Treating Parents to Reduce NICU Transmission of *Staphylococcus aureus* (TREAT PARENTS) trial: protocol of a multisite randomised, double-blind, placebo-controlled trial

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**ABSTRACT**

**Introduction:** More than 33 000 healthcare-associated infections occur in neonatal intensive care units (NICUs) each year in the USA. Parents, rather than healthcare workers, may be a reservoir from which neonates acquire *Staphylococcus aureus* (*S. aureus*) colonisation in the NICU. This study looks to measure the effect of treating parents with short course intranasal mupirocin and topical chlorhexidine antisepsis on acquisition of *S. aureus* colonisation and infection in neonates.

**Methods and analysis:** The TREAT PARENTS trial (Treating Parents to Reduce Neonatal Transmission of *S. aureus*) is a multicentre randomised, masked, placebo-controlled trial. Shortly after a neonate is admitted to the NICU, parents will be tested for *S. aureus* colonisation. If either parent screens positive for *S. aureus*, then both parents as a pair will be enrolled and randomised to one of the two possible masked treatment arms. Arm 1 will include assignment to intranasal 2% mupirocin plus topical chlorhexidine antiseptic cloths for 5 days. Arm 2 will include assignment to placebo ointment and placebo cloths for skin antisepsis for 5 days. The primary outcome will be neonatal acquisition of an *S. aureus* strain that is concordant to the parental baseline *S. aureus* strain as determined by periodic surveillance cultures or a culture collected during routine clinical care that grows *S. aureus*. Secondary outcomes will include neonatal acquisition of *S. aureus*, neonatal *S. aureus* infection, eradication of *S. aureus* colonisation in parents, natural history of *S. aureus* colonisation in parents receiving placebo, adverse reactions to treatment, feasibility of intervention, and attitudes and behaviour in consented parents. Four hundred neonate-parent pairs will be enrolled.

**Ethics and dissemination:** The study was approved by Johns Hopkins University IRB in June 2014 (IRB number 00092982). Protocol V.7 was approved in November 2014. Findings will be published in peer-reviewed journals.

**Trial registration number:** NCT02223520.

**Strengths and limitations of this study**

- This will be the first study to measure the effectiveness of treating parents as a strategy to reduce the spread of *Staphylococcus aureus* in the neonatal intensive care unit.
- Methodological strengths include: two study sites, masked intervention with placebo control, masked assessment of outcome, and intent to treat analysis plan.
- Study units have intensive *S. aureus* infection control programmes and a low incidence of *S. aureus* disease, so the primary outcome is *S. aureus* acquisition, not *S. aureus* infection.

**INTRODUCTION**

More than 33 000 healthcare-associated infections (HAIs) occur in neonatal intensive care units (NICUs) each year in the USA.1 HAIs are estimated to result in $28–$45 billion in healthcare costs annually.2 In addition to the short-term costs of HAIs, neonatal infections contribute to neurological disabilities and poor growth outcomes.3,4 *Staphylococcus aureus* (*S. aureus*) is the second most common pathogen causing HAIs in neonates.5 A study of very low birthweight infants in 20 US NICUs found that 3.7% develop bloodstream or central nervous system *S. aureus* infections with an attributable mortality approaching 20%.6 Despite aggressive measures to prevent *S. aureus* infections in neonates, the burden of *S. aureus* disease remains high in this population.7,8 Up to 40% of neonates acquire *S. aureus* in the first 2 months of life.9,10 Vertical transmission of *S. aureus* is rare, but postnatal transmission from the mother to healthy infants is common in the first few months of life.
life. Although healthcare workers have been implicated as a source of spreading \textit{S. aureus} in NICUs, they are often not the source for transmission of \textit{S. aureus} in NICUs. Parents, rather than healthcare workers, may be a key reservoir from which neonates acquire \textit{S. aureus} colonisation in the NICU. This paradigm is consistent with a changing NICU environment where skin-to-skin contact between parents and neonates is encouraged and may promote \textit{S. aureus} transmission, while at the same time, common hospital infection prevention measures have reduced healthcare worker transmission of \textit{S. aureus}. This protocol describes the TREAT PARENTS trial (Treating Parents to Reduce Neonatal Transmission of \textit{S. aureus}), a randomised, masked, placebo-controlled trial that will measure the effect of treating parents with short course intranasal mupirocin and topical chlorhexidine antiseptic on acquisition of \textit{S. aureus} colonisation and infection in neonates (Clinical Trials.gov NCT02223520). Rather than a patient-directed approach (screening and treating \textit{S. aureus} colonised neonates) which has limitations in the neonatal population, the TREAT PARENT trial tests a parent-directed approach that may eliminate or delay a neonate’s exposure to \textit{S. aureus}. Similar to treating pregnant mothers with group B \textit{Streptococcus} during labour and delivery to prevent disease in newborn infants, this study will engage parents in preventing \textit{S. aureus} infections in their neonates. The findings of the proposed study could provide a new tool for HAI prevention in the NICU.

