ORIGINAL ARTICLE

Methicillin-Resistant *Staphylococcus aureus* Transmission and Infections in a Neonatal Intensive Care Unit despite Active Surveillance Cultures and Decolonization: Challenges for Infection Prevention

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OBJECTIVE. To characterize the epidemiology of methicillin-resistant *Staphylococcus aureus* (MRSA) transmission and infections in a level IIIC neonatal intensive care unit (NICU) and identify barriers to MRSA control.

SETTING AND DESIGN. Retrospective cohort study in a university-affiliated NICU with an MRSA control program including weekly nares cultures of all neonates and admission nares cultures for neonates transferred from other hospitals or admitted from home.

METHODS. Medical records were reviewed to identify neonates with NICU-acquired MRSA colonization or infection between April 2007 and December 2011. Compliance with hand hygiene and an MRSA decolonization protocol were monitored. Relatedness of MRSA strains were assessed using pulsed-field gel electrophoresis (PFGE).

RESULTS. Of 3,536 neonates, 74 (2.0%) had a culture grow MRSA, including 62 neonates with NICU-acquired MRSA. Nineteen of 74 neonates (26%) had an MRSA infection, including 8 who became infected before they were identified as MRSA colonized, and 11 of 66 colonized neonates (17%) developed a subsequent infection. Of the 37 neonates that underwent decolonization, 6 (16%) developed a subsequent infection, and 7 of 14 (50%) that remained in the NICU for 21 days or more became recolonized with MRSA. Using PFGE, there were 14 different strain types identified, with USA300 being the most common (31%).

CONCLUSIONS. Current strategies to prevent infections—including active identification and decolonization of MRSA-colonized neonates—are inadequate because infants develop infections before being identified as colonized or after attempted decolonization. Future prevention efforts would benefit from improving detection of MRSA colonization, optimizing decolonization regimens, and identifying and interrupting reservoirs of transmission.

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The Centers for Disease Control and Prevention estimates that approximately 1.7 million healthcare-associated infections occur in US hospitals every year, including more than 33,000 in the neonatal intensive care unit (NICU).[1] Despite appropriate therapy, neonatal infections can have long-term sequelae, including poor neurodevelopmental and growth outcomes.[2,3] These infections contribute to the ballooning costs to care for preterm infants.

After coagulase-negative staphylococci, *Staphylococcus aureus* is the second most common pathogen causing healthcare-associated infections in neonates.[4] Antibiotic-resistant *S. aureus* strains, specifically methicillin-resistant *S. aureus* (MRSA), have emerged and become prevalent in NICUs.[4] In the United States, the incidence of late-onset MRSA infections in NICUs increased more than 300% from 1995 to 2004.[5] Because MRSA colonization predisposes neonates to MRSA infection, preventing MRSA transmission is an important component of programs to reduce morbidity and mortality from MRSA in NICUs. Current strategies to prevent MRSA transmission in NICUs include identifying colonized neonates and placing them on contact precautions, cohorting, healthcare worker (HCW) hand hygiene, environmental cleaning, and, in some cases, decolonization of colonized neonates and/or HCWs.[6] These measures have been successful in controlling MRSA outbreaks. Additional data, however, are needed to guide NICU MRSA control programs during

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nonoutbreak settings. Our objectives were to characterize the epidemiology of MRSA transmission and infections in an NICU with an aggressive MRSA infection prevention program, to identify barriers to MRSA control, and to suggest future areas of investigation to prevent MRSA disease in this vulnerable population.

METHODS

Setting and Design

Johns Hopkins Hospital is a tertiary-care academic medical center with an embedded 175-bed Children's Center that houses a 45-bed, level IIIC NICU. We retrospectively identified a cohort of neonates admitted to the NICU between April 15, 2007, and December 31, 2011. We conducted an observational study to assess the burden of MRSA transmission and infections in the setting of an aggressive MRSA control program. The institutional review board approved this study with a waiver of informed consent to review retrospective data.

