 (3)	13 (4)	.87		
Birth weight, g	2,285 (1,037)	2,103 (1,064)	.05	1.01 (0.99–1.03)[b]	.49
Gestational age, weeks	34.2 (5.0)	33.4 (4.9)	.07	0.98 (0.89–1.07)	.60
Age at admission, d	17 (35)	17 (31)	.88		
Operation performed	80 (45)	148 (41%)	.46	1.04 (0.54–2.01)	.92
Type of operation			.46		
Ere, nose, throat	19 (11)	11 (3)			
Gastrointestinal	49 (27)	95 (26)			
Neurosurgery	10 (6)	31 (9)			
Urology	2 (1)	11 (3)			
Maternal age, y (± SD)	28 (6.5)	28 (6.4)	.97		
Multiple gestation	17 (10)	38 (11)	.69		
Birth via cesarean-section	113 (63)	224 (63)	.90		
Prolonged ROM	19 (11)	48 (13)	.36		
Mortality	16 (9)	33 (9)	.92		
Intubated, d (± SD)	10 (15)	11 (17)	.16		
Central venous access, d (± SD)	14 (17)	19 (23)	<.01	1.00 (0.93–1.09)	.92
Infants with bed transfers	95 (53)	207 (58)	.28		
Housed in single bed	49 (27)	127 (35)	.06	**0.43 (0.23–0.81)**	**.01**[c]
Antibiotic exposure, DOT (± SD)	13.2 (15.5)	14.8 (16.7)	.21		
Anti-*Staphylococcal* β-lactams, DOT (± SD)	4.0 (6.5)	4.4 (6.4)	.53		
Non-anti-*Staphylococcal* β-lactams, DOT (± SD)	3.3 (6.1)	4.4 (8.7)	.13		
Systemic anti-MRSA antibiotic, DOT (± SD)	3.1 (7.3)	3.0 (7.1)	.92		
Aminoglycosides, DOT (± SD)	3.5 (5.5)	3.3 (5.2)	0.64		
Colonization pressure, % (± SD)	30 (9.3)	29 (10.3)	0.16	1.01 (0.98–1.03)	0.63
Hand hygiene compliance, % (± SD)	89 (7.2)	90 (7.0)	0.29	0.99 (0.96–1.02)	0.47

NOTE. MSSA, methicillin-susceptible *Staphylococcus aureus*; ROM, rupture of membranes; DOT, days of therapy.
[a]Unless otherwise specified. Controls matched by exposure time to cases 2:1 from the at-risk population.
[b]Per 100 grams.
[c]$P < .05$ was considered statistically significant.

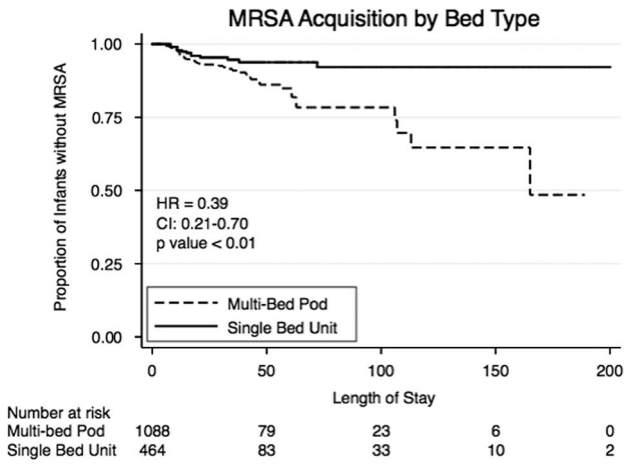


FIGURE 2a. Proportion of infants acquiring methicillin-resistant *Staphylococcus aureus* (MRSA) stratified by bed type.

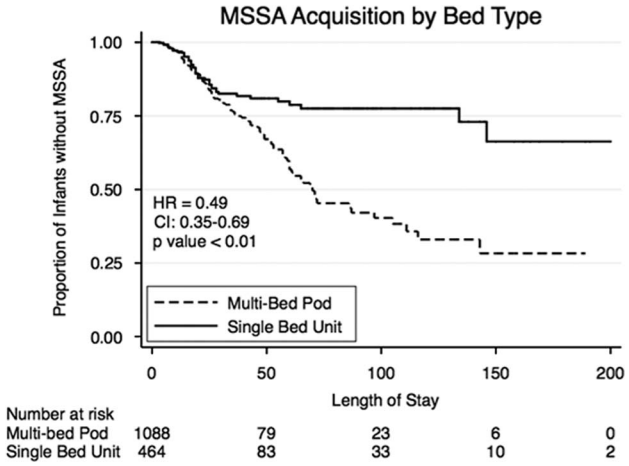


FIGURE 2b. Proportion of infants acquiring methicillin-susceptible *Staphylococcus aureus* (MSSA) stratified by bed type.

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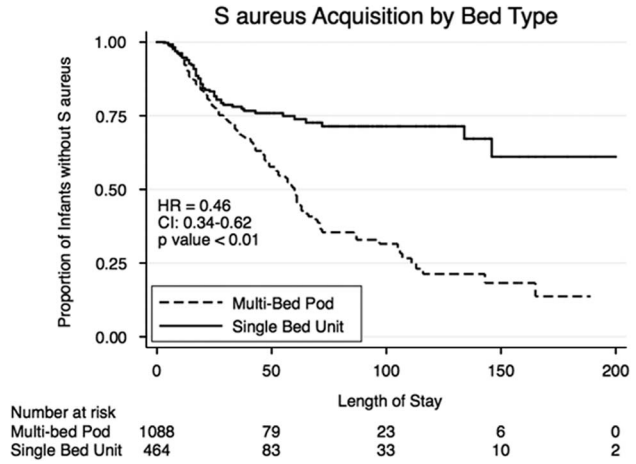


FIGURE 2C. Proportion of infants acquiring *Staphylococcus aureus* stratified by bed type.

to mitigate transmission. Additionally, multidisciplinary efforts to reduce premature birth rates would decrease the need for many prolonged NICU hospitalizations and help interrupt *S. aureus* transmission.

Our study has several limitations, including the retrospective design and inability to control for unit-specific hand hygiene compliance. Residual confounding of variables not included in the analysis, such as the colonization status of healthcare workers, families, and visitors, may have impacted the observed results. Additionally, our study was not powered to determine small effect sizes. Including additional study sites would improve the external validity of our findings. Future studies incorporating whole genome sequencing data will help in defining risk factors specific for direct infant-to-infant *S. aureus* transmission within the NICU.

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