**Primary objective**

1. To compare the effect of treating parents with short course intranasal mupirocin and topical chlorhexidine bathing or placebo on acquisition of \textit{S. aureus} colonisation in neonates.

**Secondary objectives**

1. To compare the relatedness of \textit{S. aureus} strains colonising parents and \textit{S. aureus} strains acquired by their neonates in the NICU.
2. To compare the effect of treating parents with short course intranasal mupirocin and topical chlorhexidine bathing or placebo on \textit{S. aureus} infections in neonates.
3. To determine the efficacy of short-course intranasal mupirocin and topical chlorhexidine bathing to eradicate \textit{S. aureus} colonisation in parents.

**METHODS AND ANALYSIS**

**Study design**

The TREAT PARENTS trial is a placebo-controlled, double-masked, randomised clinical trial.

**Study population and setting**

Neonates admitted to the Johns Hopkins Hospital (JHH) NICU and the Johns Hopkins Bayview Medical Center NICU and their parents or legal guardians will be screened for eligibility. We will define parents as the biological mother and the father. In the event that one of the parents is not available or does not visit the child in the NICU, we will ask the available parent to identify a primary visitor of the child in the NICU as a second study participant. The JHH NICU is a 45-bed NICU in a quaternary care centre that admits approximately 700 neonates per year. The Johns Hopkins Bayview Medical Center (Bayview) NICU is a 25-bed, level III unit with approximately 375 admissions per year.

**Inclusion criteria**

1. Neonate has never had a prior clinical or surveillance culture grow \textit{S. aureus}
2. Neonate was transferred from another hospital or admitted from home and had admission screening cultures for \textit{S. aureus} colonisation that were negative
3. Parent(s) is(are) able to visit the child at the bedside
4. Parent(s) test positive for \textit{S. aureus} at screening
5. Neonate has anticipated stay longer than 5 days in the NICU
6. Parent(s) is(are) willing to be randomised
7. No documented or reported allergies to any agent used in either treatment regimen
8. Able to perform written informed consent.

**Exclusion criteria**

1. Allergies to any agent used in either treatment regimen
2. Neonate has had a prior clinical or surveillance culture grow \textit{S. aureus}
3. Neonate admitted to NICU from home and is greater than 7 days of age
4. Neonate admitted to NICU from another hospital and is greater than 7 days of age
5. Neonate is a ward of the State
6. Not able to provide written informed consent.

**Recruitment of patients**

We will pre-screen neonates for eligibility. A member of the study team will approach all eligible parents at the bedside and request participation. After recruitment and informed consent, parents will undergo pre-randomisation screening to determine if the parents are colonised with \textit{S. aureus}. Parent screening cultures will be performed by trained study team members using standardised methodology by obtaining a swab from the anterior nares, throat, groin and peri-anal area. These samples will be analysed in the Johns Hopkins Microbiology Laboratory according to Clinical and Laboratory Standards Institute guidelines.

