HHS Public Access

Author manuscript

Infect Control Hosp Epidemiol. Author manuscript; available in PMC 2017 April 01.

Published in final edited form as:

Infect Control Hosp Epidemiol. 2016 April ; 37(4): 381–387. doi:10.1017/ice.2015.316.

Active Surveillance Cultures and Decolonization to Reduce NICU *Staphylococcus aureus* Infections

Victor O. Popoola, MBBS MPH Sc.M[1], **Elizabeth Colantuoni, PhD**[2], **Nuntra Suwantarat, MD**[3], **Rebecca Pierce, BSN MS**[4], **Karen C. Carroll, MD**[4], **Susan W. Aucott, MD**[5], and **Aaron M. Milstone, MD MHS**[1,3,6]

[1]Department of Pediatrics, Division of Pediatric Infectious Diseases, Johns Hopkins University School of Medicine, Baltimore, MD

[2]Department of Biostatistics, Johns Hopkins Bloomberg School of Public Health, Baltimore, MD

[3]Department of Pathology, Division of Medical Microbiology, Johns Hopkins University School of Medicine, Baltimore, MD

[4]Department of Epidemiology, Johns Hopkins Bloomberg School of Public Health, Baltimore, MD

[5]Department of Pediatrics, Division of Neonatology, Johns Hopkins University School of Medicine, Baltimore, MD

[6]Department of Hospital Epidemiology and Infection Control, Johns Hopkins Hospital, Baltimore, MD

Abstract

Background and Objectives—*Staphylococcus aureus (S. aureus)* is a common cause of healthcare associated infections (HAI) in neonates. Our objectives were to examine the impact of *S. aureus* decolonization on the incidence of *S. aureus* infection and to measure the prevalence of mupirocin resistance.

Methods—We retrospectively identified neonates admitted to a tertiary care NICU between April 1 2011 and September 30 2014. We compared rates of MSSA-positive cultures and infections before and after implementation of active surveillance culture and decolonization intervention for MSSA-colonized neonates. We used two measurements to identify the primary outcome, NICU-attributable MSSA: 1) any culture sent during routine clinical care that grew MSSA and 2) any culture that grew MSSA and met criteria of the NHSN's HAI surveillance definitions. *S. aureus* isolates were tested for mupirocin susceptibility. To determine the impact of the intervention on MSSA infection, we estimated incidence rate ratios using interrupted time series models.

Results—Pre- and post-intervention, 1523 neonates (29,220 patient-days) and 1195 neonates (22,045 patient-days) were admitted to the NICU, respectively. There was an immediate reduction in mean quarterly incidence rate of NICU-attributable MSSA-positive clinical cultures, of more

Corresponding author: Aaron M. Milstone, Johns Hopkins Department of Pediatric Infectious Diseases, 200 North Wolfe St. / Rubenstein 3141, Baltimore, MD 21287, Phone : 410-614-3917, Fax : 410-614-1491, amilsto1@jhmi.edu.

Potential conflicts of interest: AM reports grant support from Sage Products, LLC. All other authors report no conflicts.

than 60% (IRR=0.36, 95% CI 0.19, 0.70) after implementation of the intervention and MSSA positive culture rates continued to decrease by 21% per quarter (IRR 0.79 95% CI 0.74, 0.84). MSSA infections also decreased immediately following the intervention implementation (IRR=0.27; 95% CI=0.10, 0.79). No mupirocin resistance was detected.

Conclusions—Active surveillance cultures and decolonization may be effective in decreasing *S. aureus* infections in NICUs.

Introduction

Healthcare-associated infections (HAIs) are responsible for significant morbidity and mortality in hospitalized neonates. Preterm and low birth weight neonates have an increased susceptibility to infections due to an immature immune system, increased duration of hospitalization and increased need for invasive procedures.[1–4] The CDC estimates that there are more than 33,000 HAIs in US NICUs every year.[5] Neonates with HAIs have increased length of hospital stay and increased healthcare costs.[2,6,7] Despite appropriate therapy, neonatal infections can have long-term sequelae including adverse neurodevelopmental and growth outcomes.[8,9]

Staphylococcus aureus (S. aureus) is the second most common cause of HAIs and late-onset sepsis in neonates, second only to coagulase-negative *Staphylococcus* (CONS).[10,11] In addition to the high burden of *S. aureus*, antibiotic-resistant *S. aureus* strains, especially methicillin-resistant *S. aureus* (MRSA) have become endemic in many NICUs.[4,12,13] Despite enhanced infection control measures and strategies, *S. aureus* remains a threat to neonates. Current recommendations to prevent MRSA transmission and infections in the NICU include identifying colonized neonates and placing them on contact precautions, cohorting, hand hygiene, and in some cases, decolonizing colonized neonates and/or healthcare workers.[14,15] These strategies have focused on MRSA prevention and have overlooked potentially preventable methicillin-susceptible *S. aureus* (MSSA) disease. Recent data suggest that invasive MSSA infections occur 2 ½ times more frequently than invasive MRSA infections in neonates, and MSSA infections have comparable morbidity and mortality in this high-risk population.[3,16–19] Our objectives were to examine the impact of MSSA decolonization on the incidence of MSSA infections and to measure the prevalence of mupirocin resistance in a level IV NICU.

