INFECTIOUS OUTCOMES ASSOCIATED WITH AN ACTIVE SURVEILLANCE CULTURE AND DECOLONIZATION PROGRAM IN THE NEONATAL INTENSIVE CARE UNIT

by

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ABSTRACT

Active surveillance culture (ASC) and decolonization programs aim to reduce the risk of infection in the MRSA-colonized individual as well as to reduce the risk of MRSA transmission from patient to patient. The impact of the approach on transmission risk in MRSA-endemic settings is unclear. Furthermore, there is concern that the use of a selective antibiotic for decolonization treatment may increase gram-negative bacilli infection risk. The goal of this work was to inform the use of ASC and decolonization in the neonatal intensive care unit (NICU).

We first present a review of methodologic approaches to the study of healthcare-associated infectious outcomes. We review some of the challenges inherent in this type of data. Methodologic approaches that address these challenges as well as maximize our ability to draw inference from longitudinal data are presented.

In a single-center study, we used Poisson regression to estimate the risk of unit MRSA acquisition associated with time-varying exposure to decolonized and non-decolonized MRSA carriers. We found that each person-day of exposure to a non-decolonized MRSA carrier was associated with a 6% increase in MRSA acquisition risk (1.06, 95% confidence interval [CI]: 1.01-1.11). Risk of acquisition was not influenced by exposure to treated, isolated MRSA carriers (RR=1.01, 95% CI: 0.98-1.04). In a multi-centered study, we used a mechanistic modeling approach to validate these findings. We confirmed that decolonized MRSA carriers did not pose a transmission risk to other unit neonates (daily transmission probability=6.0 x10^-6 (95% credible interval: 3.5x10^-8 -1.0x10^-4), but also found that the process of identifying and placing MRSA carriers on contact precautions, alone, was associated with a near-complete reduction in
transmission risk (transmission probability=2.7x10^{-5}, 95% credible interval: 1.0x10^{-6}-2.2x10^{-4}). In both analyses, a substantial portion of unit-based MRSA acquisition could not be explained by patient-to-patient transmission.

Decolonization treatment was associated with a decreased risk of infection with select gram-positive organisms (HR=0.36, 95% CI: 0.17-0.76), as intended, but was not significantly associated with risk of infections with gram-negative organisms (HR=1.05; 95% CI: 0.42-2.62).

We provide evidence that ASC and decolonization programs are a safe and effective strategy for MRSA control in the NICU.
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TABLE OF CONTENTS

ABSTRACT ........................................................................................................................................................ ii

ADVISERS AND READERS ................................................................................................................................ iv

ACKNOWLEDGEMENTS ..................................................................................................................................... v

TABLE OF CONTENTS ..................................................................................................................................... vii

LIST OF TABLES ................................................................................................................................................ x

LIST OF FIGURES .............................................................................................................................................. xi

CHAPTER 1: Introduction and literature review ............................................................................................. 1

  1.1 Epidemiology of Staphylococcus aureus in neonates ............................................................... 1
  1.2 Active surveillance culture and decolonization programs ......................................................... 2
  1.3 Potential for mupirocin-driven microbiome reconstitution with gram-negative pathogens ......................................................................................................................... 3
  1.4 Methodologic challenges .............................................................................................................. 5
  1.5 Overview of dissertation ............................................................................................................. 5
  1.6 References ...................................................................................................................................... 7

CHAPTER 2: Expanding the statistical toolbox: Analytic approaches for cohort studies with healthcare-associated infectious outcomes ..................................................................................................... 12

  2.1 Abstract ............................................................................................................................................. 12
  2.2 Introduction ...................................................................................................................................... 13
  2.3 Logistic regression .......................................................................................................................... 13
  2.4 Poisson regression .......................................................................................................................... 15
  2.5 Survival models ............................................................................................................................. 16
  2.6 Mechanistic models ....................................................................................................................... 20
  2.7 Conclusion ...................................................................................................................................... 22
  2.8 Key findings ...................................................................................................................................... 24
CHAPTER 3: MRSA acquisition risk in an endemic NICU setting with an active surveillance culture and decolonization program ............................................................. 34

3.1 Abstract ............................................................................................................... 34
3.2 Introduction ........................................................................................................ 36
3.3 Methods .............................................................................................................. 37
   3.3.1 Study design and population ....................................................................... 37
   3.3.2 Infection control and prevention program .................................................. 37
   3.3.3 Definitions and data collection ................................................................... 38
   3.3.4 Exposure calculation ................................................................................... 39
   3.3.5 Analysis ...................................................................................................... 39
3.4 Results ................................................................................................................ 40
3.5 Discussion ........................................................................................................... 42
3.6 References .......................................................................................................... 51

CHAPTER 4: The impact of active surveillance culture and decolonization programs on NICU MRSA transmission: A multicenter, mechanistic modeling approach ............ 54

4.1 Abstract ............................................................................................................... 54
4.2 Introduction ........................................................................................................ 56
4.3 Methods .............................................................................................................. 57
   4.3.1 Data collection ............................................................................................ 57
   4.3.2 Model .......................................................................................................... 58
   4.3.3 Model assumptions ..................................................................................... 59
   4.3.4 Estimation ................................................................................................... 60
   4.3.5 Model assessment ....................................................................................... 60
4.4 Results ................................................................................................................ 61
4.5 Discussion ........................................................................................................... 63
4.6 Supplementary material ...................................................................................... 75
4.7 References .......................................................................................................... 77
LIST OF TABLES

Chapter 2.
Table 1. Approaches to longitudinal analysis of healthcare-associated infectious outcomes

Chapter 3.
Table 1. Patient characteristics by MRSA surveillance culture status
Table 2. Relative risk of MRSA acquisition per one unit increase in person days of exposure to mupirocin treated and untreated carriers

Chapter 4.
Table 1. Study site characteristics
Table 2. Parameter values by study site
Supplementary Table 1. Parameter estimate sensitivity to prior values
Supplementary Table 2. Parameter Gelman Rubin statistic by site & prior values

Chapter 5.
Table 1. Study site description
Table 2. Characteristics of study population
Table 3a. Clinical characteristics associated with risk of gram-positive cocci infection among MRSA-colonized neonates eligible for mupirocin treatment (Analysis 1)
Table 3b. Clinical characteristics associated with risk of gram-negative bacilli infection among MRSA-colonized neonates eligible for mupirocin treatment (Analysis 2)
LIST OF FIGURES

Chapter 2.

Figure 1. Summary of study designs for healthcare-associated infectious outcomes...... 26

Chapter 3.

Figure 1. Two-week snapshot of MRSA colonization pressure in the NICU ............... 48

Figure 2. Study flowchart .............................................................................................................. 49

Figure 3. Quarterly incidence rate of MRSA colonization acquisition during study period ........................................................................................................................................ 50

Chapter 4.

Figure 1. Assessing transmissibility of MRSA colonized neonates ............................. 71

Figure 2. Epidemiologic curves by study site ........................................................................ 72

Figure 3. Attribution of MRSA cases to acquisition mechanisms .................................... 73

Figure 4. Odds ratios of detection and decolonization ...................................................... 74

Chapter 5.

Supplementary Figure 1. Heatmap for unadjusted hazard ratios from individual Cox proportional hazards models ........................................................................................................ 97
CHAPTER 1

Introduction

1.1 Epidemiology of Staphylococcus aureus in neonates

The Centers for Disease Control and Prevention (CDC) reports that approximately 1.7 million healthcare associated infections (HAIs) occur per year[1], costing approximately 10 billion dollars[2]. Of these infections, 33,000 occur in neonatal intensive care units (NICUs)[1]. Results of a national point prevalence survey indicated that 11% of NICU patients had an HAI on the day of survey[3]. NICU patients are particularly vulnerable to HAIs due to naive immune systems, incomplete bacterial microbiome development, poor skin integrity, and frequent use of invasive devices[4,5]. Circulating pathogens in the NICU are associated with high levels of pathogenicity and antibiotic resistance due to ongoing exposure to selective pressures[4]. Early infections among NICU patients have been associated with poor growth and neurodevelopmental outcomes into childhood[6,7].

*Staphylococcus aureus* is the second most common cause of HAIs in the hospitalized neonates[8]. Mortality as high as 25% has been reported for *S. aureus* infections[9]. In contrast to the notably decreasing incidence of *S. aureus* infections in adult intensive care units[10], *S. aureus* incidence in the NICU has only shown moderates declines[11], highlighting the need for preventative strategies and improved understanding of the transmission dynamics of this organism.

Much of the work on NICU *S. aureus* has focused on methicillin-resistant *S. aureus* (MRSA). Since MRSA was recognized as a high priority NICU pathogen in the 1980s, the rising proportion of Staphylococcus infections due to MRSA as well as the significant morbidity and health care costs associated with this organism have prompted a
large amount of infection prevention work in the NICU setting[12]. In more recent years, methicillin-sensitive \textit{S.aureus} has garnered increased attention as it has been found to have similar mortality rates as MRSA in the NICU and has a higher overall burden of infection and death[11]. Nonetheless, MRSA remains a high priority target in the NICU as neonates are particularly vulnerable to MRSA colonization and infection[12]. MRSA isolates have displayed resistance primarily to two classes of antibiotics: beta-lactamase resistant penicillins and cephalosporins, prompting the Centers for Disease Control and Prevention to designate it as a ‘serious’ threat in a 2013 report on antimicrobial resistance in the US[13].

1.2 Active surveillance culture and decolonization programs

MRSA colonization plays two important roles in the epidemiology of MRSA infection. First, colonization has been shown to be a precursor to infection[14–16]. Second, in a hospital environment, colonized individuals contribute to unit colonization pressure (also called colonization prevalence). Increasing colonization pressure has been associated with an increased risk of MRSA transmission[17–19]. Active surveillance culture and decolonization (also called targeted decolonization) programs aim to prevent progression to infection in MRSA-colonized patients as well as to prevent transmission events from a colonized to non-colonized patients, typically via healthcare worker or environmental vectors [20]. The active surveillance, or targeted, component of these programs involves ongoing, typically weekly, screening to identify asymptomatic MRSA carriers on a unit. Identified MRSA carriers would then be placed on contact precautions and treated with antimicrobials to reduce or eliminate carriage.
The most common agent used for decolonization treatment in neonates is mupirocin[21], a topical antibiotic ointment typically administered intranasally, twice a day for five days. Mupirocin (pseudomonic acid A) is effective against gram-positive organisms (Staphylococcal and Streptococcal species), but its activity against many gram-negative pathogens (e.g. *Escherichia coli*, *Klebsiella* spp., *Serratia* spp., *Pseudomonas* spp.) is poor [22,23].

Reduced infection risk among decolonized carriers has been demonstrated in the NICU[24,25], but the impact on MRSA transmission is less clear, particularly in non-outbreak scenarios [20,26]. NICU MRSA rates have declined after the implementation of decolonization strategies in pediatric populations[27–29], but ongoing MRSA acquisition has raised questions about whether decolonization can effectively neutralize transmission risk from patient reservoirs and prevent MRSA acquisition in the NICU [29–31].

1.3 Potential for mupirocin-driven microbiome reconstitution with gram-negative pathogens

The primary intention of a decolonization program is the manipulation of the skin microbiome in a manner that reduces bioburden of potential pathogens, typically MRSA, without substantial disruption to a diverse microbial ecology that may confer protection against pathogen introduction [32,33]. In the past decade, there has been mounting concern that the use of mupirocin, a topical antibiotic that has activity preferential to gram-positive organisms, could result in selection for organisms not covered by the decolonizing agent or could cause significant disruption of the protective microbiome, placing decolonized individuals at increased risk of infection[20,34–36]. The disruptive effect of antibiotics has been widely documented in the gut microbiome literature[37].
Similarly, disruption in skin microbiota could shift the availability of resources and reduce bacterial competition, allowing for organisms introduced from the environment to successfully invade[38]. Of the organisms not covered by mupirocin’s spectrum of activity, the gram-negative bacilli are of particular concern. Gram-negative pathogens of interest in the NICU include the Enterobacteriaceae (e.g. *Klebsiella* spp., *Serratia* spp., *Enterobacter* spp., *Escherichia coli*) as well as other gram-negative bacilli (*Pseudomonas* spp., *Acinetobacter* spp.)[39]. These organisms have been responsible for a number of high-profile outbreaks in NICU settings both in the US and internationally[40] and are a leading cause of healthcare-associated infections[8,41]. Treatment of these infections can be challenging as gram-negative pathogens can potentially harbor multiple antibiotic resistance determinants and the optimal treatment regimens for these resistant organisms have not been well established in neonates[40,42]. Gram-negative organisms have been identified in neonatal nares[43,44] and this colonization has been associated with subsequent infection[45]. Thus, overgrowth and infection of gram-negative pathogens through mupirocin-driven loss of competing bacteria is a biologically plausible unintended outcome. A meta-analysis of adult patients found an increased risk of infection with non-*S. aureus* organisms, including gram-negatives, after mupirocin decolonization treatment[36]. Overgrowth with non-susceptible organisms after topical antibiotics have also been reported in patients treated with triple antibiotic ointments[46]. Ensuring that mupirocin-based decolonization is not detrimentally shifting unit microbial dynamics in favor of these non-targeted, gram-negative pathogens will be an important step in ensuring the safety of this approach.
1.4 Methodological challenges posed by healthcare-associated infection data

Healthcare data both confer tremendous capacity to improve our infection prevention strategies along with substantial methodological challenges and limitations. Exposure and outcome data is often accessible through electronic health record systems as well as through surveillance data collected by hospital infection control departments. The NICU is a unique setting in which to study healthcare-associated infections in that infections and their determinants are largely observable, as neonates often transition from a sterile intrauterine environment directly to a hospital unit, thereby largely avoiding the complexities of outpatient exposures.