Infection Control and Prevention Program

Following a cluster of MRSA infections in 2007, enhanced MRSA control measures were implemented in April 2007, including nares swabs performed weekly by nurses to identify MRSA-colonized neonates and at the time of NICU admission for neonates transferred from other hospitals or admitted from home, hand hygiene education, hand hygiene monitoring and feedback of compliance (started third quarter of 2008), contact precautions, private rooms if available or cohorting, decolonization of MRSA-colonized neonates, and periodic screening and decolonization of HCWs.[7] Decolonization of neonates consisted of mupirocin applied to the nares twice a day for 5 days and 2 baths with 2% chlorhexidine gluconate–impregnated clothes, administered 48 hours apart for infants greater than 36 weeks gestational age or greater than 4 weeks chronological age. HCW decolonization consisted of mupirocin applied to the nares twice daily for 5 days.

Data Collection and Outcome Ascertainment

We searched a computerized surveillance system (Theradoc, Hospira) to identify patients with surveillance cultures and cultures sent during clinical care that grew MRSA during the study period. The 2 primary study outcomes were NICU-acquired MRSA colonization and NICU-onset MRSA infections. All infants that were born at Johns Hopkins Hospital and who had a culture grow MRSA were classified as NICU-acquired MRSA. Neonates who were born at another hospital were classified as NICU-acquired MRSA if they had surveillance or clinical culture obtained 3 days or more after admission to the NICU grow MRSA and had no known prior cultures grow MRSA. MRSA infections were ascertained by a trained infection preventionist (S.M.W.) who reviewed medical records of patients in whom MRSA grew in a culture sent at the discretion of the patient's treating clinician. National Healthcare Safety Network's (NHSN's) surveillance definitions for healthcare-associated infections were applied to distinguish infection versus colonization.[8]

Laboratory Methods

All surveillance swabs collected between April 2007 and December 2011 were inoculated on selective and differential media to detect MRSA, as previously described.[9,10] Suspicious colonies were confirmed as *S. aureus* by gram stain and slide coagulase testing. We performed pulsed-field gel electrophoresis (PFGE) on available stored isolates as previously described and considered isolates to be related if their patterns had 3 or fewer band differences.[11,12]

Statistical Analysis

MRSA prevalence was calculated as the number of neonates with a culture that grew MRSA as a proportion of all admitted NICU patients. Trends in compliance with hand hygiene and the decolonization protocol were assessed using linear regression. Data were maintained in Microsoft Access 2007 (Microsoft) and analyzed using Stata (ver 11.0; StataCorp) and Microsoft Excel 2007 (Microsoft).

RESULTS

During the study period, 3,536 patients were admitted to the NICU, accounting for 66,695 patient-days; 55% were male, 49% were African-American, and 702 patients (20%) were either transferred from another hospital or admitted from home. Median length of stay in the NICU was 8 days (range, 1–185). Seventy-four neonates (2.0%) had a culture grow MRSA. Of the neonates with MRSA, 65 (88%) were initially detected by surveillance cultures, and 9 were initially detected by a culture sent during clinical care. Eight of 9 neonates detected by clinical culture met the NHSN criteria for infection, and the one that did not meet NHSN criteria was considered colonized (Figure 1). Sixty-two neonates (84%) acquired MRSA in the NICU, while 12 (16%) were identified on admission. The mean quarterly incidence of unit-acquired MRSA was 1.0 per 1,000 patient-days (95% confidence interval [CI], 0.28–2.45; Figure 2). Mean quarterly incidence of NICU-onset MRSA infection was 0.3 per 1,000 patient-days (95% CI, 0.0–0.8). MRSA transmission and infections continued during the study period, despite increases in hand hygiene compliance ($P < .001$) and a statistically nonsignificant increase in compliance with a decolonization protocol ($P = 0.11$).

The relatedness of MRSA strains was investigated using PFGE. Sixty-six (89%) of the 74 MRSA-colonized or -infected neonates had isolates available for strain typing. Fourteen unrelated strains were identified from neonates. The most frequently isolated strain was PFGE type USA300 (31% of isolates), followed by PFGE types USA100 (25%) and USA800 (19%). Within the most commonly identified PFGE types,