Patients and Methods

Setting and Design

The Johns Hopkins Hospital (JHH) is a tertiary-care academic medical center with an embedded 200-bed Children's Center that houses a 45-bed, level IV NICU. We retrospectively identified a cohort of neonates admitted to the NICU between April 1 2011 and September 30 2014. We performed a quasi-experimental, pre-post study to compare rates of MSSA-positive cultures and infections before and after implementation of active surveillance cultures (ASC) and decolonization of MSSA-colonized neonates. The Johns Hopkins Institutional Review Board approved this retrospective cohort study with a waiver of informed consent.

Infection Control and Prevention Program

The JHH NICU has a program of ASC and decolonization of MRSA-colonized neonates to prevent MRSA transmission and infections as previously described.[4,20] Nares swabs are performed weekly by nurses to identify MRSA-colonized neonates. In addition, nares swabs are performed at the time of NICU admission for neonates transferred from other hospitals or admitted from home. In April 2013, the program was expanded to include ASC to identify and decolonize MSSA-colonized neonates (`the intervention') in addition to MRSA-colonized neonates due to occurrences of serious MSSA infections. Decolonization consisted of mupirocin applied to the nares twice a day for 5 days and 2 baths with 2% chlorhexidine gluconate-impregnated cloths administered 48 hours apart for infants greater than 36 weeks gestational age or greater than 4 weeks chronological age or daily for 5 days for infants greater than 2 months chronologic age[4,20].

Data Collection and Outcome Ascertainment

We searched a computerized surveillance system (TheraDoc, Premier, Inc) to identify patients with surveillance cultures and cultures sent during clinical care that grew *S. aureus* during the study period. The primary study outcome was NICU-attributable MSSA. We compared two measurements to identify NICU-attributable MSSA: 1) MSSA clinical culture defined as any clinical culture sent as part of clinical care that grew MSSA; 2) MSSA infection defined as any clinical culture that grew MSSA and met the NHSN's surveillance definition for a specific HAI.[21] We reviewed medical records of patients whose cultures sent during clinical care grew MSSA. NHSN definitions for HAIs were applied by a trained observer (V.O.P.) who applied definitions consistently over the study period, to distinguish infection from colonization. MRSA cultures were similarly adjudicated to assess for secular changes. Cultures were further classified into present-on-admission if they were collected less than three days after admission to the NICU or NICU-attributable if they were obtained 3 days or more after admission to the NICU.

Laboratory Methods

Prior to April 2013, surveillance swabs were plated on MRSA Select (BD Diagnostics, Sparks, MD). In April 2013, surveillance swabs were also plated on BBL™ CHROMagar™ *Staph aureus* (BD Diagnostics, Sparks, MD), and beginning April 2014, swabs were plated on SaSelect™ (Bio-Rad Laboratories, Hercules, CA) in addition to MRSA Select. After 24 hours of incubation, mauve-colored colonies or pink- to orange-colored colonies respectively were confirmed as *S. aureus* by Gram's stain and coagulase testing. To monitor for emergence of mupirocin resistance among MSSA isolates, we tested consecutive isolates obtained from neonates after introduction of MSSA decolonization for mupirocin susceptibility using Etest (bioMerieux SA, Marcy-L'Etoile, France). We determined minimum inhibitory concentrations (MICs) using standard CLSI methodology.[22] Mupirocin susceptibility was defined as an MIC < 4 μg/mL, low-level mupirocin resistance (LLMR) if the MIC was between 8 and 64 μg/mL, and high-level mupirocin resistance (HLMR) if the MIC was > 512 μg/mL.[23]