However, there are substantial challenges inherent in the study of healthcare-associated pathogen acquisition. First, a patient’s infection or pathogen acquisition risk is highly depended on the infection (or colonization) status of other admitted patients. Dependent outcomes, when not accounted for, violate the assumptions of many commonly used regression approaches[47,48]. In addition, when asymptomatic colonization is a variable of interest, the best data available is typically weekly surveillance screening. This interval-censored data requires assumptions about when, in a seven day interval, transmission events occur[47]. Finally, many of the exposures that are of primary interest (e.g. antibiotic exposure, exposure to other colonized patients) are time-varying and require special consideration in statistical models[49].

1.5 Overview of dissertation

In two surveys of US NICUs, approximately one third of surveyed NICUs reported attempting decolonization for MRSA control[50,51]. In addition, some have proposed forgoing the screening component of an ASC and decolonization in favor of universal
decolonization, where all patients receive decolonization treatment irrespective of carriage status[52]. Given the substantial uptake of this strategy in neonatal intensive care units and the potential for expansion of the approach, it is essential to ensure that it is working as intended, both in terms of MRSA control and its impact on other unit pathogens.

Chapter 2 reviews the methodologic approaches to study pathogen acquisition in the healthcare setting and explores methods to overcome some of the analytic challenges posed by hospital-based infection data. Chapter 3 presents a single-centered assessment of the impact of an ASC and decolonization strategy on transmission risk in the NICU. Chapter 4 builds upon this work in a multi-centered approach that directly addresses many of the methodologic challenges identified in Chapters 2 and 3. In this analysis, we were able to make inferences about the effectiveness of the program in regards to its components, specifically addressing the role that contact precautions plays in altering transmission risk. Finally, in Chapter 5, we report the risk of gram-negative bacilli infections after mupirocin-based decolonization treatment to inform potential unintended consequences of this approach in the NICU setting.
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CHAPTER 2

Expanding the statistical toolbox: Analytic approaches for cohort studies with healthcare-associated infectious outcomes

Rebecca A. Pierce, Justin Lessler, and Aaron M. Milstone

2.1 Abstract

Purpose of review: Healthcare-associated infections (HAIs) are a leading cause of adverse patient outcomes. Further elucidation of the etiology of these infections and the pathogens that cause them has been a primary goal of research in infection control and healthcare epidemiology. Longitudinal studies, in particular, afford a range of statistical methods to better understand the process of pathogen acquisition or HAI development. This review intends to convey the scope of available statistical methodology.

Recent findings: Despite the range of methods available, logistic regression remains the dominant statistical approach in use. Poisson regression, survival methods, and mechanistic (mathematical) models remain underutilized. Recent studies that use these approaches are looking beyond associations to answer questions about the timing, duration, and mechanism of infectious risk.

Summary: Logistic regression remains an important approach to the study of healthcare associated infections, but in the context of cohort studies, it is most appropriate for short observation periods, where mechanism is not of primary interest. Additional statistical methodologies are available to build upon risk factor analysis to better inform the process of risk and infection in the hospital setting.

Key words: Healthcare-associated infection; logistic regression; Poisson regression; survival analysis; mathematical models
2.2. Introduction

Healthcare-associated infections (HAIs) are a major threat to patient safety. A large literature exists on the etiology of HAIs, the transmission dynamics and risk factors for acquiring specific healthcare-associated pathogens, and the impact of interventions to prevent HAIs and organism transmission. Most available data are from observational cohort studies. Randomization of hospital and patient-level exposures is often not feasible or presents ethical dilemmas. A number of statistical approaches are available for longitudinal data, and each method can inform distinct aspects of the infection or colonization process. Logistic regression is the most frequent method of analysis. Other methods include Poisson regression, survival analyses, or mechanistic (mathematical) models. Below we discuss approaches to the analysis of data from cohort studies and important considerations for each approach.

2.3. Logistic regression

Commonly employed to analyze case-control studies, logistic regression (LR) has many other applications. Its use in healthcare epidemiology is widespread as it is easily performed and interpreted by the infection control community. In a review of observational studies published in 2014 from two major journals within the field (American Journal of Infection Control and Infection Control and Hospital Epidemiology), almost half (43%) reported longitudinal cohort designs for the study of HAI occurrence or pathogen-acquisition, as opposed to case-control or interrupted time series studies. Of these cohort studies, 63% used LR for the primary analysis (Figure 1).
However, three important limitations require consideration when using LR for cohort studies in healthcare epidemiology.

First, LR necessitates the classification of outcomes (e.g. infected or not infected) at some arbitrary point in time (e.g. by time of discharge). This approach informs whether or not an event occurred, as opposed to when an event occurred [1,2]. There are many scenarios where the timing of an event will have important implications and could be of primary interest. Consider the demonstrated impact of antibiotic exposure and risk of *Clostridium difficile* infection [3*]. In this case, we know the *if*, what we are missing is the *when*. The primary question of interest then may not be “is antibiotic exposure associated with infection?”, but instead “what antibiotics or patterns of antibiotic treatment are associated with faster progression to infection?” or “when is the period of highest risk post-exposure?” [4**]. These questions are not answered easily with LR.

Second, simple LR does not account for the change in risk imposed by an exposure over time. For example, risk factors and causative pathogens for early-onset sepsis in neonates (0-3 days of life) are notably different than those for late-onset sepsis (4-120 days of life), with the former associated with vertical transmission processes and the latter with hospital exposures [5]. Thus, without awareness of these time-dependent trends, a risk factor analysis for all sepsis types by time of discharge could be misleading.

Finally, LR does not account for varying lengths of stay (LOS) typically observed in a cohort of hospital patients. Investigators will often address this by adjusting for LOS in multivariable models to improve comparability of exposed and unexposed patients [6–8]. When doing so, investigators must carefully consider the composition of comparison groups at different time points during follow up. Comparisons made among those with a
prolonged length of stay may differ from those made early in follow up among a potentially more heterogeneous group of individuals who have not yet been removed from observation through death or discharge. In addition, LOS may be a common effect of a risk factor and healthcare-associated infectious outcome and not a confounder of the association [9–12]. Therefore, conditioning for LOS in LR, although intuitive, may introduce bias [9,13,14].

In general, results from LR may approximate those from alternative time to event approaches described below when the following conditions are met: the outcome event is rare, effect size is weak, and the follow-up period is short [15**,16]. These conditions are unlikely to hold in many scenarios, particularly in the context of prolonged hospital stays or outbreaks. Therefore, an LR approach to hospital-based longitudinal studies is best applied to research questions targeting narrow time windows, in which risk is constant. Below we suggest alternative approaches to the analysis of data from cohort studies along with recommendations for their use. Though complexity increases with each of these approaches, overcoming obstacles inherent in hospital data is important to advance the science of infection prevention.

2.4. Poisson regression

Poisson regression models can approximate estimates obtained from logistic or log-binomial regression models [17,18]. Unlike LR, Poisson regression can account for time under observation by including a denominator of person-time at risk. These Poisson models estimate incidence rates that inform how quickly events are occurring in the population and account for each individual’s contribution to person-time [19]. A
common approach is to analyze aggregated numbers of events and total person-time. For example, Iwamoto et al. [20*] used a combination of Methicillin-resistant Staphylococcus aureus (MRSA) infection data from the Active Bacterial Core Surveillance system and US census-based person-time estimates and then applied Poisson regression to estimate changes in rates over time. Poisson regression can also be used with individual-level data [4**]. The Poisson model is highly adaptable and can be fit in a manner that mimics survival approaches (discussed below) [21].

The Poisson model has strict assumptions about the variability in event frequency that must be considered [19]. Hospital data often include rare events with greater variability than the model allows. This is particularly problematic when multiple mechanisms, some of which are not easily measured, are responsible for the variability in the outcomes. For instance, acquisition of MRSA in a neonatal intensive care unit may be related to healthcare worker-mediated transmission directly to neonates, healthcare worker-mediated patient-to-patient transmission, parent-mediated transmission to neonates, or spread from contaminated products or environment. If we cannot account for the mechanisms underlying transmission, a Poisson model may output misleading standard errors that underestimate the true variability and may impact inference [19,22]. This phenomenon is referred to as overdispersion and can be overcome through the use of negative binomial or quasi-Poisson regression models [19].

### 2.5. Survival models

Survival analysis is a powerful tool for analyzing the occurrence of HAIs or pathogen acquisition as well as the timing of these events [23]. Survival models can be
particularly informative when risk of the outcome changes over time or is influenced by an exposure that changes over time. For hospital infection data, there is usually a time origin, often hospital or unit admission, that marks the beginning of the time a person is at risk for the outcome. In survival models, the time origin guides alignment and comparison of individuals with the same time at risk for the event of interest. We then can assess the likelihood, or hazard, of an event given survival to that point (i.e. being event-free and still under observation) [24].

Cox regression is a widely used survival model that makes no assumptions about the underlying hazard (which can vary over time) but assumes that the hazard ratio is constant over time. Latibeaudiere et al. [25**] assessed the hazard of *Acinetobacter baumannii* infection over the duration of admission among colonized versus non-colonized individuals. The findings estimated a 16 times higher hazard of infection in colonized individuals, and assumes that this effect was constant over the duration of hospitalization. Methods are available if this proportionality over time assumption is not met [26,27]. For example, by accounting for non-proportional hazards, one study was able to report the time-varying effect of race on HAI risk. Specifically, they showed that non-Hispanic black patients compared to white patients had a higher hazard of HAI around the time of admission but this effect decreased with increasing length of stay [28*]. Parametric models are a useful alternative to Cox regression when the shape of the underlying hazard is of particular interest or when modeling time-varying effects [27].

By accounting for person-time, Poisson regression can approximate survival methods by estimating the average hazard. Typically, variables representing intervals of time will be added to the model, presuming a constant hazard in those intervals. The
narrower the intervals, the more Poisson regression approximates continuous time 
survival approaches, such as Cox regression [21]. Both Poisson and Cox models have 
been used to report the time-dependent relationship between device dwell times and 
infections with consistent findings [29*–31*].

Time at risk needs to be carefully allocated in both survival analysis as well as 
Poisson regression. First, the time-varying nature of exposures is frequently overlooked 
in hospital-based analyses. Many hospital exposures, including mechanical ventilation, 
central line dwell time, and exposure to antibiotics vary over time. These variables are 
likely to be poorly characterized by their overall presence or absence and would be better 
defined by their duration, intensity, or particular timing in reference to outcome 
occurrence [32,33**]. Note that time-varying exposures differ from the time-varying 
effects of exposures discussed above [26]. For example, survival analysis was used to 
assess the effect of time-varying antibiotic exposure on incident colonization with 
fluoroquinolone (FQ)-resistant *Escherichia coli* in a long-term care facility and found 
that the receipt of amoxicillin-clavulanate after colonization with FG-susceptible *E. coli* 
was associated with increased risk of resistant colonization [34*]. This type of analysis 
can be accomplished with survival methods by constructing data in terms of person-
periods, delineated by a change in exposure status. Similarly, Brown et al. [4**] utilized 
a Poisson approach with a data structure in which each record represented one person-day 
under observation. Therefore, investigators were able to account for the time-varying 
nature of antibiotic treatment on *C. difficile* risk. With the application of the person-period 
based approaches, comes the need to account for the within-patient correlation in 
responses. This is typically accounted for during survival analysis set-up, but can also be
addressed in Poisson regression through the use of generalized estimating equations [35], which can also be used to account for facility-level clustering in multi-center studies.