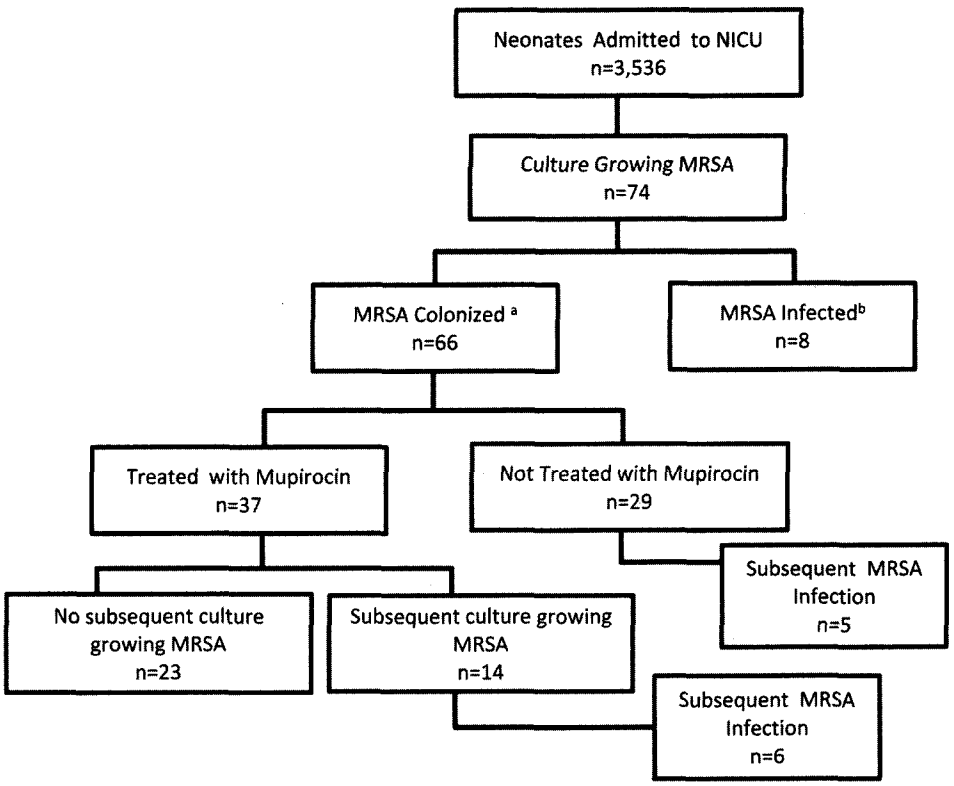

FIGURE 1. Flowchart detailing the identification of neonates with methicillin-resistant *Staphylococcus aureus* (MRSA) colonization and infection in a neonatal intensive care unit with an active surveillance and decolonization program. a, Neonate did not meet National Healthcare Safety Network criteria for infection at time of first culture growing MRSA. b, Neonate met NHSN criteria for infection at time of first culture growing MRSA. NICU, neonatal intensive care unit.

there were multiple subtypes with 3 or fewer band differences, including 4 USA300s, 6 USA100s, and 6 USA800s. Figure 3 demonstrates the distribution of MRSA strains acquired over time. Of the 62 unit-acquired MRSA cases, 58 (94%) had isolates available for typing, and 12 unrelated strains were found. The most frequently isolated strain was PFGE type USA300 (34% of isolates), followed by PFGE types USA100 (27%) and USA800 (20%).

Given continued MRSA transmission, all 204 NICU HCWs were screened in 2011 by using nares specimens. Seven HCWs (3.4%) were MRSA colonized. HCW MRSA strains included PFGE types USA800 ($N = 3$), USA300 ($N = 2$), USA100 ($N = 1$), and 1 unique strain. All 7 HCWs were decolonized. Because there was evidence of continued MRSA transmission, the 5 previously colonized HCWs who remained in the NICU 4–6 months later had repeat nares cultures. Four (80%) had recurrent colonization (including 2 with USA800), and they were again decolonized.

Of the 74 neonates that had a culture grow MRSA, 19 neonates (26%) had an MRSA infection; 1 was present on admission, and 18 were acquired in the unit. Five neonates had multiple MRSA infections. Infections included 4 bacteremias, 14 lower respiratory infections, 1 upper respiratory infection, 5 skin and soft tissue infections, and 1 conjunctivitis. Three of the 19 infected neonates (16%) died, but only 1 death was due to an MRSA infection. Eight neonates became infected before they were identified as MRSA colonized (Figure 1), including 6 that had between 2 and 6 negative nares cultures prior to MRSA infection. Of 66 colonized neonates, 11 (17%) developed a subsequent infection in the NICU. The median time from identification of MRSA colonization to infection was 5 days (range, 0–29).