Statistical Analysis

We compared characteristics of neonates admitted during the pre-intervention and post-intervention periods using chi-square tests for categorical variables and the two-sample t-tests for continuous variables. The outcomes were calculated as the quarterly incidence rate of NICU-attributable MSSA clinical cultures and the quarterly incidence rate of NICU-attributable MSSA infections expressed as the number of outcomes in a quarter per 1000 patient-days. We measured the impact of the intervention on *S. aureus* in the NICU by first comparing the mean quarterly incidence rates during the pre- and post-intervention periods using Poisson regression and then using a quasi-experimental interrupted-time series (ITS) model for the log-transformed quarterly incidence rates.[24] From the ITS, the effect of the intervention is reported as a) the "immediate" effect of the intervention as the relative change in quarterly incidence rate comparing the first quarter of the post-intervention period to the last quarter of the pre-intervention period, and b) the "sustained" effect of the intervention as the relative change in the quarterly incidence rate per quarter during the post-intervention period. Due to the small numbers of MRSA positive cultures, we quantified the impact of the intervention by only comparing the mean quarterly incidence rates of MRSA pre- and post-intervention, using Poisson regression. To determine the robustness of our findings, we carried out a sensitivity analysis by varying the start time of the intervention period in the ITS model. Data were maintained in Microsoft Access 2007 (Microsoft) and analyzed using StataSE (ver 13.1; StataCorp) and Microsoft Excel 2007 (Microsoft). The interrupted time-series models were fit using the *itsa* module in Stata.

Results

During the 24 month pre-intervention period, 1,523 neonates were admitted to the NICU accounting for 29,220 patient days. In the 18 months after the MSSA screening and decolonization program began, 1,195 neonates were admitted to the NICU accounting for 22,045 patient days. Of the neonates admitted in the post-intervention period, 899 (75.2%) were screened for MSSA colonization and 89 had a surveillance culture grow MSSA. Of those MSSA-colonized neonates, 72 (78.7%) were treated with mupirocin and chlorhexidine per protocol. Neonates admitted in the pre- and post-intervention periods demonstrate minor differences in demographic and clinical characteristics that are unlikely to impact findings (Table 1). There were 683 female neonates admitted during the pre-intervention period and 521 during the post intervention period (44.8% vs. 43.7%, p=0.55); median birth weight during the pre-intervention period was 2820g (IQR = 1360g) and 2860g (IQR=1390) during the post-intervention period (p=0.51); median length of NICU stay (IQR) was 7.2 days (17.7) pre-intervention compared with 6.5 days (16.5) post-intervention (p=0.20).

During the study period, 83 patients had 153 NICU-attributable *S. aureus* clinical isolates. Clinical isolates included 142 (92.8%) MSSA and 11 (7.2%) MRSA cultures. Forty-three of 142 (30.3%) MSSA cultures met the NHSN's definition for a HAI. Sites of MSSA infection included blood stream infections (n=14, 32.6%), lower respiratory tract (n=12, 27.9%), skin and soft-tissue (n=8, 18.6%), pneumonia (n=3, 7.0%), conjunctivitis (n=3, 7.0%), meningitis (n=1, 2.3%), phlebitis (n=1, 2.3%), and intra-abdominal infection (n=1, 2.3%).

During the pre-intervention period there were 106 MSSA-positive clinical cultures compared to 36 MSSA positive clinical cultures during the post-intervention period. Overall, incidence rate of MSSA clinical cultures was 3.62 per 1000 patient days during the pre-intervention period compared to 1.62 per 1000 patient days during the post-intervention period (IRR = 0.45; 95% CI = 0.22, 0.92). In the quarter following introduction of an ASC and decolonization protocol, MSSA clinical culture incidence rates decreased by an estimated 64% (IRR= 0.36; 95% CI = 0.19, 0.70). This reduction in MSSA clinical culture incidence rates was sustained during the post-intervention period with an estimated quarterly decrease of 21% (IRR = 0.79; 95% CI = 0.74, 0.84). On carrying out a sensitivity analysis with varying start dates for the post-intervention period (the start date was adjusted backwards into the pre-intervention period by one quarter at a time for four quarters), a decrease in the post-intervention slope of MSSA clinical culture rates was observed at each of the tested start dates; however, a statistically significant immediate drop in level of MSSA clinical culture rates only occurred at the actual start date.

Thirty-one MSSA infections (per NHSN criteria) occurred during the pre-intervention period compared to 12 MSSA infections during the post-intervention period. Overall, incidence rate of MSSA infections was 1.07 per 1000 patient-days during the pre-intervention period compared to 0.55 per 1000 patient-days during the post intervention period (IRR = 0.51; 95% CI = 0.14, 1.82). Immediately following the intervention, the incidence rate of MSSA infections decreased in level by an estimated 73% (IRR=0.27; 95% CI=0.10, 0.79). There was not a sustained reduction in incidence rates of MSSA infections during the post-intervention period (IRR = 0.83 95% CI = 0.62, 1.12).