Another important consideration related to allocation of person-time is accounting for time deemed by the investigator as not at risk, sometimes called immortal person-time [36]. For example, if a 48-hour rule is utilized to distinguish community-acquired cases from hospital-acquired cases, this time should not be included as at-risk time in analyses of hospital-acquired events as a patient cannot have the event within this 48 hour period. The impact of immortal person-time has typically been studied in the context of chronic conditions [33**]. It has been shown that inclusion of person-time attributed to prevalent carriers of vancomycin-resistant enterococcus (VRE) notably inflated person-time denominators and, therefore, underestimated the incidence rate of VRE acquisition [37]. Additional research is needed to assess the impact of this issue in healthcare epidemiology.

A final issue to consider in time-to-event analyses is competing risks. A competing risk is an event that will preclude the observation of the outcome. In the context of hospital infection data, proposed competing events include hospital discharge and death as HAIs are often not captured after discharge and cannot occur after death [38**,39]. This issue is of particular concern when the exposure is associated with the competing event [38**]. Consider a hypothetical study investigating the association between antibiotic exposure and risk of carbapenem-resistant Enterobacteriaceae (CRE) acquisition. Patients who receive antibiotics may have longer lengths of stay. If true, antibiotic exposure is associated with a competing event (discharge). Thus, simply censoring discharged individuals (who are less likely to be exposed to antibiotics) may
result in an underestimation of the overall effect of antibiotic exposure on pathogen acquisition as it does not account for the fact that exposed individuals are more likely to have longer stays. Approaches are available to account for competing risks in survival analysis, including the estimation of the sub-distribution hazards based on the cumulative incidence function [40] or parametric mixture models [41]. A competing risk approach may give more accurate characterization of the risk that someone will experience after an exposure or intervention. Risk estimates that do not account for competing risks are not necessarily wrong, but do have a different meaning than those that do; hence, investigators should carefully consider whether a competing risk approach is appropriate.

Importantly, all of the approaches discussed above assume independence, that an individual’s risk of pathogen acquisition in the hospital setting is independent of the colonization or infection status of others present on the unit. Due to the temporal and spatial relationships of healthcare-providers, patients, and the healthcare environment we know this assumption is often not met in the context of hospital infection data [42,43]. One way to address this issue common to all regression-type models is to account for the unit-level burden of colonization at a given time [44–46*]. Alternatively, mechanistic or mathematical models can be used as discussed below.

2.6. Mechanistic models

Mechanistic models, which include models often termed ‘mathematical models’ and agent-based models, extend purely statistical approaches with some explicit representation of the disease process. These types of models are intended to describe the spread of nosocomial pathogens and inherently address the dependency issue discussed
above by taking into account modes of transmission [47]. Mechanistic models have been
used to describe pathogen transmission dynamics or to predict the effectiveness of a
novel intervention given a range of scenarios [48**]. Models are also able to address
limitations in available data, such as interval-censored observations of colonization status
(i.e. weekly surveillance screening) or testing limitations (e.g. single anatomic site
surveillance cultures compared to multiple anatomic sites).

A number of different types of mechanistic models have been applied to the study
of HAIs. These models can be distinguished by whether they describe subgroups or
individuals, the degree to which they are data-driven, and how they incorporate random
variation in event occurrence (stochasticity) [49]. Compartmental models divide the study
population into homogenous subgroups and assess the degree of movement between
these compartments as a function of a series of differential equations. These equations
reflect what is known about the process of transitioning between stages of colonization or
infection. The aggregated impact of these transitions is estimated at the unit or population
level. One such study modeled transitions from susceptible to colonized/infected states
and found that environmental reservoirs may perpetuate transmission even when
healthcare worker and patient reservoirs are no longer a factor, highlighting the need for
thorough environmental disinfection [50].

Other approaches, such as agent-based models, explicitly represent the individual
by accounting for heterogeneity in the model actors and characterizing the spatial aspects
of transmission. Often these models simulate transmission for a set of parameters
informed by available data or prior literature [51,52*]. Highly data-driven approaches
typically involve the estimation of unknown parameters (e.g. transmission rate) by fitting
models directly to empirical data [49]. Finally, models can also be distinguished by the degree of stochasticity that is incorporated. In healthcare epidemiology, stochastic models are typically used to account for the role of chance in transmission processes within hospital units of relatively small sample size [49]. Markov process models form the basis of many stochastic approaches. A particular subtype, hidden Markov models, are particularly useful in the study of pathogen acquisition, as they can account for the largely unobserved process of transitioning from a non-colonized to colonized state [42,53,54].

Mechanistic approaches have been widely used in infectious disease epidemiology and are an ideal alternative to models that make assumptions that cannot hold under contagion-based processes. Careful crafting of models requires appropriate expertise in modeling methods and healthcare epidemiology. Collaboration is key to produce the most informed and appropriately fit models of healthcare-associated transmission [47,55]. Additional considerations for mechanistic approaches are discussed in Table 1.

2.7. Conclusion

There are numerous methodologies available for the analysis of epidemiologic cohort data. Poisson regression and survival analysis are able to exploit the highly granular nature of hospital-based data through the incorporation of time at risk, the ability to address time-varying exposures, and the flexibility to account for a hazard of infection or colonization that changes over time. Mechanistic models, though more complex in their development, offer benefits when compared to many out of box solutions in that they explicitly account for and model uncertainty in the transmission process. Although
over-utilized in some contexts, logistic regression remains an important tool for risk factor analyses over short observation periods. The continued morbidity and mortality associated with HAIs and the threat posed by continually emerging, increasingly-antibiotic resistant organisms make uncovering etiology and intervening a priority. We hope that investigators will take full advantage of the data and statistical resources available to address these challenges.
2.8. Key findings

- Cohort studies represent a large portion of investigations of healthcare-associated infectious outcomes. Despite the range of statistical methods available for longitudinal studies, logistic regression remains the dominant approach.

- Poisson models and survival analysis provide the opportunity to assess variation in time to the event of interest as well as address data complexities, such as time-varying exposures, time-varying hazards, and competing risks.

- Mechanistic models explicitly characterize the infection process, are able to account for the uncertainty in our measurements and observations, and can be flexibly modified to assess the impact of interventions or exposures for strategic purposes.

- Healthcare-associated infections remain a major threat to patient safety. Statistical methodologies are available to assess etiology of infection or colonization, inform transmission dynamics, and determine the impact of novel interventions.
<table>
<thead>
<tr>
<th>Model</th>
<th>Strengths</th>
<th>Considerations</th>
<th>Solutions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Logistic Regression</td>
<td>Easily performed in statistical packages</td>
<td>Does not allow for assessment of variation in time to event</td>
<td>Consider Poisson regression, survival approaches, or mechanistic models</td>
</tr>
<tr>
<td></td>
<td>Highly interpretable output</td>
<td>Exposure typically classified as time-fixed</td>
<td></td>
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<tr>
<td></td>
<td></td>
<td>Does not consider censoring or varying contributions of person-time</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Model overfitting should be avoided in the context of small sample sizes or sparse events</td>
<td></td>
</tr>
<tr>
<td>Poisson Regression</td>
<td>Easily performed in statistical packages</td>
<td>Has stringent distributional assumptions about variability of count data that may not hold</td>
<td>Test for over/under dispersion</td>
</tr>
<tr>
<td></td>
<td>Can be used for binary or count, aggregated or individual data</td>
<td>Overdispersed data will result in inaccurate standard errors, which can impact inference</td>
<td>Consider negative binomial models</td>
</tr>
<tr>
<td></td>
<td>Allows for inclusion of at-risk person-time</td>
<td>Model overfitting should be avoided in the context of small sample sizes or sparse events</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Can approximate survival approaches</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Does not require clear time origin as is necessary for survival methods</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Can be modeled to incorporate time-varying effects &amp; time-varying exposures</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Survival Methods</td>
<td>Easily performed in statistical packages</td>
<td>Requires indexing from a time origin when a meaningful time origin may not be present</td>
<td>Consider Poisson models that do not require a time origin and can accommodate grouped data</td>
</tr>
<tr>
<td></td>
<td>Allows for assessment of time to event</td>
<td>Cannot be used with non-individual, aggregated data</td>
<td>If competing risks are of concern, subdistribution hazards approach or mixture models can be used</td>
</tr>
<tr>
<td></td>
<td>Can be modeled to incorporate time-varying effect of exposure (non-proportional hazard)</td>
<td>Requires removal of immortal person time</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Can account for competing risks</td>
<td>Model overfitting should be avoided in the context of small sample sizes or sparse events</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Can incorporate time-varying nature of exposures</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mechanistic Models</td>
<td>Can more flexibly characterize the infection process, not restricted by model assumptions</td>
<td>Consider interaction between actors in model</td>
<td>Consider and account for facility-specific factors</td>
</tr>
<tr>
<td></td>
<td>Can fully account for the dependencies between individuals in outcome status</td>
<td>Requires epidemiologic analysis to understand mechanisms of pathogen acquisition</td>
<td>[48]</td>
</tr>
<tr>
<td></td>
<td>Can incorporate measurement uncertainty</td>
<td>Though tools are available for model implementation, computing skills required</td>
<td>Perform epidemiologic studies to inform and validate models [48,49]</td>
</tr>
<tr>
<td></td>
<td>Can address interval-based measurements of outcome status (i.e. weekly surveillance culture)</td>
<td>Model predictions should be validated</td>
<td>Consider collaboration with colleagues experienced in the application of mathematical models</td>
</tr>
</tbody>
</table>

25
Table 1. Superscript denotes that information was not addressed in text. All statistical approaches are susceptible to overfitting due to the addition of too many variables, often despite a small sample size or a small number of events. Overfitting can lead to spurious findings that cannot be replicated [56,57]. Considerations and solutions for mechanistic models.

Figure 1. Summary of study designs for healthcare-associated infectious outcomes. The following outcomes are included: healthcare-associated infections (central line-associated blood stream infection, catheter-associated urinary tract infection, ventilator-associated pneumonia, and surgical site infection) and pathogen acquisition. Analytic approaches to cohort studies with healthcare-associated infectious outcomes are presented.

Abbreviations: ITS, interrupted time series; AJIC, American Journal of Infection Control; ICHE, Infection Control and Healthcare Epidemiology
2.9. References


   Investigators performed a systematic review and metanalysis of observational studies investigating the effect of antibiotic exposure on risk for *C. difficile* infection. The majority were risk factor analyses using a case-control study approach, highlighting the need for longitudinal analyses to further elucidate the patterns and timing of exposures important for the development of *C. difficile* infection.


   Brown et al. assessed the pattern of risk for *C. difficile* infection during after after antimicrobial exposure through the use of weighted Poisson regression models. The time-varying nature of antibiotic exposure was considered as well as it's cumulative impact. Authors addressed dependency of outcomes through the inclusion of a measure of *C. difficile* burden. Through the use of this overall approach, which builds upon current survival methodologies, investigators were able to target specific times of elevated risk of *C. difficile* infection during and post-antibiotic exposure that could serve to inform intervention. In addition, the methodology used in this investigation could be applied to the study of many of time-varying exposures in the healthcare setting.


15. Buffet-Bataillon S, Saunders L, Campillo-Gimenez B, Haegelen C. Risk factors for neurosurgical site infection after neurosurgery in Rennes, France: Comparison of logistic and Cox models. American Journal of Infection Control. 2013;41(12):12901292. Authors compare the use of Cox regression to logistic regression for the analysis of risk factors for surgical site infection. Although the models target different questions (logistic regression is assessing whether an event occurred during some observation period and Cox regression, in contrast, assesses time until an event occurred), results are similar using the two methods. This may be due to a relatively short observation period and assumed complete follow up on individuals under observation. Cox regression is recommended in situations where longitudinal data is available and events are common.


This study informs trends in invasive MRSA infection through the use of Poisson regression applied to aggregated data and demonstrates lack of a downward trend among children, in contrast to that found in adults in previous studies. This highlights one of the benefits of Poisson approaches, that it can be applied when only aggregate data is available.


Investigators assessed time to Acinetobacter baumannii infection according to colonization status. Multivariable Cox regression models were used. Variation in risk based on the timing of surveillance culture was considered. Acinetobacter baumannii colonization was identified as an important risk factor for subsequent infection and, importantly, through the use of survival approaches, authors were able to report a notable difference in the proportion of patients that were A. baumanni infection-free at 30 days of admission comparing those colonized with non-colonized individuals.


Investigators demonstrated the time-varying effect of race on HAI risk through the use interaction terms (race by time) within the context of Cox regression. They were able to demonstrate that race may be an important risk factor for HAI early in admission, but the risk imposed by race dissipates over time, perhaps implicating other mechanisms of HAI risk at later time points.

In a multi-center study Milstone et al. demonstrate the flexibility of the Poisson model to assess time-dependent effects of PICC dwell time on infectious risk. Investigators used a cubic spline approach to model fit and reported a period of elevated risk from 2 weeks post-insertion until removal.