Of 66 MRSA-colonized neonates, 37 (66%) underwent decolonization. Twenty-three of 37 (62%) decolonized neonates had no further MRSA-positive cultures prior to unit discharge. Seven of 14 (50%) neonates that underwent decolonization and remained in the NICU for 21 days or more became recolonized with MRSA. Six of 37 neonates (16%) developed a subsequent infection despite attempted decolonization, including 5 neonates that had become recolonized and 1 neonate that became infected despite a negative nares culture. Of 29 patients in whom decolonization was not attempted, 13 (45%) were discharged from the unit within 2 days of the positive surveillance culture, and 5 (17%) developed a subsequent infection during their NICU stay.

DISCUSSION

Control of MRSA remains a continuous challenge in NICUs. Despite aggressive infection control measures—including

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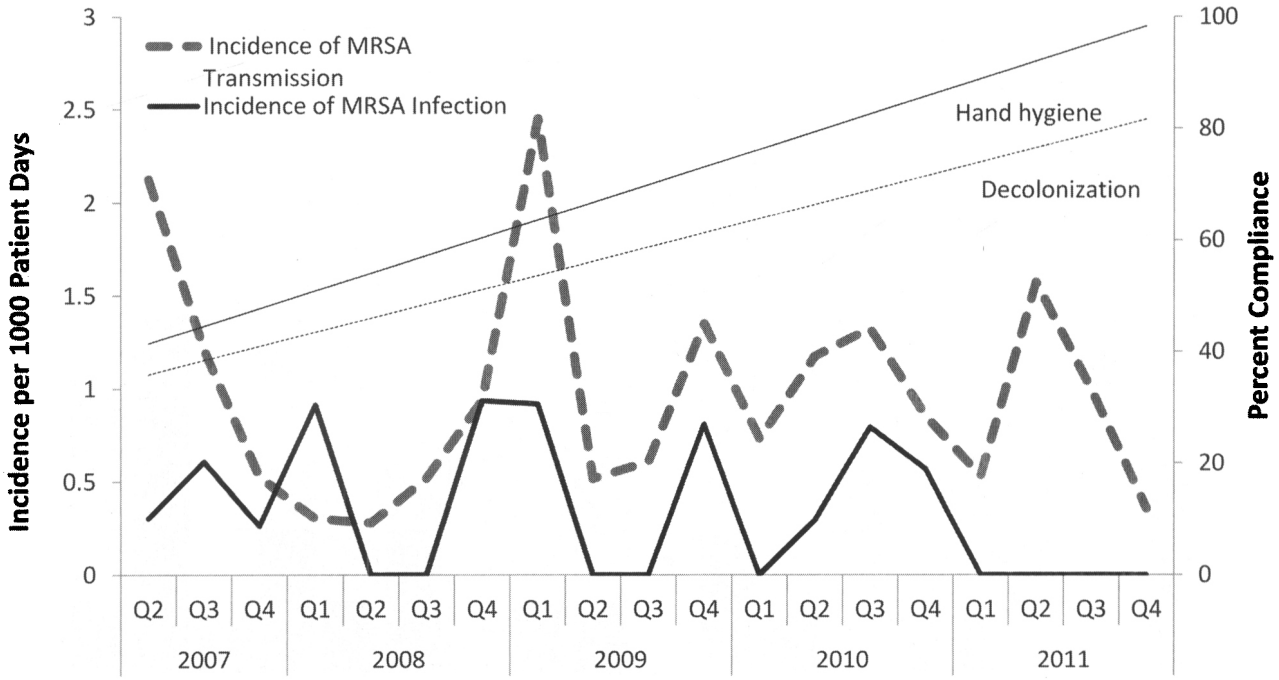

FIGURE 2. Quarterly incidence of methicillin-resistant *Staphylococcus aureus* (MRSA) transmission and infection from 2007 to 2011 in a setting of active surveillance and decolonization. Straight lines represent the trend in compliance with hand hygiene (solid line, Prob > F = 0.0001; R^2 = 0.75) and an MRSA decolonization protocol (dotted line, Prob > F = 0.11; R^2=0.14), as estimated by linear regression.

routine surveillance cultures, private rooms or cohorting and contact precautions, decolonization of infants and HCWs, and increasing hand hygiene compliance—we found ongoing MRSA transmission and infection in our NICU over a 4-year study period. Using data from an active surveillance program, this is the first study to describe the molecular epidemiology of endemic MRSA transmission in a US NICU and identify clusters of related strains occurring amidst a background of unrelated MRSA strains.[9,13] Our data highlight limitations to MRSA decolonization as an infection prevention strategy in a city with high endemicity of community-acquired MRSA and in this high-risk population. MRSA infections frequently occur before neonates are identified as colonized, and subsequent infections occur in colonized neonates despite attempted decolonization.