Because other infection control measures in the unit would have impacted MRSA and MSSA rates over time, MRSA clinical cultures and infections were assessed to help confirm an independent effect on the addition of screening and decolonizing MSSA carriers. There was not a difference in the rate of positive MRSA cultures and MRSA infections comparing the post- to pre- intervention periods. There were 8 positive MRSA clinical cultures during the pre-intervention period and 3 positive MRSA clinical cultures during the post-intervention period. Of the 11 NICU-attributable clinical cultures that grew MRSA during the study period only two (18.18%), one each in the pre- and post-intervention periods met the NHSN's definition for a specific HAI. The mean quarterly incidence rate of NICU-attributable MRSA positive clinical cultures was 0.27 and 0.16 per 1000 patient-days during the pre- and post-intervention periods, respectively (IRR = 0.60; 95% CI = 0.05, 7.77).

Of the first 85 neonates that had a surveillance or clinical culture grow MSSA post-intervention, 65 had an isolate available for mupirocin susceptibility testing. None of the 65 tested MSSA isolates were resistant to mupirocin. The median mupirocin MIC was 0.19 μg/mL.

Discussion

S. aureus remains a major cause of HAIs and late-onset sepsis in neonates. Active surveillance cultures and decolonization for MSSA successfully decreased *S. aureus* disease in our NICU. Quarterly incidence rates of MSSA-positive clinical cultures and MSSA

infections decreased more than 50% immediately following implementation of this strategy. Quarterly incidence rates of MSSA-positive cultures continued to decrease by nearly 30% per quarter for the remainder of the study period. To our knowledge, this is the first study to evaluate the impact of active surveillance and targeted decolonization for decreasing MSSA burden in the NICU in a non-outbreak setting.

ASC coupled with decolonization has been shown to be an effective strategy in decreasing *S. aureus* transmission and infection.[12,20,25] Current guidelines suggest that decolonization may be considered in high risk neonates during an MRSA outbreak or to combat endemic MRSA when other strategies have failed.[26] Recommendations are less clear for MSSA and few data exist on the safety and efficacy of decolonization in this population.[27] Delaney et al found that after instituting a mupirocin prophylaxis regimen for 7 years, incidence rate of *S. aureus* (MSSA and MRSA) infections in their NICU decreased from 1.88 per 1000 patient-days to 0.33 per 1000 patient-days.[28] They found no mupirocin resistant *S. aureus* isolates.

While MRSA has been the target of most NICU *S. aureus* prevention and control programs, MSSA may cause comparable morbidity and mortality and is likely more prevalent in most centers. [16–19] Ericson and colleagues recently reported that MSSA was responsible for 2.5 times more infections than MRSA.[19] In Shane and colleagues' study of 8,444 VLBW neonates with *S. aureus* bacteremia or meningitis, MSSA was nearly thrice as prevalent as MRSA and both strains were associated with high mortality.[3] In our study, MSSA accounted for greater than 90% of all *S. aureus* clinical isolates and a third of all MSSA infections were BSIs. A higher absolute burden of disease and mortality from MSSA compared to MRSA strains justifies refocusing prevention strategies to include MSSA in addition to MRSA.

Our findings are consistent with previous reports of a low prevalence of mupirocin resistance among *S. aureus* isolates from mupirocin treated neonates. Hitomi et al described the use of universal decolonization using mupirocin as a strategy for eradicating an outbreak of MRSA in their NICU.[29] As discussed above, Delaney and colleagues reported treating all neonates in their NICU with intranasal mupirocin for 7 years.[28] Mupirocin resistance was not observed in either study. During our recent study of mupirocin resistance among MRSA isolates from hospitalized neonates, we found a low prevalence (3 of 84 isolates, 3.6%) of low level mupirocin resistance and no isolates with high level resistance to mupirocin.[23] Although high level mupirocin resistance has been associated with treatment failure, the clinical significance of low level mupirocin resistance is unclear.[30] Similarly, in this study, we performed susceptibility testing on 65 available isolates from the first 85 neonates that had a culture grow MSSA post intervention and found no mupirocin-resistant MSSA isolates. Acquisition of mupirocin resistance is often a concern when considering a more aggressive decolonization strategy such as one that includes decolonizing MSSA-colonized neonates. However, while mupirocin resistance has been reported following widespread use in hospitalized adults[31–33], this has not been reported in neonates.

Data on the cost effectiveness of ASC and decolonization for prevention of *S. aureus* are limited. You et al, using decision analysis modeling, recently examined the potential clinical outcomes and cost of ASC for MRSA with and without decolonization in Hong Kong

NICUs.[34] Even at very low levels of decolonization efficacy for prevention of MRSA infections in colonized neonates, decolonization, when combined with ASC was both cost-saving and effective in decreasing incidence of MRSA infections and MRSA-associated mortality. For programs already collecting surveillance cultures for MRSA colonization, there is little additional expense to identify MSSA colonized infants. Additional studies are needed to determine the cost-effectiveness of *S. aureus* surveillance and decolonization programs in the NICU.