**Randomisation and allocation concealment**

If either parent screens positive for \textit{S. aureus}, then both parents as a pair will be eligible for randomisation to one of the two possible masked treatment arms (figure 1). The neonate–parent “pair” will be the unit of randomisation and each parent will be allocated to the
same group if both consent. Since couples can re-expose each other after treatment (especially in households), both parents will be treated even if only one parent is colonised with *S. aureus*. Stratified permuted-block randomisation will be performed using R statistical software to achieve balanced allocation of participants within study site and within strata of birth weight (≥ or <1500 g). Use of varying block sizes (4, 6 and 8) will decrease the risk of imbalance. Neonates of multiple gestations and their parents will be randomised as a single family unit. Investigators and participants will be masked to treatment assignment. A pharmacist will dispense treatment in pre-sealed opaque packaging to preserve the concealment of treatment. Additionally, the treating clinicians of the neonates will be masked to treatment assignment. In the event of a medical emergency where knowledge of the participant’s blinded treatment is critical to their medical management, the blind may be broken by the investigator after consultation with the Data Safety Monitoring Board (DSMB).

**Intervention**

Participants will be randomly assigned to one of two arms.

1. **Treatment**: Intranasal mupirocin twice daily for 5 days plus topical antisepsis with chlorhexidine gluconate impregnated cloths daily for 5 days.
2. **Placebo**: placebo intranasal ointment (petrolatum) twice daily for 5 days and placebo cloths (not chlorhexidine gluconate impregnated) for skin antisepsis daily for 5 days.

**Participant timeline**

**Parent evaluation time points**

All participants will begin the 5-day treatment course at randomisation. The study team members will contact study participants during the treatment period to promote compliance. After completion of the treatment period, residual treatment will be retrieved and returned to pharmacy for compliance measurements. Participant self-reported adverse events will be recorded by the study team. Parent(s) will be re-tested for colonisation at 2-week intervals from randomisation for the first 8 weeks and then every 4 weeks until discharge. The final visit and testing will be performed at the time of a neonate’s discharge from the NICU or at the time the child is identified to have acquired *S. aureus*. Data will be obtained via interviews and from the electronic medical record and directly entered into REDCap (a secure web application for building and managing online databases). To promote participant retention, remuneration will be provided when participants reach pre-specified milestones.

**Neonate evaluation time points**

After randomisation of parents, the neonate will undergo baseline testing to determine baseline *S. aureus* colonisation status. This testing will occur on study day 1, the same day that parents begin treatment. Screening cultures will be performed by obtaining a swab from the anterior nares, umbilicus, groin and peri-anal area. Those neonates who test positive for *S. aureus* colonisation at the time of randomisation will not be included in the primary outcome analysis. After baseline testing, repeat testing will be performed every 7 days. The final visit and testing will be performed at the time of a neonate’s discharge from the NICU. Results of cultures collected as part of routine patient care (e.g., blood cultures, respiratory cultures, wound cultures, surveillance cultures) will also be available to identify *S. aureus* acquisition in neonates (table 1).

**OUTCOMES**

**Primary end point**

Primary outcome is neonatal acquisition of an *S. aureus* strain that is concordant to the parental *S. aureus* strain as determined by periodic surveillance cultures or cultures collected during routine clinical care. Acquisition will be defined as meeting two criteria:

1. A neonate who had baseline surveillance cultures that were negative for *S. aureus*.
2. A neonate who has a subsequent surveillance culture or culture collected during routine clinical care that grows *S. aureus*.

Concordant strains must meet the following criteria:

1. Strains that are related using pulsed-field gel electrophoresis analysis. Isolates will be considered related if their patterns have ≤3 band differences. Isolates with >3 band differences will be considered epidemiologically different strain types. Alternative typing methods may be used to further discriminate highly prevalent strains.
2. The same strain from the initial parent screening is identified from the neonate.