Our findings confirm previous studies showing that multiple strains of MRSA can be identified circulating in NICUs during a nonoutbreak setting. Carey et al[14] characterized the molecular epidemiology of MRSA strains isolated from MRSA-infected and -colonized neonates in an NICU over a period of 8 years. Although the authors did not have data from routine weekly surveillance cultures to assess periods without MRSA infections, they similarly found that colonization and infection with multiple strain types occurred throughout the study period. Gregory et al[15] reported on a long-standing MRSA control program, including routine MRSA surveillance cultures, but they did not have isolates available for strain typing, and their conclusions about transmission were based on antibiotic susceptibility patterns. In an NICU in Taiwan with highly endemic MRSA (41% of neonates colonized), Huang et al[16] demonstrated molecular diversity of acquired MRSA strains after implementation of infection control measures. During our comprehensive assessment of the molecular epidemiology of endemic MRSA transmission in an NICU, we found 14 distinct strains—including ongoing transmission of USA800, USA300, and USA100—and 10 strains that were each identified only once. All 3 studies illustrate that endemic transmission persists despite current strategies, including HCW hand hygiene, environmental disinfection, contact precautions and cohorting, and, in some cases, identifying asymptomatic MRSA carriers and attempting decolonization.[6]

Uncovering reservoirs for ongoing MRSA transmission in NICUs has proved challenging. Our findings agree with previous reports of HCWs as a source of MRSA transmission.[17,18] Recurrent colonization of HCWs with USA800 may have contributed to acquisition of this strain by 13 neonates in the NICU. However, the distribution of strain types identified in colonized HCWs does not fully mirror those strains found in colonized or infected neonates in the NICU, suggesting additional bacterial reservoirs. Previous studies have identified mothers and fathers as potential reservoirs for MRSA transmission to neonates in the NICU.[19,20] Healthy newborns frequently acquire *S. aureus* colonization in the first few months of life from their mothers.[21,22] New technologies including genome-based analyses may help to further clarify

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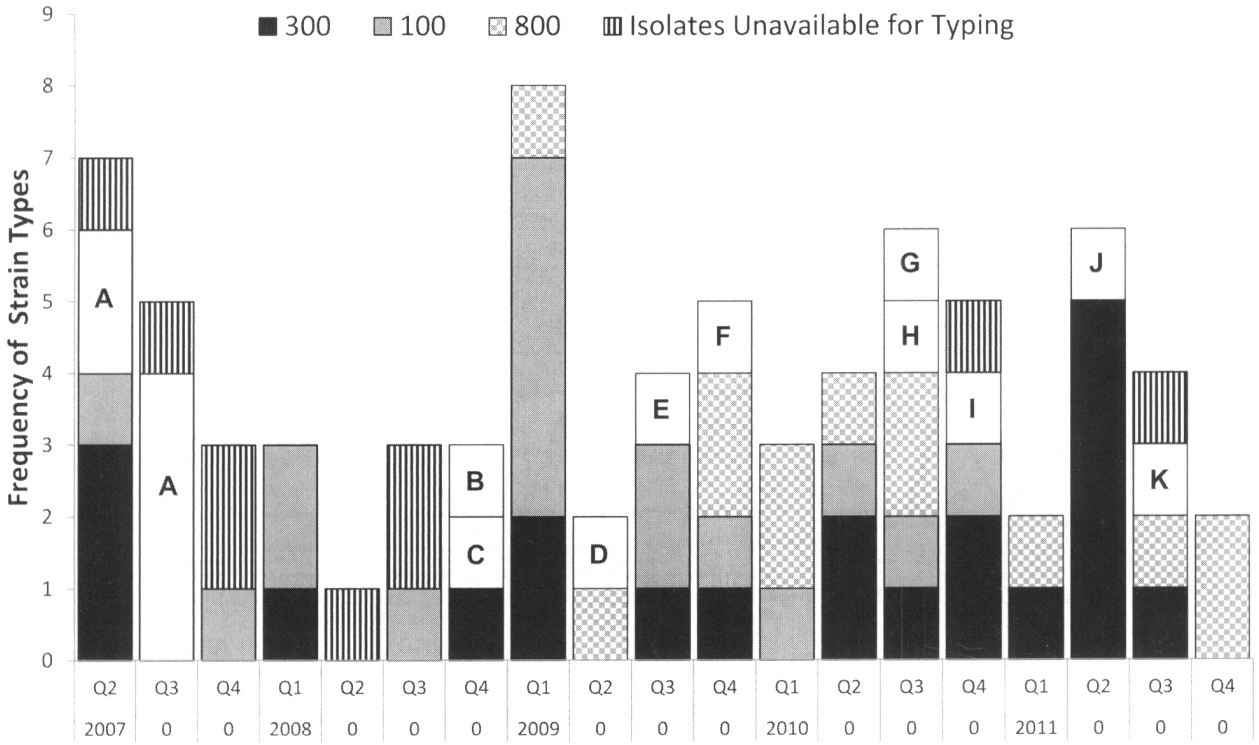