Despite its benefits, decolonization may negatively impact the developing neonatal nasal microbiome.[35] Although chlorhexidine was well-tolerated in our population with no skin toxicity observed, the broad antimicrobial activity of mupirocin and chlorhexidine could predispose the neonate to colonization by more harmful pathogens. When considering decolonization as an infection control strategy in the NICU, therefore, the risks must be carefully weighed against benefits. Neonates should be closely monitored for acquisition of mupirocin resistance and replacement of the nasal flora by fungi and other pathogens. By targeting neonates for decolonization through ASC rather than universal treatment, the risks are minimized to those infants who may have the most benefit.

The primary outcome (positive clinical culture) has been used before as a surrogate outcome for MRSA infection and burden.[36] This outcome likely overestimates the burden of disease, but our conclusions are supported by the similar observed reduction in MSSA infections that met the NHSN's surveillance definition for a specific HAI. All quasi-experimental studies are at risk of influence by unobserved changes in practices over time. To account for this possibility, the burden of MRSA was evaluated during the study period and no change was observed reflecting the targeted nature of this intervention. The decrease in incidence rates of MSSA-positive clinical cultures and NHSN-defined MSSA infections may represent a return to baseline rates following an outbreak or a regression to the mean. However, during sensitivity analyses, while shifting the start of the intervention period backwards did not change the post-intervention slope significantly, the immediate drop in rates of MSSA was only statistically significant at the actual intervention start time. Compliance with the intervention was only 78%, but this is partially due to the fact that some neonates were discharged from the NICU before culture results were reported. Finally, although median birth weight is comparable between the pre-and post-intervention period, it is possible that there is a difference in the number of very low birth weight neonates in each period but we think this is unlikely.

Preterm and low birth weight neonates are particularly vulnerable to *S. aureus* infections. ASC and decolonization may be effective in decreasing the burden of *S. aureus* in NICUs and preventing infections and should not be limited to MRSA colonized neonates. Additional studies are needed to confirm the impact of decolonization on reducing MSSA infections among hospitalized neonates and to monitor for unanticipated consequences.

Acknowledgements

We would like to thank the Johns Hopkins Hospital (JHH) Clinical Microbiology Laboratory staff, the JHH Neonatal Intensive Care Unit nursing staff, and the JHH Department of Hospital Epidemiology and Infection Control for their support of this study.

Financial Support: This work was supported by the National Institute of Allergy and Infectious Disease, National Institutes of Health R03AI117169, the Agency for Healthcare Research and Quality R01HS022872 and the Sherrilyn and Ken Fisher Center for Environmental Infectious Diseases, Division of Infectious Diseases of the Johns Hopkins University School of Medicine and Grant UL1 RR 025005 from the National Center for Research Resources (NCRR), a component of the National Institutes of Health (NIH), and NIH Roadmap for Medical Research. The contents are solely the responsibility of the authors and do not necessarily represent the official view of the Fisher Center, NCRR, NIH, or AHRQ.