Investigators assessed the role of PICC dwell time on venous catheter complications, both infectious and non-infectious. Poisson regression was used with catheter dwell time modeled with cubic spline terms to address the nonlinear association with complications over time, highlighting the application of Poisson regression to time-varying hazards with informative visual depictions.


The concept of immortal person time is discussed. The mishandling of immortal time in survival analyses is a common threat to validity in a number of fields. The error comes in two forms: the misallocation of person-time when exposure status changes over time and the inclusion of an 'eligibility period' or person-time in which participants cannot, by definition, have the event of interest to be included in the study. This has implications for both time-varying covariates as well as periods where patients are deemed not at risk for healthcare associated infections (e.g. 48 hour rule).

Han et al. followed a cohort of long term care patients, all of whom were colonized with fluoroquinolone-susceptible Escherichia coli and assessed the role of antibiotic exposure on the development of fluoroquinolone-resistant Escherichia coli. Authors used Cox regression, accounting for the time-varying nature of exposures and found receipt of amoxicillin-clavulanate to be a risk factor for resistant colonisation.


38. Wolkewitz M, Cooper BS, Bonten MJ, Barnett AG, Schumacher M. Interpreting and comparing risks in the presence of competing events. BMJ. 2014 Jan 3;349:g5060. A review and study of competing risks is presented in the context of hospital epidemiology. Competing risks are those that cause censoring and alter the chance of having the event of interest. Potential completing risks for studies with an outcome of HAI include death and discharge. Authors provide real data and scenario examples to demonstrate the effect of competing risks on interpretation of risk estimates. Competing risks have the most notable impact when the exposure is associated with the competing event.


44. Ajao AO, Harris AD, Roghmann M-CC, Johnson JK, Zhan M, McGregor JC, et al. Systematic review of measurement and adjustment for colonization pressure in studies


Popoola et al. review the concept of colonization pressure in a larger discussion of the motivations behind decolonization treatment for MRSA prevention. Colonization pressure remains an important mechanism of controlling for dependency of outcomes in regression-type analyses.


Authors review the effectiveness of infection control measures in the context of mathematical modeling approaches. In particular, authors focused on compartmental models. A common approach to compartmental models in the study of healthcare-associated infections is to use a vector-host model, where a vector, typically healthcare workers, facilitate the transition from an uncolonized to a colonized state. Therefore, the effect of infection control measures can be assessed by varying model parameters, such as healthcare worker decotamination expected from a hand hygiene initiative.


Barnes et al. use an agent-based model to assess the impact of hand hygiene and
environmental disinfection on multi-drug resistant organism transmission. Relative to environmental disinfection, improvements in hand hygiene compliance were associated with higher reductions in pathogen-acquisition.


CHAPTER 3

MRSA acquisition risk in an endemic NICU setting with an active surveillance culture and decolonization program

Rebecca Pierce, Justin Lessler, Victor O. Popoola, and Aaron M. Milstone

3.1. Abstract

Background. MRSA is a leading cause of healthcare-associated infections in the NICU. Decolonization may eliminate bacterial reservoirs that drive MRSA transmission.

Aim. To measure the association between colonization pressure from decolonized and non-decolonized neonates and MRSA acquisition to inform use of this strategy for control of endemic MRSA.

Methods. We conducted an 8-year retrospective cohort study in a level-IV NICU that utilized active surveillance cultures and decolonization for MRSA control. Weekly colonization pressure exposures were defined as the number of patient-days of concurrent admission with treated (decolonized) and untreated (non-decolonized) MRSA carriers in the preceding 7 days. Poisson regression was used to estimate risk of incident MRSA colonization associated with colonization pressure exposures. The population attributable fraction was calculated to assess the proportion of overall unit MRSA incidence attributable to treated or untreated patients in this setting.

Findings. Every person-day increase in exposure to an untreated MRSA carrier was associated with a 6% increase in MRSA acquisition risk (RR 1.06, 95% CI: 1.01-1.11). Risk of acquisition was not influenced by exposure to treated, isolated MRSA carriers (RR=1.01, 95% CI: 0.98-1.04). In context of this MRSA control program, 22% (95% CI:
4.0%-37%) of MRSA acquisition could be attributed to exposures to untreated MRSA carriers.

**Conclusion.** Untreated MRSA carriers were an important reservoir for transmission. Decolonized patients on contact isolation posed no detectable transmission threat, supporting the hypothesis that decolonization may reduce patient-to-patient transmission. Non-patient reservoirs may contribute to unit MRSA acquisition and require further investigation.

**Keywords.** Methicillin-resistant *Staphylococcus aureus*; decolonization; transmission; intensive care unit; Staphylococcal Infections/prevention & control
3.2. Introduction

Methicillin-resistant *Staphylococcus aureus* (MRSA) remains a major causative agent of healthcare-associated infections (HAIs) in the neonatal intensive care unit (NICU)[1,2]. NICU patients are particularly vulnerable to HAIs due to naive immune systems, incomplete bacterial microbiome development, poor skin integrity, prolonged lengths of stay, and frequent use of invasive devices[3,4]. MRSA colonization is an important precursor to infection[5–7], and risk of healthcare-associated transmission has been shown to increase as the density of colonized patients increases, a phenomenon called colonization pressure[8–11]. The prevalence of MRSA colonization upon NICU admission has been estimated at only 1.5%[6], implicating unit-acquired MRSA colonization as the likely driver of MRSA endemicity in this setting.

Active surveillance culture (ASC) and decolonization programs have been introduced as an adjunct to basic infection control strategies to target both the individual- and population-level risk associated with MRSA colonization. Decolonization not only aims to reduce infection risk in the colonized patient, but also intends to reduce the likelihood that healthcare workers’ hands or the environment become contaminated and result in transmission to other patients[8]. Reduced infection risk among treated carriers has been reported in NICU populations[12,13], but the impact on transmission is less clear, particularly for MRSA-endemic NICU settings[8,14]. Rates of MRSA have been shown to decrease after the implementation of decolonization strategies in pediatric populations[15–17]. However, ongoing MRSA acquisition in the presence of decolonization programs has been reported[17,18], raising questions about whether
decolonization can neutralize transmission risk from patient reservoirs and prevent MRSA acquisition in the NICU[19].

A survey of US NICUs found that only 37% of facilities had implemented a decolonization program for MRSA control[20], reflecting an ongoing lack of consensus regarding routine use of decolonization in endemic settings[21]. An improved understanding regarding the impact of decolonization strategies on MRSA acquisition risk will inform the ability of these programs to effectively prevent healthcare-associated MRSA acquisition. Our objective was to test the hypothesis that treated neonates no longer contribute to colonization pressure in the context of a NICU setting with a well-established infection control program and ongoing low-level endemic MRSA.

3.3. Methods

3.3.1. Study Design and Population
An observational cohort study was conducted to assess the risk of MRSA transmission while an ASC and decolonization strategy was in place. We retrospectively identified a cohort of neonates admitted to the Johns Hopkins Hospital (JHH) level IV, 45-bed NICU from April 1, 2007 to December 31, 2014. An ASC and decolonization program was in place for the entirety of the study period. The institutional review board approved this study with a waiver of consent.

3.3.2. Infection Control and Prevention Program
An ASC and decolonization program for MRSA was introduced on April 1, 2007. Laboratory methods and decolonization protocols for this population have been described previously[11,18]. Briefly, nurses obtained nasal surveillance swabs for unit neonates weekly as well as upon admission for neonates admitted from home or other hospitals to
identify MRSA carriers. Decolonization consisted of intranasal mupirocin administered twice daily for five days. Infants greater than 36 weeks gestational age or greater than 4 weeks chronological age were eligible for washing with 2% chlorhexidine gluconate (CHG)-impregnated cloths twice, 48 hours apart and infants greater than 2 months chronologic age were eligible for daily CHG washing for five days. All MRSA carriers were flagged as MRSA positive in the medical record and were placed on contact isolation until discharge. Contact isolation included donning of gown and gloves for all healthcare staff as well as visitors. In 2012, the NICU was moved to a new facility consisting only of private bays. Prior to 2012, the NICU consisted of open as well as private bays. MRSA positive neonates were placed in private rooms. Neonates who became recolonized were retreated with mupirocin.

3.3.3. Definitions and Data Collection

The primary outcome was incident MRSA colonization defined by laboratory identification of first MRSA-positive nasal surveillance culture. Neonates were at risk for incident MRSA colonization if: 1) they had no previous MRSA-positive cultures (clinical or surveillance) and 2) had at least one surveillance culture at day three or later of their NICU stay. Neonates remained at risk from day three of hospitalization until first positive test or unit discharge. Neonates with MRSA-positive cultures within two days of admission were considered prevalent cases. Once MRSA-colonized, neonates no longer contributed to at-risk person time and began contributing to treated or untreated colonization pressure as discussed below. Culture results were obtained from a computerized surveillance system (TheraDoc, Premier, Inc). Decolonization treatment was defined as dispensed mupirocin noted in an administrative database.
3.3.4. Exposure Calculation

To characterize each neonate’s unique, time-varying exposures to treated or untreated colonization pressure, we first classified the NICU stays of MRSA-colonized neonates as treated or untreated according to timing of first day of mupirocin treatment. A MRSA carrier was considered untreated from the estimated time of conversion to MRSA-colonized until the date of first treatment with intranasal mupirocin, after which they were considered treated until discharge (Figure 1). For our primary analysis, we assumed that MRSA colonization status conversion occurred on the date of culture collection for the first positive surveillance screen. Treated neonates were also on contact isolation. Untreated neonates were placed on contact isolation once flagged as MRSA positive on culture result date.

Next, for the at-risk NICU population, we enumerated neonates with concurrent admission that were classified as either treated or untreated. We defined colonization pressure variables as the number of treated and untreated patient-days in the seven days that preceded each weekly surveillance screen for incident MRSA.

3.3.5. Analysis

We compared characteristics of neonates with and without incident MRSA colonization using chi-square tests for categorical variables and Wilcoxon Rank Sum tests for continuous variables. A Poisson generalized estimating equation (GEE) with robust standard error estimation was used to account for intra-individual correlation and to estimate the relative risk of MRSA colonization acquisition per person-day increase in exposure to treated and untreated patients[22,23]. Potential confounders identified a priori included year of admission, monthly NICU staff hand hygiene compliance
(compliant events/total observations per month), the number of neonates in the NICU each day, time-updated length of stay, and whether the at-risk neonate was inborn at the JHH NICU. In order to further contextualize the role of treated and untreated MRSA carriers in overall unit MRSA-dynamics, the population attributable fraction (PAF) was used to quantify the proportion of unit acquisition associated with patient-to-patient exposures[24]. Due to the asymptomatic nature of MRSA nasal colonization, a sensitivity analysis was conducted to assess whether results were robust to changes in the estimated date of conversion to MRSA-positive between a negative and positive surveillance screen. We assessed the impact when conversion was assumed to have occurred three and five days prior to positive screen. Data were analyzed using STATA v13.1 (College Station, TX: StatCorp LP) and R v3.2.1.

3.4. Results

Of the 5,956 neonates admitted to the NICU during the study period, 4,296 had at least one surveillance culture and contributed to exposure calculations. Of the surveilled population, a total of 101 (2.4%) neonates were identified as MRSA-positive via surveillance screen, including prevalent cases identified in the first two days of admission, incident cases, and those identified after clinical MRSA infection (Figure 2). Of the 101 MRSA-colonized neonates, 63 (62%) underwent decolonization. Mean time to initiation of decolonization treatment among those treated was 4.0 days (range:1-51 days). Of the 63 decolonized neonates, 28 (44%) had a post-treatment positive surveillance culture, requiring re-treatment. MRSA-colonized neonates contributed 688 untreated patient-days and 2,459 treated patient-days of exposure time.
The at-risk population consisted of 3,783 screened neonates (100,839 patient-days) who were not found to harbor MRSA in the first two days of admission (Figure 2). Eighty-seven (2%) of the at-risk neonates met the case definition for incident MRSA colonization. Mean quarterly incidence of MRSA colonization was 0.9 per 1000 patient-days (95% confidence interval [CI]: 0.7-1.1) (Figure 3). Demographic distributions were similar among incident MRSA-positive and MRSA-negative neonates, while incident positive neonates had significantly longer lengths of stay (median 19 days vs. median 15 days, p=0.04) and were less likely to be inborn at JHH (49% vs. 58%, p<0.001) (Table 1).