**Secondary end points**

1. Neonatal acquisition of *S. aureus* as determined by periodic surveillance cultures or a culture collected during routine clinical care that grows *S. aureus*.
2. Neonatal *S. aureus* infection as determined by cultures collected during routine clinical care.
3. Eradication of *S. aureus* colonisation in parents following treatment.
4. Natural history of *S. aureus* colonisation in parents.
5. Adverse reactions to treatment.
6. Feasibility of intervention in this population as applied.
7. Attitudes and behaviour in all consented parents.

**STATISTICAL ANALYSIS PLAN**

**Sample size and power calculations**

The assumed Placebo group concordant colonisation rate is 10% and power calculations are conservatively based on the unadjusted Cox proportional hazards model where the primary covariate is the treatment group indicator. Given that we expect 10% of the...
parent–neonate pairs will be non-singleton births, we assessed the conservative power of the trial assuming that the outcomes from the non-singleton neonates are completely dependent. On the basis of the above assumptions, a total sample size of 400 neonates will provide 80% or 90% power to detect a reduction in the hazard of concordant colonisation of roughly 60% or 65%, respectively. The total sample size of 400 neonates will provide power of at least 85% to detect an absolute difference in the rate of concordant colonisation comparing the Treatment group (2%) to the Placebo group (10%). Some neonates may test positive at baseline for *S. aureus* colonisation after randomisation and will not be eligible for primary outcome analysis, so the actual enrolment will most likely exceed 400 neonates.

### Interim analysis

Several interim analyses will be performed. We will perform interim analyses for both efficacy and harm after 200 and 300 neonates that are eligible for analysis have been consented, enrolled, randomised and followed for 8 weeks. After accruing the 200 and 300 neonates eligible for analysis, we will stop the trial for efficacy if the test statistic for the primary analysis (see below) falls within the O’Brien Fleming rejection region defined by $|Z_r|=2.96$ or 2.36. If the trial continues to recruit the full 400 neonates eligible for analysis, the treatment effect will be deemed statistically significant if the test statistic for the primary analysis falls within the O’Brien Fleming rejection region defined by $|Z_r|=2.01$.

The O’Brien Fleming stopping rule for harm will be applied if we observe more concordant colonisations on
the treated group relative to placebo and the trial will be stopped according to the following rejection regions after accrual of 200, 300 or 400 neonates eligible for analysis; \( Z = 2.45, 2.00 \) or 1.73, respectively.

In addition, an interim analysis for futility will be conducted after 200 neonates that are eligible for analysis have been consented, enrolled, randomised and followed for 8 weeks. Assuming that colonisation of the neonates occur uniformly over the study, we expect to observe 10 concordant colonisations in the Placebo group (rate of 10%) at the interim analysis. We will stop the trial if the upper bound on the 95% confidence for the concordant colonisation rate among the Placebo group at the interim analysis is <10%. Therefore, we will stop the trial for futility if the observed number of concordant colonisations in the Placebo group is \( \leq 4 \).

### Statistical analysis

Exploratory analyses will compare baseline characteristics of the treatment groups using Student t test for continuous variables and Pearson’s \( \chi^2 \) test or Fisher’s exact test for categorical variables. Analyses of all aims will follow the intention-to-treat principle. For the primary analysis, the parent–neonate pair will be the unit of analysis and survival analysis techniques will be used to compare the hazard of concordant colonisation comparing the Treatment and Placebo groups.22 Time will be administratively censored at 90 days after randomisation or when a neonate dies or is discharged from the NICU (except in cases where a child is transferred between the study units). To improve the precision of the estimated treatment effect, the analysis will adjust for several baseline covariates.23 All of the selected baseline covariates will be included in the analysis as main effects. To account for the cluster randomisation among parent–neonate dyads with multiple gestations, the SE for the treatment effect will be estimated via a bootstrap where dyads are resampled to preserve the correlation structure. If missing data should occur, data missing at random will be assumed and the principal investigator will inform, along with exploratory analyses, the relevant covariates that correlate with missingness.