References

1. Chu A, Hageman JR, Schreiber M, Alexander K. Antimicrobial Therapy and Late Onset Sepsis. NeoReviews. 2012; 13:e94–e102. doi:10.1542/neo.13-2-e94.
2. Stoll BJ, Hansen N, Fanaroff AA, Wright LL, Carlo WA, Ehrenkranz RA, Lemons JA, Donovan EF, Stark AR, Tyson JE, Oh W, Bauer CR, Korones SB, Shankaran S, Laptook AR, Stevenson DK, Papile LA, Poole WK. Late-onset sepsis in very low birth weight neonates: the experience of the NICHD Neonatal Research Network. Pediatrics. 2002; 110:285–291. [PubMed: 12165580]
3. Shane AL, Hansen NI, Stoll BJ, Bell EF, Sanchez PJ, Shankaran S, Laptook AR, Das A, Walsh MC, Hale EC, Newman NS, Schrag SJ, Higgins RD. Methicillin-resistant and susceptible Staphylococcus aureus bacteremia and meningitis in preterm infants. Pediatrics. 2012; 129:e914–922. [PubMed: 22412036]
4. Popoola VO, Budd A, Wittig SM, Ross T, Aucott SW, Perl TM, Carroll KC, Milstone AM. MRSA Transmission and Infections in a Neonatal Intensive Care Unit Despite Active Surveillance Cultures and Decolonization - Challenges for Infection Prevention. Infection Control and Hospital Epidemiology. 2014; 35:412–418. [PubMed: 24602947]
5. Klevens RM, Edwards JR, Richards CL Jr. Horan TC, Gaynes RP, Pollock DA, Cardo DM. Estimating health care-associated infections and deaths in U.S. hospitals, 2002. Public Health Rep. 2007; 122:160–166. [PubMed: 17357358]
6. Payne NR, Carpenter JH, Badger GJ, Horbar JD, Rogowski J. Marginal increase in cost and excess length of stay associated with nosocomial bloodstream infections in surviving very low birth weight infants. Pediatrics. 2004; 114:348–355. doi:114/2/348 [pii]. [PubMed: 15286215]
7. Sohn AH, Garrett DO, Sinkowitz-Cochran RL, Grohskopf LA, Levine GL, Stover BH, Siegel JD, Jarvis WR. Prevalence of nosocomial infections in neonatal intensive care unit patients: Results from the first national point-prevalence survey. The Journal of pediatrics. 2001; 139:821–827. [PubMed: 11743507]
8. Stoll BJ, Hansen NI, Adams-Chapman I, Fanaroff AA, Hintz SR, Vohr B, Higgins RD. Neurodevelopmental and growth impairment among extremely low-birth-weight infants with neonatal infection. Jama. 2004; 292:2357–2365. [PubMed: 15547163]
9. Schlapbach LJ, Aebischer M, Adams M, Natalucci G, Bonhoeffer J, Latzin P, Nelle M, Bucher HU, Latal B. Impact of Sepsis on Neurodevelopmental Outcome in a Swiss National Cohort of Extremely Premature Infants. Pediatrics. 2011; 128:e348–e357. [PubMed: 21768312]
10. Hornik CP, Fort P, Clark RH, Watt K, Benjamin DK Jr. Smith PB, Manzoni P, Jacqz-Aigrain E, Kaguelidou F, Cohen-Wolkowiez M. Early and late onset sepsis in very-low-birth-weight infants from a large group of neonatal intensive care units. Early human development. 2012; 88(Suppl 2):S69–74. doi:10.1016/S0378-3782(12)70019-1 S0378-3782(12)70019-1 [pii]. [PubMed: 22633519]
11. Hocevar SN, Edwards JR, Horan TC, Morrell GC, Iwamoto M, Lessa FC. Device-associated infections among neonatal intensive care unit patients: incidence and associated pathogens reported to the National Healthcare Safety Network, 2006–2008. Infect Control Hosp Epidemiol. 2012; 33:1200–1206. [PubMed: 23143356]
12. Huang YC, Lien RI, Su LH, Chou YH, Lin TY. Successful control of methicillin-resistant Staphylococcus aureus in endemic neonatal intensive care units--a 7-year campaign. PLoS One. 2011; 6:e23001. doi:10.1371/journal.pone.0023001 PONE-D-11-07509 [pii]. [PubMed: 21857979]
13. Nelson MU, Bizzarro MJ, Baltimore RS, Dembry LM, Gallagher PG. Clinical and Molecular Epidemiology of Methicillin-Resistant Staphylococcus aureus in a Neonatal Intensive Care Unit in

the Decade following Implementation of an Active Detection and Isolation Program. J Clin Microbiol. 2015; 53:2492–2501. doi:10.1128/JCM.00470-15. [PubMed: 26019206]