Baseline risk of MRSA acquisition was 5.50 per 1,000 neonates (95% CI: 3.87-7.72). Increasing exposure to treated, isolated neonates was not significantly associated with increased transmission risk (adjusted Relative Risk[aRR]=1.01, 95% CI: 0.98-1.04). In contrast, every one person-day of increasing exposure to an untreated MRSA carrier was associated with a 6% increase in the risk of incident MRSA colonization (aRR=1.06, 95% CI: 1.01-1.11). Findings were robust when conversion to MRSA-colonized as identified by a positive surveillance screen was assumed to occur three or five days prior to culture (Table 2). None of the confounders examined, including unit census (RR=1.02, 95% CI: 0.97-1.07), length of stay (RR=1.00, 95% CI: 0.99-1.00), monthly staff hand hygiene compliance (RR=1.01, 95% CI: 0.99-1.02), year of admission (RR=0.92, 95% CI: 0.79-1.07), or inborn status (RR=0.79, 95% CI: 0.52-1.20), were significantly associated with increased transmission risk.

Twenty-two percent of overall unit MRSA acquisition was attributable to exposure to an untreated carrier (PAF=22%, 95% CI: 4.0%-37%). No significant portion
of unit acquisition could be attributed to exposure to a treated, isolated MRSA carrier (PAF=5%, 95% CI: -0.24-0.27).

We conducted a post-hoc sensitivity analysis to consider the role of contact isolation. We restricted untreated person-time to person-time contributed from the result date of first MRSA-positive culture, representing the time which a MRSA colonized individual was on contact isolation but had not received decolonization treatment. Result date was assumed to occur 24-hours post-culture collection, which is consistent with the use of CHROMagar (BD Diagnostics, Sparks, MD, USA) selective media for MRSA detection. Each person-day of exposure to untreated neonates on contact isolation was associated with a 6% increased risk of incident MRSA colonization (aRR=1.06, 95% CI:1.00-1.11), controlling for admission year, staff hand hygiene, unit census, length of stay, and inborn status.

3.5. Discussion

We report the association of colonization pressure and transmission risk from an 8-year period, during which an ASC and decolonization strategy was employed to control endemic MRSA in a NICU. Previous reports have demonstrated the strong association between unit colonization pressure and transmission risk[9–11]. Colonization pressure has been used as a metric of pathogen burden in a given healthcare space, where patients are typically classified as colonized or not colonized[25]. In the current study, we differentiated between the colonization pressure exerted by decolonized and non-decolonized neonates to ascertain the impact of decolonization on risk of transmission. Neonates who received decolonization treatment posed no detectable transmission risk, while every day of increased exposure to a colonized-untreated neonate was associated
with a 6% increase in transmission risk. This finding remained consistent when varying the estimated time of conversion to MRSA-colonized. Our models suggest that if 1000 neonates stay in the NICU for seven days with non-colonized or colonized-treated patients, approximately six MRSA acquisitions would be expected, but the presence of just one untreated carrier among them would increase expected MRSA acquisitions to nine.

Our findings validate reports of MRSA reductions after decolonization implementation from previous NICU studies[15,16], and inform our understanding of a particular mechanism at play—that decreasing MRSA prevalence or colonization pressure may reduce transmission risk. Our results are also consistent with prior mathematical modeling studies in adult patient populations. Worby et al.[26] reported that the combination of isolation and decolonization reduced transmission by 64%, with the majority of observed transmission attributed to unisolated and untreated MRSA carriers. Gurieva et al.[27] used a stochastic simulation model to assess the impact of decolonization and found that decolonization was highly effective even with imperfect efficacy in eliminating carriage.

In our study, untreated neonates accounted for 22% of NICU MRSA acquisition, leaving a substantial portion of unit acquisition that could not be explained by exposure to known patient sources. This suggests that although untreated neonates are an important reservoir for ongoing MRSA acquisition, efforts to reduce patient-to-patient transmission, including increasing decolonization compliance or improving the timeliness of decolonization, may eliminate only a fraction of MRSA acquisition. This is further evidenced by the visible decline, but not elimination of MRSA acquisition in the NICU.
during the study period (Figure 3). This background risk of acquisition, not linked to patient-to-patient transmission, has been well-described using mathematical modeling approaches[26], and has been shown to account for the majority of MRSA acquisition in adult settings[28]. Similarly, Price et al. report that only 18.9% of *S. aureus* acquisitions in an adult intensive care unit could be explained by patient-to-patient transmission when whole-genome sequencing was used[29]. Residual acquisition risk could be attributed to challenges associated with ASC and decolonization programs, most notably the low sensitivity of colonization detection by nasal culture alone[30]. Other nosocomial sources of acquisition could include: prolonged colonization of healthcare workers, organism introduction from other hospital locations, transmission from parents or visitors, and ongoing environmental contamination. Additional research is needed to prioritize these reservoirs in pediatric settings.

We investigated the role of mupirocin-based decolonization in a setting that utilized generally accepted infection control strategies, including contact isolation for MRSA positive patients. Hence, effects should be interpreted as those observed under the full infection control protocol. As decolonization treatment and contact isolation are typically linked, it is unlikely that independent effects can be quantified definitively outside of a randomized design. Our results do suggest that untreated individuals, even when on contact isolation, may pose transmission risk and that decolonization, in the presence of isolation, can reduce MRSA patient-to-patient transmission. However, given the substantial portion of unit acquisition that could not be attributed to patient-to-patient transmission, these strategies, even in combination, may not be sufficient to eradicate endemic MRSA-acquisition in the NICU.
Our study has several limitations. First, our study was limited to MRSA, despite increased recognition of methicillin-sensitive *Staphylococcus aureus* as an important NICU pathogen[31], for which decolonization strategies may be warranted[32]. Second, as is typical with characterizations of colonization pressure, our models aggregate risk over weekly intervals and therefore cannot inform the impact of variation in intensity of colonization pressure exposures during the seven-day exposure period. Additional limitations include the inability to generalize to patient populations with short length of stay and the lack of longitudinal molecular data to confirm transmission source.

In conclusion, we inform the use of decolonization for control of MRSA in an endemic NICU setting. ASC and decolonization programs can reduce the risk of acquiring healthcare-associated MRSA from MRSA carriers, particularly in settings where patient-to-patient transmission is a major driver of acquisition. Non-patient reservoirs may play an important role in endemic MRSA acquisition and warrant further investigation.
Table 1. Patient characteristics by MRSA surveillance culture status

<table>
<thead>
<tr>
<th>Patient characteristics</th>
<th>Incident Cases</th>
<th>Non-Cases</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N=87</td>
<td>N=3696</td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>N (%)</td>
<td>N (%)</td>
<td>1.00</td>
</tr>
<tr>
<td>Race</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Asian</td>
<td>0 (0)</td>
<td>108 (3)</td>
<td></td>
</tr>
<tr>
<td>Black or African-American</td>
<td>46 (53)</td>
<td>1665 (45)</td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>33 (38)</td>
<td>1499 (41)</td>
<td></td>
</tr>
<tr>
<td>Other/Unknown</td>
<td>8 (9)</td>
<td>424 (11)</td>
<td>0.26b</td>
</tr>
<tr>
<td>Ethnicity</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hispanic</td>
<td>5 (6)</td>
<td>184 (5)</td>
<td></td>
</tr>
<tr>
<td>Non-Hispanic</td>
<td>79 (91)</td>
<td>3312 (90)</td>
<td></td>
</tr>
<tr>
<td>Unknown</td>
<td>3 (3)</td>
<td>200 (5)</td>
<td>0.76b</td>
</tr>
<tr>
<td>Length of NICU stay, median (IQR)</td>
<td>19 days (33)</td>
<td>15 days (22)</td>
<td>0.04c</td>
</tr>
<tr>
<td>Inborn</td>
<td>43 (49)</td>
<td>2497 (68)</td>
<td>p&lt;0.001</td>
</tr>
<tr>
<td>Mortality</td>
<td>4 (5)</td>
<td>91 (2)</td>
<td>0.17</td>
</tr>
<tr>
<td>Unit hand hygiene compliance, median (IQR)</td>
<td>80% (24)</td>
<td>83% (29)</td>
<td>0.04c</td>
</tr>
</tbody>
</table>

Incident MRSA-positive refers to surveillance MRSA-positive neonates that met incident colonization case definition (study outcome). MRSA-negative neonates (non-cases) had negative surveillance cultures for MRSA while under observation. Neonates remained under observation until discharge or positive MRSA-culture. aLength of NICU stay includes only pre-colonization length of stay for incident cases. bP values obtained from Fisher’s Exact Test. cP values obtained from Wilcoxon Rank Sum test. d Unit hand hygiene during month of admission was compared for cases versus non-cases. Abbreviations: IQR, Interquartile range.
Table 2. Relative risk of MRSA acquisition per one unit increase in person days of exposure to mupirocin treated and untreated carriers

<table>
<thead>
<tr>
<th>Variable</th>
<th>Primary Analysis</th>
<th></th>
<th>Sensitivity Analysis</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No lag</td>
<td>3-day lag</td>
<td>5-day lag</td>
<td></td>
</tr>
<tr>
<td></td>
<td>RR</td>
<td>95% CI</td>
<td>aRR</td>
<td>95% CI</td>
</tr>
<tr>
<td>Days of exposure to untreated carrier</td>
<td>1.07</td>
<td>1.02-1.11</td>
<td>1.06</td>
<td>1.01-1.11</td>
</tr>
<tr>
<td>Days of exposure to treated carrier</td>
<td>1.01</td>
<td>0.99-1.05</td>
<td>1.01</td>
<td>0.98-1.04</td>
</tr>
</tbody>
</table>

At-risk neonates (n=3783) neonates were included in analysis. Relative risks calculated from Poisson generalized estimated equations. Exposures measured in person-days. Lag time refers to the number of days prior to each weekly surveillance screen that colonization status conversions were assumed to have occurred. Adjusted models control for year of admission, daily unit census, whether neonate was inborn at JHH, length of stay, and unit hand hygiene compliance. *Significant at p<0.05. Abbreviations: RR, unadjusted relative risk; aRR, adjusted relative risk.
Figure 1. Two-week snapshot of MRSA colonization pressure in the NICU.
Three hypothetical patients are shown. Some neonates that acquire MRSA colonization are decolonized (treated). Above we depict how neonates contribute to and are exposed to treated and untreated colonization pressure. In week 1, patients 1 and 3 are at risk for MRSA colonization and are exposed to seven days of untreated person-time from an untreated MRSA carrier (patient 2). In week 2, only patient 1 remains at-risk for incident MRSA colonization and is exposed to two days of untreated person-time (patient 3) as well as seven days of treated person-time (patient 2).
Figure 2. Study flowchart.
Flowchart detailing the population used to calculate colonization pressure exposures (left) and the at-risk population that was followed for outcome of incident MRSA colonization (right). Of the 3,783 at-risk neonates who were surveilled at least once after the first two days of admission (prevalent period), 91 neonates acquired MRSA colonization during NICU stay. Four colonization cases identified after MRSA infection, as indicated by clinical culture obtained during routine care, were not included as incident cases as colonization was assumed to be acquired through an endogenous process.
Figure 3. Quarterly incidence rate of MRSA colonization acquisition during study period.
Rates are reported per 1,000 patient-days. Figure depicts low-level, endemic transmission throughout study period. Poisson regression line shown in blue. There was not a significant downward trend in rate of incident MRSA colonization (p=0.62).
3.6. References


CHAPTER 4

The impact of active surveillance culture and decolonization programs on NICU MRSA transmission: A multicenter, mechanistic modeling approach.

Rebecca Pierce, Alexis Elward, Kristina Bryant, Aaron M. Milstone, and Justin Lessler

4.1. Abstract

Objective. The aim of this study was to assess the effectiveness of active surveillance cultures (ASC) and decolonization in reducing MRSA transmission in the neonatal intensive care unit (NICU).

Methods. Retrospective cohort data, including admission and discharge times, weekly surveillance culture results and mupirocin-administration information, were collected from three urban, tertiary care NICU in the US. The study period was 2007-2014, during which ASC and decolonization strategies were employed at study sites for MRSA control. We used Markov-Chain Monte Carlo methods to fit a probabilistic transmission model to the data. To account for the interval-censored nature of weekly surveillance screening, we used an integrated Bayesian framework to impute the date of conversion to MRSA-positive. We estimated the risk of MRSA acquisition associated with non-patient sources, undetected MRSA carriers, detected MRSA carriers on contact precautions, and MRSA carriers on contact precautions that also received decolonization treatment.

Results. Of the 12,677 neonates that were screened for nasal MRSA colonization at study sites, 533 (4.2%) had a MRSA-positive surveillance culture. Neonates with undetected MRSA colonization were estimated to be the source of 67% (95% credible interval [CI]: 0.64-0.69) of MRSA acquisition. Compared with undetected MRSA carriers, detection and placement on contact precautions significantly deceased the odds of transmission by
99.8% (odds ratio [OR]: 0.0016, 95% CI: 0.0000026-0.033), 99.6% (OR=0.0036, 95% CI: 0.0000025-0.13), and 99.8% (OR=0.0024; 95% CI: 0.00000042-0.043) at sites A, B, C, respectively. A 99.9% reduction in transmissibility was sustained among MRSA carriers who also received decolonization treatment (OR=0.0014, 95% CI: 0.0000080-0.024).