FIGURE 3. Distribution of methicillin-resistant *Staphylococcus aureus* strains isolated from patients. Each letter represents a unique strain.

MRSA transmission dynamics.[23] In a changing NICU environment where parents are encouraged to have direct physical contact with their child, the role of parents in MRSA transmission in NICUs requires further study.

There is high correlation between strains that colonize neonates and cause subsequent infections; therefore, some NICUs attempt either targeted or universal decolonization as an MRSA infection prevention strategy.[7,16,24-27] However, our data highlight the limitations of targeted decolonization as an MRSA prevention strategy. First, despite weekly surveillance cultures, 42% of infections occurred before the neonates were identified as MRSA colonized, leaving no opportunity to attempt decolonization. This finding confirms observations in previous studies that a large proportion of NICU MRSA infections occur before neonates are identified as colonized by active surveillance.[15,28] Second, the interval between colonization and infection in many neonates was short (median, 5 days), suggesting a narrow window of opportunity for intervention in colonized neonates to reduce the risk of subsequent infection.[28,29] Third, 38% of neonates who received decolonization treatment became recolonized during their NICU stay, and 16% developed an MRSA infection, so the efficacy of decolonization to eradicate MRSA colonization and prevent MRSA infections may be limited. Some authors have described universal treatment of all neonates with mupirocin to successfully reduce MRSA infections in neonates.[26,27] A universal approach in some settings had led to emergence of mupirocin resistance, and the long-term impact of indiscriminately treating all neonates—including those not colonized with *S. aureus*—is unknown.[30] A prospective randomized trial is needed to formally evaluate the efficacy and safety of mupirocin with or without chlorhexidine for eradicating MRSA colonization and preventing MRSA infections in neonates. This may need to include those who surround the infant beyond healthcare providers and include family members or care givers.

A number of limitations should be considered when interpreting these data. Only nares cultures were collected routinely, and not all neonates were cultured on admission, so we may have misclassified MRSA-colonized neonates. Sampling multiple sites may have identified some neonates as colonized prior to becoming infected. Compliance with the use of chlorhexidine gluconate clothes in our NICU as a part of the decolonization protocol was not captured in these data, so the impact of this practice cannot be measured here. Furthermore, treatment options for skin, rectal, or throat colonization—such as topical chlorhexidine, oral chlorhexidine rinses, and systemic antibiotics—are not routinely used in this population because of lack of safety and efficacy data.[31] This was a single-center observational study in an academic tertiary care NICU, and the findings may not be generalizable to other settings. We had limited data on HCW MRSA colonization prevalence, so this assessment likely underestimated MRSA strains colonizing HCWs during the study period.

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Finally, we did not explore host-specific factors (such as indwelling endotracheal tubes) and organism-specific factors (including mupirocin resistance) that may have impacted the efficacy of our intervention.

MRSA has become endemic in many NICUs and continues to cause invasive disease and even death. Neonates may acquire MRSA from ongoing low-level HCW transmission or from undiscovered MRSA reservoirs, possibly parents; thus, wider decolonization may be needed in this setting. Current strategies to prevent infections—including active identification and decolonization of MRSA-colonized neonates—may be inadequate, since many infants develop infections before being identified as colonized or after attempted decolonization. Future studies should evaluate and compare strategies to prevent MRSA disease in this population, including improved detection of MRSA colonization, optimized decolonization regimens, or identifying and interrupting reservoirs of transmission.

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