14. Gerber SI, Jones RC, Scott MV, Price JS, Dworkin MS, Filippell MB, Rearick T, Pur SL, McAuley JB, Lavin MA, Welbel SF, Garcia-Houchins S, Bova JL, Weber SG, Arnow PM, Englund JA, Gavin PJ, Fisher AG, Thomson RB, Vescio T, Chou T, Johnson DC, Fry MB, Molloy AH, Bardowski L, Noskin GA. Management of outbreaks of methicillin-resistant Staphylococcus aureus infection in the neonatal intensive care unit: a consensus statement. Infect Control Hosp Epidemiol. 2006; 27:139–145. doi:ICHE2005124 [pii] 10.1086/501216. [PubMed: 16465630]
15. Popoola VO, Milstone AM. Decolonization to prevent Staphylococcus aureus transmission and infections in the neonatal intensive care unit. J Perinatol. 2014 doi:10.1038/jp.2014.128 jp2014128 [pii].
16. Carey AJ, Duchon J, Della-Latta P, Saiman L. The epidemiology of methicillin-susceptible and methicillin-resistant Staphylococcus aureus in a neonatal intensive care unit, 2000–2007. J Perinatol. 2010; 30:135–139. doi:10.1038/jp.2009.119 jp2009119 [pii]. [PubMed: 19710681]
17. Kuint J, Barzilai A, Regev-Yochay G, Rubinstein E, Keller N, Maayan-Metzger A. Comparison of community-acquired methicillin-resistant Staphylococcus aureus bacteremia to other staphylococcal species in a neonatal intensive care unit. European journal of pediatrics. 2007; 166:319–325. doi:10.1007/s00431-006-0238-5. [PubMed: 17051356]
18. Graham PL 3rd, Morel AS, Zhou J, Wu F, Della-Latta P, Rubenstein D, Saiman L. Epidemiology of methicillin-susceptible Staphylococcus aureus in the neonatal intensive care unit. Infect Control Hosp Epidemiol. 2002; 23:677–682. [PubMed: 12452296]
19. Ericson JE, Popoola VO, Smith PB, Benjamin DK, Fowler VG, Benjamin DK Jr. Clark RH, Milstone AM. Burden of Invasive Staphylococcus aureus Infections in Hospitalized Infants. JAMA pediatrics. 2015:1–8. doi:10.1001/jamapediatrics.2015.2380.
20. Milstone AM, Budd A, Shepard JW, Ross T, Aucott S, Carroll KC, Perl TM. Role of decolonization in a comprehensive strategy to reduce methicillin-resistant Staphylococcus aureus infections in the neonatal intensive care unit: an observational cohort study. Infect Control Hosp Epidemiol. 2010; 31:558–560. [PubMed: 20334509]
21. CDC/NHSN. Surveillance Definitions for Specific Types of Infections. 2013.
22. CLSI. Performance standards for antimicrobial susceptibility testing. Clinical and Laboratory Standards Institute - informational supplement. 2014; 24
23. Suwantarat N, Carroll KC, Tekle T, Ross T, Popoola VO, Milstone AM. Low prevalence of mupirocin resistance among hospital-acquired methicillin-resistant Staphylococcus aureus isolates in a neonatal intensive care unit with an active surveillance cultures and decolonization program. Infect Control Hosp Epidemiol. 2015; 36:232–234. doi:10.1017/ice.2014.17. [PubMed: 25633010]
24. Linden, A. *itsa*: Stata module for conducting interrupted time series analysis for single and multiple groups. 2014.
25. Khoury J, Jones M, Grim A, Dunne WM Jr, Fraser V. Eradication of methicillin-resistant Staphylococcus aureus from a neonatal intensive care unit by active surveillance and aggressive infection control measures. Infect Control Hosp Epidemiol. 2005; 26:616–621. [PubMed: 16092741]
26. Calfee DP, Salgado CD, Milstone AM, Harris AD, Kuhar DT, Moody J, Aureden K, Huang SS, Maragakis LL, Yokoe DS. Strategies to prevent methicillin-resistant Staphylococcus aureus transmission and infection in acute care hospitals: 2014 update. Infect Control Hosp Epidemiol. 2014; 35(Suppl 2):S108–132. [PubMed: 25376072]
27. Nelson MU, Bizzarro MJ, Dembry LM, Baltimore RS, Gallagher PG. One size does not fit all: why universal decolonization strategies to prevent methicillin-resistant Staphylococcus aureus colonization and infection in adult intensive care units may be inappropriate for neonatal intensive care units. J Perinatol. 2014; 34:653–655. doi:10.1038/jp.2014.125. [PubMed: 25010223]
28. Delaney HM, Wang E, Melish M. Comprehensive strategy including prophylactic mupirocin to reduce Staphylococcus aureus colonization and infection in high-risk neonates. J Perinatol. 2012

29. Hitomi S, Kubota M, Mori N, Baba S, Yano H, Okuzumi K, Kimura S. Control of a methicillin-resistant Staphylococcus aureus outbreak in a neonatal intensive care unit by unselective use of nasal mupirocin ointment. J Hosp Infect. 2000; 46:123–129. [PubMed: 11049705]

30. Walker ES, Vasquez JE, Dula R, Bullock H, Sarubbi FA. Mupirocin-resistant, methicillin-resistant Staphylococcus aureus: does mupirocin remain effective? Infect Control Hosp Epidemiol. 2003; 24:342–346. doi:10.1086/502218. [PubMed: 12785407]

31. Miller MA, Dascal A, Portnoy J, Mendelson J. Development of mupirocin resistance among methicillin-resistant Staphylococcus aureus after widespread use of nasal mupirocin ointment. Infect Control Hosp Epidemiol. 1996; 17:811–813. [PubMed: 8985769]

32. Jones JC, Rogers TJ, Brookmeyer P, Dunne WM Jr. Storch GA, Coopersmith CM, Fraser VJ, Warren DK. Mupirocin resistance in patients colonized with methicillin-resistant Staphylococcus aureus in a surgical intensive care unit. Clin Infect Dis. 2007; 45:541–547. [PubMed: 17682986]

33. Choudhury S, Krishnan PU, Ang B. Prevalence of high-level mupirocin resistance among meticillin-resistant Staphylococcus aureus isolates in a tertiary care hospital in Singapore. J Hosp Infect. 2012; 82:56–57. doi:10.1016/j.jhin.2012.07.002. [PubMed: 22854355]