Conclusions. In this multi-centered NICU cohort, ASC and decolonization programs were highly effective in reducing transmission risk from MRSA carriers. Detection of MRSA carriers and use of contact precautions, alone, were associated with a near-complete reduction in transmission risk. Improving time-to-detection as well as prioritizing non-patient reservoirs of MRSA could further reduce MRSA acquisition in the NICU.
4.2. Introduction

Staphylococcus aureus is the second most common cause of health-care associated infections among hospitalized neonates[1]. Methicillin resistant *S. aureus* (MRSA) has been associated with significant morbidity and excess healthcare cost in the neonatal intensive care unit (NICU)[2,3]. MRSA colonization is a risk factor for subsequent MRSA infection as well as MRSA transmission in healthcare settings[4]. MRSA transmission has typically been characterized by the concept of colonization pressure, a phenomenon in which increasing unit MRSA colonization prevalence leads to an increase in colonization events[4–7]. NICU patients are at high risk for MRSA acquisition[8], which has prompted the use of active surveillance culture (ASC) and decolonization programs for MRSA control. Such programs screen for asymptomatic MRSA carriage, place MRSA carriers on contact precautions, and administer decolonization treatment. Mupirocin, a topical antibiotic, is the most common decolonizing agent in NICU settings and is typically administered intranasally, targeting a major ecologic niche for MRSA-carriage. These strategies have been shown to be effective in reducing the risk of MRSA infection in colonized neonates[9], but the impact on transmission risk is less clear in MRSA-endemic settings as ongoing acquisition has been frequently observed in the context of decolonization programs[4,10,11]. Moreover, the relative impact of detection and isolation vs. decolonization treatment, has yet to be elucidated in this population.

Mechanistic modeling approaches confer several benefits when characterizing unit-transmission dynamics. First, they can explicitly model the highly dependent nature of the transmission process. The concept of colonization pressure can be directly
accounted for by model structure, and, therefore, improve model interpretation when compared with out-of-box regression methods[12]. Second, we can address one of the fundamental limitations when characterizing patient-to-patient transmission, the imperfect observation of MRSA carriage status by surveillance cultures. MRSA colonization is typically assessed via weekly surveillance screening. To account for this, assumptions are often made about when conversion from MRSA-negative to MRSA-positive occurred, often assuming conversion occurred on date of culture or the midpoint of consecutive screens[13]. Integrated approaches to multiple imputation of missing data within a Bayesian estimation process can avoid unnecessary assumptions. In doing so, we select a colonization time for MRSA carriers that is most consistent with the data and more accurately characterize the transmission process. The goal of this work was to utilize a mechanistic modeling approach to characterize the role of ASC and decolonization programs on NICU MRSA transmission in three US, tertiary care NICUs.

4.3. Methods

4.3.1. Data Collection

We performed a retrospective analysis of data collected from three US, tertiary care hospitals in urban settings. Data was collected from 2007-2014, during which an ASC and decolonization strategy was employed for MRSA control. Two sites provided data for the entirety of the study period. Data was available from Site B from for a shorter period (2009-2013). ASC and decolonization programs included weekly nasal surveillance screening, and intranasal mupirocin administration for MRSA-positive neonates twice daily for five days. Due to imperfect compliance with the decolonization
component of the strategy, mupirocin was administered late or was not administered at all to some unit neonates. Date of mupirocin administration was obtained from administrative databases or chart review. Contact precautions were in place for MRSA-colonized neonates from date of culture result for the duration of NICU stay (Figure 1). Chlorhexidine bathing was conducted for some neonates of higher gestational ages (typically > 36 weeks), but was not documented for inclusion in this analysis.

4.3.2. Model

We used Markov chain Monte Carlo (MCMC) methods with an integrated Bayesian framework to fit a probabilistic transmission model to these data. To account for the interval censored nature of weekly surveillance screening, we imputed most likely first date of conversion to MRSA-positive given the data. Our transmission model was specified as follows:

$$\Pr(y_{it} = 1) = 1 - [(1 - \alpha)(1 - \kappa)C_{pre-ID_t} (1 - \phi)C_{post-ID_t})(1 - \beta)^{Dt}]$$

where $y_{it}$ is equal to 1 if patient $i$ has a first MRSA positive nasal surveillance screen at time at time $t$; $\alpha$ is the daily probability of acquisition from sources other than patient to patient transmission (e.g. visitor introduction, prolonged colonization of healthcare worker or the environment); $\kappa$ is the probability of becoming colonized from a MRSA colonized, not-treated neonate prior to detection of carriage status with $C_{pre-ID_t}$ referring to the number of MRSA-colonized, undetected, and untreated neonates present in the unit at time $t$; $\phi$ is the probability of becoming colonized from a MRSA carrier that has been detected but has not yet received decolonization treatment with $C_{post-ID_t}$ referring to the number detected, but not yet decolonized, neonates present on the unit at time $t$; and $\beta$ is the probability of becoming colonized from a MRSA carrier that has received
decolonization treatment with $D_t$ referring to the number of decolonized neonates present on the unit at time $t$. We used non-informative priors for $\alpha$ and $\kappa$ parameters, while moderately strong, null-directed priors were used to fit $\phi$ and $\beta$ parameters, providing conservative estimates of the effect of detection and decolonization and facilitating model convergence. Sensitivity analyses were performed to assess robustness of findings to prior values. Model parameters are reported as probabilities of MRSA acquisition scaled to 100,000 patient-days of exposure.

NICU neonates are considered at-risk for MRSA colonization from the day of admission until the imputed date of conversion to MRSA-colonized or discharge. MRSA colonized neonates were considered undetected carriers from imputed conversion date until date of culture result; detected, not decolonized from the day culture result to date of decolonization; and decolonized from the day following mupirocin initiation (Figure 1).

4.3.3. Model Assumptions

1) We limited our analysis to MRSA colonized individuals and, therefore, assumed homogeneity in transmissibility among MRSA carriers.

2) We assumed risk for colonization among non-colonized, at-risk neonates was homogenous.

3) Once MRSA-colonized, individuals were considered either undetected, detected but not decolonized (prior to mupirocin treatment), or decolonized (after first day of decolonization treatment). We continued to consider individuals decolonized after the completion of decolonization treatment irrespective of post-decolonization surveillance cultures as individuals who became recolonized were retreated. This characterization intended to estimate the transmission potential
imposed by decolonized neonates overall, accounting for the possibility that some neonates will fail treatment or that neonates remain colonized but with a bioburden that is undetectable by standard culture techniques.

4) Due to low rates of importation in NICU settings[8], we assumed that there were no neonates entering the NICU in a colonized state.

4.3.4. Estimation

Models were fit individually for each site to account for inter-site variation in MRSA dynamics and infection control practice. Each MCMC iteration randomly generated new parameter values and an augmented dataset, the later consisting of iterated colonization times between weekly observations for a randomly selected group of colonized neonates. Proposed parameter values and datasets were accepted with a probability in accordance with the relative likelihood of the proposals compared with that from the current specifications. Posterior distributions were obtained after 200,000 iterations with a 100,000 iteration burn-in period. As part of the estimation process, we calculated the probabilistic attributable fraction of MRSA acquisition for undetected, detected, and decolonized carriers, as well as the proportion attributable to background acquisition risk. In addition, we calculated the proportion of colonized-person time that was undetected as part of the conversion time imputation process. Analyses were conducted in R v3.3.3[14].

4.3.5. Model Assessment

We performed multiple MCMC runs, or chains, for each site, varying the parameter start value to ensure consistency of results. Convergence of MCMC chains was assessed visually via trace plots. In addition, the Gelman Rubin diagnostic was calculated to
assess the degree of variation within and between several chains using the Convergence Diagnosis and Output Analysis (CODA) for MCMC package[15] in R.

**4.4. Results**

MRSA acquisition rates were 1.5 (95% CI: 1.3-1.7), 3.0 (95% credible interval [CI]: 2.6-3.4), and 1.0 (95% CI: 0.9-1.2) per 1000 patient-days, for Sites A, B, and C, respectively. For Site A, an estimated 5.6% (95% CI: 5.3%-6.1%) of the total number of colonized patient days were undetected. Site B had a similar proportion of undetected MRSA carriers (6.9%, 95% CI: 6.1-7.7%), while Site C had a 13.9% (95% CI:12.9%-15.2%) estimated undetected proportion. Additional study site characteristics are provided in Table 1. Figure 2 depicts epidemiologic curves for each site, highlighting low-level endemic MRSA acquisition at Sites A (median cases/quarter=7, interquartile range[IQR]: 5-9) and C (median cases/quarter=4, IQR=2-4). Site B experienced higher levels of acquisition (median cases/quarter=11, IQR: 8-16).

Posterior estimates of parameters are shown in Table 2. Daily background acquisition probability per 100,000 patient days varied from 32.2 (95% CI: 18.6-47.5) to 91.9 (95% CI: 59.9-131.0) at study sites. Of the MRSA acquisition observed at each site, background acquisition accounted for an estimated 32% (95% CI: 23%-44%), 31% (95% CI: 24%-40%), and 31% (95% CI: 22%-38%) of MRSA colonization events, at sites A, B, and C, respectively (Figure 3).

The majority of MRSA acquisition at all sites was attributed to undetected MRSA carriers, which accounted for a 67% (95% CI: 0.64-0.69) of acquisitions across the three sites. Daily transmission probabilities per 100,000 patient-days of exposure to a MRSA
colonized neonate who had not yet been detected ranged from 369.7 (95% CI: 272.5-476.6) to 465.7 (95% CI: 345.7-606.3).

The effect of detection and placement of MRSA-colonized neonates on contact precautions is shown in Figure 4. Compared with undetected MRSA carriers, detection significantly deceased the odds of transmission by 99.8% (odds ratio[OR]: 0.0016, 95% CI:0.0000026-0.033), 99.6% (OR=0.0036, 95% CI: 0.0000025-0.13), and 99.8% (OR=0.0024; 95% CI: 0.00000042-0.043) at sites A, B, C, respectively. Minimal MRSA acquisition could be attributed to detected carriers as shown in Figure 3.

The combined effect of decolonization and detection compared to the effect of detection alone is shown in Figure 4. At all sites, it was found that the combined effect of decolonization and detection trended towards further reductions in transmissibility risk when compared to detection alone, but this finding was not significant. The average reduction in transmission risk from decolonized neonates (also on contact precautions) compared with undetected carriers across all sites was 99.9% (OR=0.0014, 95% CI: 0.0000080-0.024). The daily probability of transmission per 100,000 patient days of exposure to a decolonized neonate approached zero for all sites (Site A:0.023 (95% CI: 0.0000026-2.4); Site B: 0.13 (95% CI: 0.0000039-28.3); Site C: 0.18 (95% HDI: 0.000011-13.4).

Sensitivity to prior value specification is provided in supplementary material. Overall, results were robust when varying the strength of priors supplied to fit detection and decolonization parameters (Supplementary Table 1). Convergence statistics are provided in the supplementary material.
4.5. Discussion

Our results strongly indicate that an active surveillance culture and decolonization strategy neutralizes the transmission risk of MRSA carriers in the NICU, as demonstrated by the elimination of transmission by those detected and placed on contact precautions as well as among those who were also decolonized. The observed reduction of transmission risk was greater than what has been previously reported in adult settings, where the combination of decolonization and contact isolation was associated with a 64% reduction in transmission[16].

In addition, we note the following conclusions relevant to our understanding of overall MRSA transmission dynamics in the NICU. First, untreated, MRSA carriers, and, in particular, undetected MRSA carriers, were an important reservoir for transmission in the NICU. This confirms prior work demonstrating elevated transmission risk associated with undetected MRSA carriers in both NICU[17], and adult in-patient settings[16]. This suggests that increasing compliance and timeliness of detection, isolation, and decolonization may prevent a substantial portion of acquisition.