Planned secondary analyses will include the following:

1. Repeat the primary analysis where time to concordant colonisation will not be censored at 90 days after randomisation; time will be defined as the time from randomisation and NICU discharge or death.

2. Define the treatment effect as the difference in the proportion of neonates acquiring concordant S. aureus by 4 and 8 weeks into their NICU stay comparing the treatment and control groups. The analysis will adjust for the same baseline covariates as described for the primary analysis and will be based on novel methods proposed by Rotnitzky et al and described in further detail in Colantuoni and Rosenblum that improve precision of estimated treatment effects incorporating prognostic baseline covariates.24 25

3. Define outcome as acquisition of S. aureus (regardless of concordant status) using both time to acquisition and the binary indicator for any acquisition.

4. Repeating the primary analysis within strata of neonates with methicillin-resistant Staphylococcus aureus (MRSA) and those with methicillin-susceptible Staphylococcus aureus (MSSA).

5. Repeating the primary analysis within strata of neonates defined by whether or not the parent became recolonised with S. aureus during the study.

6. Repeat the primary analysis stratified by site of parent colonisation.

7. Perform a sensitivity analysis of the primary analysis accounting for gestational age, and also stratify by large or small size for gestational age.

### Monitoring

An independent, multidisciplinary DSMB will be assembled to oversee the study. The DSMB will review

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**Table 1** Frequency of neonate and parent swab collection

| Time point | Screening | Randomisation | Weeks 1, 3, 5, … | Weeks 2, 4, 6, 8, (then) 12, 16, 20, … | Time neonate acquires *Staphylococcus aureus* | NICU discharge |
|------------|-----------|---------------|-----------------|--------------------------------------|---------------------------------|---------------|
| Site       | Parent only | Neonate only | Neonate Only    | Neonate and parent                  | Neonate and parent              | Neonate and parent |
| Nares      | X          | X             | X               | X                                    | X                               | X             |
| Throat     | X          |               |                 |                                       |                                 |               |
| Umbilicus  | X†         |               |                 | X†                                   | X†                              | X†            |
| Groin      | X          | X             | X               | X                                    | X                               | X             |
| Peri-anal  | X          |               | X               | X                                    | X                               | X             |

*Parent only.
†Neonate only; the umbilicus will be tested if the neonate has an attached umbilical cord.
NICU, neonatal intensive care unit.
interim analyses after accrual of 200 and 300 neonates eligible for analysis. Interim analyses will be conducted for efficacy and futility. The DSMB will also review safety data and provide guidance about continuation, alternation or termination of the study on a periodic basis. The Institution for Clinical and Translational Research at Johns Hopkins will audit trial conduct periodically.

ETHICS AND DISSEMINATION
The research study team will obtain written informed consent for all participants. Consented participants will be assigned a screening number and a study identification number that will be the primary mode of identification throughout the study. All research staff will be instructed regarding the security of data and maintain the highest ethical standards in protocol adherence and data collection. During the course of the study, information collected will not be disclosed to anyone other than the study personnel. At the conclusion of the trial, only study staff will have full access to the final trial data set. Part of the informed consent will include an understanding that parents will be made aware of their S. aureus colonisation status. If either or both parents are colonised, parents will be informed that one or both parents are colonised, but they will not be told which parent is colonised to protect confidentiality. Also, participants will be consented to store biospecimens for future research. The study protocol and consent forms received IRB approval in June 2014. The authors commit to report data as recommend by CONSORT guidelines and findings will be published in peer-reviewed journals within 12 months of study completion and disseminated through scientific and professional conferences. Access to trial results will be provided to participants by posting results on the study website. The final trial report will link the full protocol, protocol amendments, consent form, final statistical analysis plan and laboratory methods.