34. You JH, Chan CY, Wong MY, Ip M. Active Surveillance and Decolonization of Methicillin-Resistant Staphylococcus aureus on Admission to Neonatal Intensive Care Units in Hong Kong: A Cost-Effectiveness Analysis. Infect Control Hosp Epidemiol. 2012; 33:1024–1030. [PubMed: 22961022]

35. Carey AJ. War on Staphylococcus aureus. J Perinatol. 2014; 34:803–804. doi:10.1038/jp.2014.129. [PubMed: 25359411]

36. Huang SS, Septimus E, Kleinman K, Moody J, Hickok J, Avery TR, Lankiewicz J, Gombosev A, Terpstra L, Hartford F, Hayden MK, Jernigan JA, Weinstein RA, Fraser VJ, Haffenreffer K, Cui E, Kaganov RE, Lolans K, Perlin JB, Platt R. Targeted versus universal decolonization to prevent ICU infection. N Engl J Med. 2013; 368:2255–2265. doi:10.1056/NEJMoa1207290. [PubMed: 23718152]

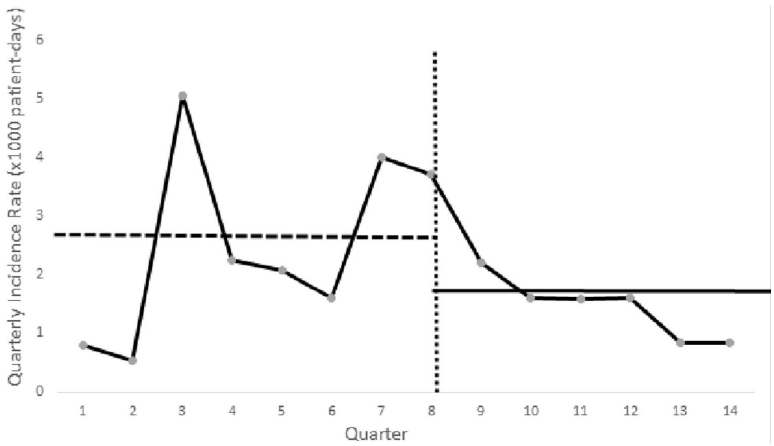

Figure 1.

Mean quarterly incidence of MSSA before and after implementation of an ASC and decolonization protocol. The dashed, horizontal and solid, horizontal lines represent the incidence rate of MSSA averaged over the pre- and post-intervention periods respectively and the dotted, vertical line (beginning of the 9th study quarter) marks the start of the intervention.

Table 1

Characteristics of neonates admitted in the NICU during pre-intervention (April 1, 2011 through March 31, 2013) and post-intervention (April 1, 2013 through September 30, 2014)

Patient characteristics	Pre-intervention period N=1524(%)	Post-intervention period N=1193(%)	P-value
Female (%)	683 (44.8)	521 (43.7)	0.55
Race			
Asian	58 (3.8)	54 (4.5)	0.35
Black or African-American	710 (46.6)	522 (43.8)	0.14
White	577 (37.9)	445 (37.3)	0.76
Other	179 (11.8)	172 (14.5)	0.04
Birth Weight, median (IQR)	2820 (1360)	2860 (1390)	0.51
Length of NICU Stay, median (IQR)	7.2 (17.7)	6.5 (16.5)	0.20
Inborn	1287 (84.5)	968 (81.1)	0.02
Mortality	49 (3.2)	37 (3.1)	0.87
Quarterly Device Utilization Ratio	0.47	0.48	0.64
Mean Quarterly Patient Days	3653	3674	0.76

Table2a

Distribution of clinical culture categories

Specimen Category (n)	Period		
	Pre*	Post**	Total
Abscess drainage	2	0	2
Blood	16	3	19
Body fluid, other	0	1	1
Broncho alveolar lavage	3	0	3
Catheter tip	1	0	1
Cerebrospinal fluid	1	0	1
Eye	7	3	10
Other	2	1	3
Peritoneal fluid	0	1	1
Sputum, non-cystic fibrosis	59	23	82
Urine	5	1	6
Wound	10	3	13
Total	106	36	142

* Pre-intervention period (24 months)

** Post-intervention period (18 months)

Table2b

Distribution of infections

Category of Infection (n)	Period		
	Pre*	Post**	Total
BSI	11	3	14
CNSI	1	0	1
CVSI-VASC	1	0	1
EENTI	2	1	3
IAB	0	1	1
LRTI	10	2	12
PNEU	1	2	3
SSTI	5	3	8
Total	31	12	43

* Pre-intervention period (24 months)

** Post-intervention period (18 months)