Second, we found that the process of identifying MRSA carriers and placing them on contact precautions, alone, achieved near-complete elimination of transmission risk. This suggests that the combination of healthcare worker behavior change associated with becoming recently aware of a patient’s MRSA status (e.g. improved hand hygiene compliance) as well the use of contact precautions may be an important component of the effectiveness of this strategy in the NICU. This is informative as there is currently debate, largely in adult inpatient settings, about the use of contact precautions for multi-drug resistant organism prevention[18]. Contact precautions have been shown to be highly
effective in reducing NICU MRSA transmission in epidemic scenarios[19]. Here, we provide evidence that detection and contact precautions reduce transmission from MRSA carriers in MRSA-endemic NICU settings. In addition, this is notable as universal decolonization programs, which typically forego the identification of MRSA carriers and, instead, provide decolonization treatment to all unit patients irrespective of carriage status, have been suggested as a way to limit the cost- and time-intensive nature of an active surveillance culture and decolonization strategy[20]. Until there is evidence that decolonization, alone, can match the reductions associated with detection and placement of carriers on contact precautions, universal decolonization programs that do not detect asymptomatic MRSA carriage should be used with caution in the NICU setting. The sustained reductions in transmissibility observed in neonates who are decolonized in addition to being on contact precautions is important as decolonization treatment failure has been estimated to occur in 10%-75% of treated adults[21] and approximately half of NICU neonates[22,23]. In addition, decolonized neonates may continue to harbor MRSA on additional body sites[24] or at a level that is undetectable by culture techniques. These results suggest that the combination of detection and decolonization is sufficient to prevent transmission from these potential latent reservoirs.

Third, the level of MRSA acquisition linked to background, non-patient to patient sources was notable, suggesting that other sources of acquisition likely play an important role. Potential non-patient reservoirs include: prolonged colonization of healthcare workers, organism introduction from other hospital locations, transmission from parents or visitors, and ongoing environmental contamination. It is possible that undetected MRSA carriers play a role in these unexplained acquisitions. However, this is unlikely to
explain all occurrences of acquisition not linked to patient reservoirs, as background sources accounted for approximately one third of MRSA acquisition at all sites, irrespective of varying degrees of screening coverage. In addition, all sites used selective chromogenic media, which have been shown to have an equivalent or higher sensitivity than standard nonselective culture techniques[25]. The important role of non-patient reservoirs for MRSA acquisition in in-patient settings has been well-documented in mathematical modeling literature[16,26], a prior single-center analysis of one of our study sites[22], and when using whole genome sequencing to link transmission events[27].

Strengths of this study include the multi-centered approach, which allowed us to assess the role of an ASC and decolonization in the context of multiple sites with distinct MRSA-transmission dynamics. We found that despite varying degrees of overall MRSA burden, program-based detection of carriers, as well as detection combined with decolonization, effectively eliminates transmissibility. An additional strength of the study use of a modeling approach that explicitly represents transmission. This highly flexible approach allowed for direct comparison of the transmissibility of undetected, detected, and decolonized MRSA carriers, facilitated the probabilistic attribution of MRSA-acquisition to background or patient-to-patient transmission mechanisms, and accounted for the interval censored nature of weekly surveillance cultures. Importantly, because contact precautions and mupirocin-based decolonization treatment were not administered concurrently in all patients, we were able to estimate the impact of detection and isolation alone as well as providing a combined effect.
This study is limited in its ability to definitively isolate the effect of decolonization alone. Instead the effect of targeted decolonization is a combined effect of mupirocin-based decolonization, detection, contract precautions, and other standard infection prevention strategies. To address this issue, we estimated the effect of detection and contact isolation, independent of decolonization and found this to be highly protective. Further research is needed to isolate the incremental benefits conferred by decolonization. This study alone is insufficient to support abandoning decolonization as it is unclear what its relative role in transmission prevention is, particularly at late stages of a NICU admission. Posterior distributions for parameters estimating the effect of detection and decolonization reached stationary, but were left-skewed due to the use of informative priors that conservatively biased estimates towards the null (i.e. having no effect on transmission) to facilitate model convergence. Due to the use of these priors, estimates of the effect of detection and decolonization should be considered conservative estimates as it is possible that they confer some additional reduction in transmission risk. We believe this is unlikely to impact findings as probability of transmission from these neonates was estimated at approximately zero even with this conservative approach. CHG bathing was used at sites for neonates with higher gestational ages and chronologic ages and may have impacted the transmissibility of unit neonates. CHG use was not documented at sites and could not be included in the current study, but it is unlikely to explain findings as site CHG guidelines recommend CHG non-differentially to unit neonates irrespective of mupirocin treatment and therefore it’s impact, if any, would likely be to obscure the ability to characterize the relative transmissibility of undetected vs. detected/decolonized MRSA carriers. An additional limitation is the characterization
of transmission events through concurrency of neonatal admissions. Though this is consistent with prior literature on MRSA transmission[28], it may overestimate the role of patient-to-patient transmission when compared with molecular methods of transmission event linkage. Finally, we estimate transmissibility from a colonized state, we do not quantify the risk imposed by infected individuals as clinical infections were rare and the degree of transmissibility from those infected at different sites (e.g. bloodstream versus wound infection) is likely heterogeneous. We believe the focus on colonized individuals is appropriate given that reducing MRSA carriage is the primary goal of decolonization strategies. Future work characterizing the heterogeneous nature of MRSA transmissibility and of MRSA acquisition risk is needed and may allow NICUs to streamline screening and decolonization to particularly high-risk neonates. Finally, this study does not characterize the impact of an ASC and decolonization on methicillin-sensitive \textit{S.aureus} (MSSA), which, when compared to MRSA, is responsible for more infections and deaths in neonatal intensive care units with a similar mortality rate.[29] The transmission dynamics of MSSA and the impact that decolonization may have on the risk of acquiring MSSA colonization requires further study.

Our analysis indicates that the detection, isolation, and decolonization of NICU MRSA carriers can eliminate their transmissibility. Ongoing acquisition of MRSA in the context of ASC and decolonization programs is explained by the combination of highly-transmissible, undetected MRSA carriers as well as non-patient-to-patient, background sources. ASC and decolonization programs are an effective strategy for MRSA control in the NICU. Future research is needed to clarify the added benefit from decolonization
treatment alone. MRSA elimination in this setting will require improved time-to-
detection as well as further elucidation of non-patient reservoirs of acquisition.
<table>
<thead>
<tr>
<th>Variable</th>
<th>Site A</th>
<th>Site B</th>
<th>Site C</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bed size</td>
<td>75</td>
<td>100</td>
<td>45</td>
</tr>
<tr>
<td>Mupirocin course</td>
<td>BID x 5 days</td>
<td>BID x 7 days</td>
<td>BID x 5 days</td>
</tr>
<tr>
<td>Admitted neonates</td>
<td>5,653</td>
<td>3,135</td>
<td>5,978</td>
</tr>
<tr>
<td>Screened neonates</td>
<td>5,376</td>
<td>2,982</td>
<td>4,319</td>
</tr>
<tr>
<td>MRSA colonized neonates</td>
<td>234</td>
<td>189</td>
<td>110</td>
</tr>
<tr>
<td>Patient-days under observation</td>
<td>155,516</td>
<td>73,615</td>
<td>105,756</td>
</tr>
<tr>
<td>Total colonized patient-days(^a) (95% CI)</td>
<td>10,306 (10,265-10,359)</td>
<td>7,252 (7,191-7,314)</td>
<td>3,576 (3,536-3,630)</td>
</tr>
<tr>
<td>Undetected patient-days(^a) (95% CI)</td>
<td>584 (543-637)</td>
<td>502 (441-564)</td>
<td>498 (458-552)</td>
</tr>
<tr>
<td>Detected patient-days(^b)</td>
<td>2,577</td>
<td>2,108</td>
<td>876</td>
</tr>
<tr>
<td>Decolonized patient-days(^b)</td>
<td>7,145</td>
<td>4,642</td>
<td>2,202</td>
</tr>
<tr>
<td>Median length of stay (days) (IQR)</td>
<td>17 (6-47)</td>
<td>15(8-32)</td>
<td>14 (8-31)</td>
</tr>
<tr>
<td>Mupirocin treatment compliance (%)</td>
<td>73</td>
<td>69</td>
<td>65</td>
</tr>
<tr>
<td>Median number of surveillance cultures per screened neonate (IQR)</td>
<td>3 (2-7)</td>
<td>3 (2-5)</td>
<td>2 (1-4)</td>
</tr>
</tbody>
</table>

\(^a\)The number of undetected and total colonized person-days were obtained through estimation process as MRSA conversion date was imputed.  \(^b\)The number of detected and decolonized person-days are fixed.  Abbreviations: IQR, interquartile range; BID, twice daily; CI, confidence interval.
Table 2: Parameter values by study site

<table>
<thead>
<tr>
<th>Study Site</th>
<th>Background Acquisition Probability (x10^5)</th>
<th>Transmission Probability From Undetected MRSA Carriers (x10^5)</th>
<th>Transmission Probability From Detected, Non-Decolonized MRSA Carriers (x10^5)</th>
<th>Transmission Probability From Decolonized MRSA Carriers (x10^5)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Site A</td>
<td>Median 48  33-66</td>
<td>Median 370  273-477</td>
<td>Median 0.6  0.00096-12</td>
<td>Median 0.023  0.0000026-2.4</td>
</tr>
<tr>
<td>Site B</td>
<td>Median 92  60-131</td>
<td>Median 448  336-583</td>
<td>Median 1.6  0.0012-58</td>
<td>Median 0.13  0.0000039-28</td>
</tr>
<tr>
<td>Site C</td>
<td>Median 32  19-48</td>
<td>Median 466  345-606</td>
<td>Median 1.1  0.0020-19</td>
<td>Median 0.18  0.000011-13</td>
</tr>
</tbody>
</table>

Parameter values scaled by 100,000 patient-days of admission in the case of background acquisition parameter. All transmission parameters shown are scaled by 100,000 patient-days of exposure to neonates in specified categories (undetected MRSA carrier, detected MRS carrier, decolonized carrier). Abbreviations: CI, 95% credible interval.
**Figure 1. Assessing transmissibility of MRSA colonized neonates.**
Hypothetical example showing how MRSA colonized neonates contribute to mutually exclusive categories of potential transmission risk. Our model estimates the relative transmissibility of neonates in these categories. Also shown is the infection prevention strategies applied during these periods.
Figure 2: Epidemiologic curves by study site.
The number of MRSA colonized neonates by quarter (according to date of first culture positive) shown. Note: Site B data available from Q3 2009 to Q1 2013, when an active screening and decolonization program was used for MRSA-control. Portion of study period for which data were not available marked in dark grey. Site C applied this strategy from Q2 2007-2014. Site A contributed data for all quarters in the study period (2007-2014).
Figure 3: Attribution of MRSA cases to acquisitions mechanisms.
Probabilistic attribution of cases to the following acquisition mechanisms: background acquisition risk, person-to-person transmission from an undetected MRSA carrier, person-to-person transmission from a detected, but not decolonized MRSA carrier, person-to-person transmission from a decolonized neonate. Median number of cases attributed to each category shown. Credible intervals represent 0.025% and 0.975% quantiles.
Figure 4: Odds ratios of detection and decolonization.
Log odds ratio of the incremental effect of detection vs. non-detection (left) and decolonization vs. detection alone (right). The effect of decolonization represents a combined effect of decolonization and detection, as neonates who receive decolonization treatment are, by definition, also detected and remain on contact precautions. Median estimates and 95% credible intervals shown. Intervals that do not cross zero indicate statistically significant reductions.
4.6. Supplementary Material

Effectiveness of active screening and decolonization programs was modeled as follows:

\[ \Pr(y_{it} = 1) = 1 - [(1 - \alpha)(1 - \kappa)^{C_{Pre-IDt}} (1 - \phi)^{C_{Post-IDt}} (1 - \beta)^{D_{t}}], \]

where,

\[ \kappa = B_0 \]
\[ \phi = B_0 + B_1 \]
\[ \beta = B_0 + B_1 + B_2 \]

Prior Value Sensitivity Analysis

Supplementary Table 1 shows parameter values by site and prior set. Three sets of priors were used, all providing varying degrees of conservative estimates of the effect of detection (B1) and decolonization + detection (B2). Prior values varied from weakly informative (N(0,10)) towards the null hypothesis of no effect of detection and decolonization + detection to strongly informative (N(0,1)). Moderate strength priors were reported as primary findings (N(0,5)). Width of high density intervals increased with decreasing prior strength, but findings were consistent across prior value sets.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Prior Value Set 1</th>
<th>Prior Value Set 2</th>
<th>Prior Value Set 3</th>
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<td>N(0,1000)</td>
<td>N(0,1000)</td>
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75
Model Convergence

Model convergence was assessed by Gelman Rubin statistic and by visual inspection of trace plots. We ran four chains per site per set of prior values. Gelman Rubin statistic values remained below 1.1 for all sites and prior value sets (Supplementary Table 2).

<table>
<thead>
<tr>
<th>Prior Value Set 1</th>
<th>Parameter Value</th>
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<th>Total - (log likelihood)</th>
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<td>Median 1.00</td>
</tr>
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<td>Site C</td>
<td>Median 1.00</td>
<td>Upper 95% CI 1.00</td>
<td>Median 1.00</td>
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</tr>
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</table>
4.7. References


CHAPTER 5

Bacterial Infections in Neonates Following Mupirocin-based MRSA Decolonization: A Multicenter Cohort Study

Rebecca Pierce, Kristina Bryant, Alexis Elward, Justin Lessler, and Aaron M. Milstone

5.1. Abstract

Objective. To characterize the risk of infection after Staphylococcus aureus decolonization with intranasal mupirocin.