PROTOCOL AMENDMENTS
All protocol changes will be submitted to the IRB and the DSMB for approval.

DISCUSSION
The TREAT PARENTS trial will test whether detection and treatment of S. aureus colonised parents with intranasal mupirocin and topical chlorhexidine bathing will decrease the risk of their infant acquiring S. aureus in the NICU, and therefore decrease infections. This study looks to shift treatment from a patient-directed approach to a parent-directed approach with the goal of eliminating or delaying a neonate’s exposure to S. aureus. Novel strategies are needed to prevent HAIs and alleviate the billions of dollars in healthcare costs and the long-term neurological disabilities in children who survive neonatal infections. The findings of this trial could change HAI prevention in the NICU from one that focuses on healthcare workers and the environment to one that recognises and highlights parents and visitors as important sources of exposure to pathogens that contribute to HAIs.

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REFERENCES
1. Klevens RM, Edwards JR, Richards CL Jr, et al. Estimating healthcare-associated infections and deaths in U.S. hospitals, 2002. Public Health Rep 2007;122:160–6.
2. Scott RD. The Direct Medical Costs of Healthcare-Associated Infections in U.S. Hospitals and the Benefits of Prevention, Second The Direct Medical Costs of Healthcare-Associated Infections in U.S. Hospitals and the Benefits of Prevention. 2009. http://www.cdc.gov/HAI/pdfs/hai/Scott_CostPaper.pdf
3. Schlapbach LJ, Aebischer M, Adams M, et al. Impact of sepsis on neurodevelopmental outcome in a Swiss National Cohort of extremely premature infants. Pediatrics 2011;128:e498–e57.
4. Stoll BJ, Hansen NI, Adams-Chapman I, et al. Neurodevelopmental and growth impairment among extremely low-birth-weight infants with neonatal infection. JAMA 2004;292:2357–65.
5. Hocevar SN, Edwards JR, Horan TC, et al. 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;33:1200–6.
6. Shane AL, Hansen NI, Stoll BJ, et al. Methicillin-resistant and susceptible Staphylococcus aureus bacteremia and meningitis in preterm infants. Pediatrics 2012;129:e914–22.
7. Ericson J, Popoola VO, Smith PB, et al. Burden of invasive Staphylococcus aureus infections in hospitalized infants. JAMA Pediatr (in press).
8. Milstone AM, Budd A, Shepard JW, et al. 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;31:558–60.
9. Jimenez-Truque N, Tedeschi S, Saye EJ, et al. Relationship between maternal and neonatal Staphylococcus aureus colonization. Pediatrics 2012;129:e1252–9.

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REFERENCES
1. Klevens RM, Edwards JR, Richards CL Jr, et al. Estimating healthcare-associated infections and deaths in U.S. hospitals, 2002. Public Health Rep 2007;122:160–6.
2. Scott RD. The Direct Medical Costs of Healthcare-Associated Infections in U.S. Hospitals and the Benefits of Prevention, Second The Direct Medical Costs of Healthcare-Associated Infections in U.S. Hospitals and the Benefits of Prevention. 2009. http://www.cdc.gov/HAI/pdfs/hai/Scott_CostPaper.pdf
3. Schlapbach LJ, Aebischer M, Adams M, et al. Impact of sepsis on neurodevelopmental outcome in a Swiss National Cohort of extremely premature infants. Pediatrics 2011;128:e498–e57.
4. Stoll BJ, Hansen NI, Adams-Chapman I, et al. Neurodevelopmental and growth impairment among extremely low-birth-weight infants with neonatal infection. JAMA 2004;292:2357–65.
5. Hocevar SN, Edwards JR, Horan TC, et al. 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;33:1200–6.
6. Shane AL, Hansen NI, Stoll BJ, et al. Methicillin-resistant and susceptible Staphylococcus aureus bacteremia and meningitis in preterm infants. Pediatrics 2012;129:e914–22.
7. Ericson J, Popoola VO, Smith PB, et al. Burden of invasive Staphylococcus aureus infections in hospitalized infants. JAMA Pediatr (in press).
8. Milstone AM, Budd A, Shepard JW, et al. 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;31:558–60.
9. Jimenez-Truque N, Tedeschi S, Saye EJ, et al. Relationship between maternal and neonatal Staphylococcus aureus colonization. Pediatrics 2012;129:e1252–9.
10. Leshem E, Maayan-Metzger A, Rahav G, et al. Transmission of Staphylococcus aureus from mothers to newborns. Pediatr Infect Dis J 2012;31:360–3.

11. Mitsuda T, Arai K, Fujita S, et al. Demonstration of mother-to-infant transmission of Staphylococcus aureus by pulsed-field gel electrophoresis. Eur J Pediatr 1996;155:194–9.

12. Sax H, Poslay-Barke K, Harbarth S, et al. Control of a cluster of community-associated, methicillin-resistant Staphylococcus aureus in neonatology. J Hosp Infect 2006;63:93–100.

13. Al-Tawfiq JA. Father-to-infant transmission of community-acquired methicillin-resistant Staphylococcus aureus in a neonatal intensive care unit. Infect Control Hosp Epidemiol 2006;27:636–7.

14. Barbe C, Santerne B, Lemartelleur L, et al. Prevalence of meticillin-resistant Staphylococcus aureus in expressed breast milk in a neonatal intensive care unit. J Hosp Infect 2008;69:195–7.

15. Behari P, Englund J, Alcasid G, et al. Transmission of methicillin-resistant Staphylococcus aureus to preterm infants through breast milk. Infect Control Hosp Epidemiol 2004;25:778–80.

16. Gastelum DT, Dassey D, Mascola L, et al. Transmission of community-associated methicillin-resistant Staphylococcus aureus from breast milk in the neonatal intensive care unit. Pediatr Infect Dis J 2005;24:122–4.

17. Pinter DM, Mandel J, Hulten KG, et al. Maternal-infant perinatal transmission of methicillin-resistant and methicillin-sensitive Staphylococcus aureus. Am J Perinatol 2009;26:145–51.

18. Morel AS, Wu F, Della-Latta P, et al. Nosocomial transmission of methicillin-resistant Staphylococcus aureus from a mother to her preterm quadruplet infants. Am J Infect Control 2002;30:170–3.

19. Conceicao T, Aires de Sousa M, Miragaia M, et al. Staphylococcus aureus reservoirs and transmission routes in a Portuguese Neonatal Intensive Care Unit: a 30-month surveillance study. Microb Drug Resist 2012;18:116–24.

20. Popoola VO, Budd A, Wittig SM, et al. Methicillin-resistant Staphylococcus aureus transmission and infections in a neonatal intensive care unit despite active surveillance cultures and decolonization: challenges for infection prevention. Infect Control Hosp Epidemiol 2014;35:412–18.

21. Popoola VO, Milstone AM. Decolonization to prevent Staphylococcus aureus transmission and infections in the neonatal intensive care unit. J Perinatol 2014;34:895–10.

22. Pocock SJ, Clayton TC, Altman DG. Survival plots of time-to-event outcomes in clinical trials: good practice and pitfalls. Lancet 2002;359:1686–9.

23. Tsiatis AA, Davidian M, Zhang M, et al. Covariate adjustment for two-sample treatment comparisons in randomized clinical trials: a principled yet flexible approach. Stat Med 2008;27:4658–77.

24. Colantuoni E, Rosenblum M. Leveraging prognostic baseline variables to gain precision in randomized trials. Stat Med 2015;34:2602–17.

25. Rotnitzky A, Lei Q, Sued M, et al. Improved double-robust estimation in missing data and causal inference models. Biometrika 2012;99:439–56.