Design. Multicenter, retrospective cohort study.

Setting. Tertiary care neonatal intensive care units (NICUs) from three urban hospitals in US. Bed size range: 45-100.

Methods. MRSA-colonized neonates were identified from NICU admissions occurring from January 2007-December 2014, during which a targeted decolonization strategy was used for MRSA control. In two time-to-event analyses, MRSA-colonized neonates were observed from date of first MRSA positive surveillance screen until 1) first occurrence of novel gram-positive cocci in sterile culture or discharge and 2) first occurrence of novel gram-negative bacilli in sterile culture or discharge. Mupirocin exposure was treated as time varying.

Results. A total of 522 MRSA-colonized neonates were identified from 16,144 neonates admitted to site NICUs. Of the MRSA-colonized neonates, 384 (74%) received mupirocin. Average time from positive culture to mupirocin treatment was 3.5 days ($sd=7.2$ days). The adjusted hazard of gram-positive cocci infection was 64% less among mupirocin-exposed versus mupirocin-unexposed neonates (HR=0.36, 95% CI: 0.17-
0.76), while the adjusted hazard ratio of gram-negative bacilli infection comparing mupirocin-exposed and -unexposed neonates was 1.05 (95% CI: 0.42-2.62).

Conclusions. In this multi-centered cohort of MRSA-colonized neonates, mupirocin-based decolonization treatment appeared to decrease the risk of infection with select gram-positive organisms, as intended, and was not significantly associated with risk of subsequent infections with organisms not covered by mupirocin’s spectrum of activity.
5.2. Introduction

*Staphylococcus aureus* is the second most common cause of healthcare-associated infections (HAIs) in hospitalized neonates and remains a leading cause of morbidity and excess cost in pediatric settings[1–3]. Decolonization is a strategy to prevent *S. aureus* by reducing the bioburden of skin colonization that may otherwise increase risk of subsequent *S.aureus* infection or transmission. In neonatal intensive care units (NICUs), decolonization primarily has been used to control epidemic and endemic methicillin-resistant *S. aureus* (MRSA)[2]. Mupirocin (pseudomonic acid A), a topical antibiotic, is a widely used decolonizing agent and is typically administered in the nares twice daily for five days. Mupirocin is highly active against staphylococci and streptococci, but has poor in vitro activity against gram-negative bacilli[4,5].

Despite calls for more expansive use of mupirocin-based decolonization as a prophylactic infection prevention tool[6], few studies have evaluated possible unintended consequences of this approach[7]. One potential unintended outcome is pathogen replacement, an issue addressed in mupirocin (Bactroban®) prescribing information via the caution that application “may result in overgrowth of nonsusceptible microorganisms”, but ascribes this only to prolonged use[8]. Increased susceptibility to infection after systemic antibiotic exposure has been well-described in the microbiome literature[9,10]. Antibiotics may either select for or provide sufficient disruption of the protective microbiota to facilitate infections with other pathogens. There is mounting concern that mupirocin, with its specificity for gram-positive organisms, may facilitate infection with non-targeted, gram-negative pathogens[2,11–13]. Gram-negative bacilli are significant NICU pathogens[14], as they are associated with high morbidity and
mortality as well as treatment challenges secondary to high-levels of antimicrobial resistance[15]. The possibility of organism replacement after topical antibiotic ointment is particularly salient for infants in the NICU, as they are subject to recurrent pathogen introduction events from the healthcare setting and are particularly vulnerable to infections due to naive immune systems, a nascent microbiome, poor skin integrity, and frequent use of invasive devices[1,16,17].

Our objective was to characterize the intended and unintended outcomes associated with mupirocin use among MRSA carriers in the NICU by estimating 1) the risk of infection with targeted, gram-positive cocci and 2) the risk of infection with non-targeted, gram-negative bacilli.

5.3. Materials and Methods

5.3.1. Study Design and Population

We conducted a retrospective, multicenter cohort study from January 2007 to December 2014. Data were obtained from three tertiary care NICUs for the portion of the study period when a targeted MRSA decolonization program was employed for MRSA-control. Detailed facility data are available in Table 1. We included neonates who were identified as MRSA-colonized by surveillance culture and were, therefore, eligible for decolonization treatment. In addition to decolonization, sites employed other standard elements of NICU infection control practice, including contact precautions for neonates positive for MRSA or other multi-drug resistant organisms and chlorhexidine (CHG) bathing for neonates of higher gestational age (typically > 36 weeks).
5.3.2. Definitions and Data Collection

MRSA-colonized neonates were identified via weekly nasal surveillance cultures conducted as part of a targeted decolonization strategy, the protocol for which has been described previously[18]. Neonates enter study observation on date of first positive MRSA nasal surveillance culture and were followed until outcome occurrence or discharge.

We considered two outcomes for two separate time-to-event analyses. Outcomes included composites of organisms that are either covered by mupirocin’s spectrum of activity (analysis 1) or are not (analysis 2). In analysis 1, we characterized the occurrence of novel gram-positive cocci in sterile culture. This included staphylococci and streptococci spp., organisms covered by mupirocin. In analysis 2, we observed neonates for the occurrence of novel gram-negative bacilli in sterile culture. This outcome included Enterobacteriaceae and other gram-negative rods (Pseudomonas spp., Acinetobacter spp.) not covered by mupirocin’s spectrum of activity. Outcomes were ascertained from clinical cultures obtained during routine care in the NICU. Sterile sites include blood, urine (obtained from urine catheter), cerebrospinal fluid, abscess fluid, and pleural fluid. Neonates were followed for the novel occurrence of an outcome organism in sterile culture, meaning that neonates were observed only for outcome organism species that had not already been detected in clinical culture prior to study entry. This accounted for the possibility of multiple, distinct infections with organisms of interest during admission and eliminated those that originated prior to study entry. For example, in analysis 2, if a neonate was admitted to the NICU with a Klebsiella pneumoniae positive clinical culture and subsequently became MRSA-colonized, then he or she would
be followed for the occurrence of a non-*Klebsiella pneumoniae* gram-negative organism. As neonates who had a pre-study entry culture-positive with an outcome organism may have increased or decreased risk of an additional infection with another species within the same outcome type, we included the occurrence of any pre-entry gram-positive cocci or gram-negative bacilli in clinical culture as a potential confounding variable in analysis 1 and analysis 2, respectively. In sensitivity analyses, we restricted to neonates that were free of all outcome organisms prior to study entry.

Our primary exposure was intranasal mupirocin administration. Mupirocin exposure information was obtained from administrative databases and chart review. A patient was classified as non-exposed from date of first positive MRSA nasal surveillance culture to date of first mupirocin exposure, after which they were considered mupirocin-exposed.

Additional sensitivity analyses were performed for each time-to-event analysis to explore construction of composite outcomes. First, we restricted outcomes to include only bloodstream infections (BSIs) to assess whether our effects were robust when holding outcome specimen source constant. We additionally conducted a post-hoc sensitivity analysis, in which we further assessed the impact of characterizing outcomes with different organism and specimen type combinations to ensure consistency of results.

5.3.3. Statistical Methods

Bivariate associations between study variables and mupirocin exposure were assessed with chi-square, Fisher’s exact, and non-parametric tests. Crude incidence rates were calculated. We conducted survival analyses using Cox proportional hazards regression to assess differences in the occurrence and timing of infection by mupirocin receipt.
Mupirocin exposure was time varying as described above. Time at risk was calculated from date of first MRSA positive culture to outcome or discharge, resulting in risk set comparisons being among those with similar time since initial MRSA-colonization and, therefore, start of eligibility for mupirocin. *A priori* confounders of interest included calendar year, pre-study entry length of stay, gestational age, birth weight, occurrence of an outcome organism in culture prior to study entry (described above), and study site. The proportional hazards assumption was tested by assessment of Schoenfeld residuals and tests of interaction of primary study variables with time. Data were analyzed using STATA v13.1 and R v3.2.1.

### 5.4. Results

#### 5.4.1. Characteristics of Study Population

Of 16,144 total neonates admitted to site NICUs throughout the study period, we identified 522 (3.2%) MRSA-colonized neonates. Of these, 246 (47%) were female. Race composition was 59% White, 34% Black, and 7% unknown or other. Mupirocin treatment was administered to 380 (73%) of MRSA-colonized neonates between first identification of colonization and discharge or outcome occurrence in analysis 1 and 384 (74%) in analysis 2. Compliance for mupirocin administration after MRSA positive surveillance screen ranged by site from 69%-79%. Average time to mupirocin receipt among those treated was 3.5 days (*sd*=7.2 days). Distribution of study variables by mupirocin exposure are presented in Table 2.

#### 5.4.2. Primary Survival Analyses

Thirty-seven novel gram-positive coci infection events were detected during the study period, corresponding to an incidence rate (IR) of 2.0 per 1000 patient-days. The rate of
novel gram-positive cocci infection was 64% lower for mupirocin-exposed neonates compared to mupirocin-unexposed neonates (1.4 vs. 3.9 infections per 1000 patient-days, p=0.001). Median follow up time was 22 days (IQR: 8-45). The adjusted hazard of gram-positive cocci infection was 64% less among mupirocin-exposed versus mupirocin-unexposed neonates (HR=0.36, 95% CI: 0.17-0.76), controlling for length of stay prior to study entry, calendar year, birth weight, gestational age, study site, and whether a gram-positive cocci organism had been identified prior to study entry (Table 3a). Table 2 shows the distribution of observed gram-positive outcome organisms and sterile specimen types by mupirocin exposure. Outcomes included coagulase-negative staphylococci (51%), *S. aureus* (35%), streptococci (14%). Blood cultures were the most common sterile specimen type, accounting for 22 (59%) observed outcomes.

Twenty-nine novel gram-negative bacilli infection events were observed, corresponding to a rate of 1.6 per 1000 patient-days. Median follow up time was 23 days (IQR: 8-49). The crude IR of novel gram-negative bacilli infection was not significantly different among mupirocin-exposed and -unexposed neonates (IRR=1.19, 95% CI: 0.49-3.31). Similarly, the adjusted hazard ratio of gram-negative bacilli infection comparing mupirocin-exposed and mupirocin-unexposed neonates was 1.05 (95% CI: 0.42-2.62), controlling for length of stay prior to study entry, calendar year, birth weight, gestational age, study site, and whether a gram-negative organism had been identified prior to study entry (Table 3b). Gram-negative organism and specimen type distribution is shown in Table 2. Enterobacteriaceae, most notably *Klebsiella* spp. (38%), *Escherichia coli* (21%), and *Enterobacter* spp. (14%), were most common. Urine cultures accounted for 21 (72%) of observed gram-negative bacilli outcomes.
Visual inspection of Schoenfeld residuals and tests of interaction of mupirocin exposure with time revealed no evidence that the proportional-hazards assumption was violated and no significant time-dependent effects were noted.

5.4.3. Sensitivity Analyses

When restricting to only neonates free of any gram-positive cocci organisms in clinical culture prior to study entry (n=439), the effect of mupirocin exposure on gram-positive cocci infection risk remained highly protective (HR=0.30, 95% CI: 0.13-0.66).

Mupirocin exposure was associated with a non-significant protective effect on the hazard of gram-negative bacilli infection among neonates without any gram-negative bacilli identified prior to study entry (n=479; HR=0.81, 95% CI: 0.32-2.03).

Additional sensitivity analyses ensured consistency of results when restricting the specimen-type and pathogen components that are included in composite outcomes. First, outcomes were restricted to those found in blood culture alone. The hazard of gram-positive cocci BSI was reduced among mupirocin-exposed neonates (HR=0.37, 95% CI: 0.15-0.88) compared to those mupirocin-unexposed, a finding consistent with that for the primary outcome including all sterile specimen sites. The hazard of BSI with gram-negative organisms was, again, not significantly different among mupirocin-exposed versus –unexposed neonates (HR=0.82, 95% CI: 0.15-4.36). We further assessed robustness of findings when altering the organism or sterile specimen type combinations that define outcomes. Results were highly robust irrespective of organism or specimen type, demonstrating a strong protective effect for organisms covered by mupirocin (S.aureus, coagulase-negative staphylococci, streptococci) and hazard ratios that approach one for non-covered organisms. Notably, the rate of S.aureus BSI was
decreased among mupirocin exposed neonates (IRR=0.10, 95% CI: 0.01-0.51) as was the hazard of *S. aureus* BSI in Cox regression analysis (HR=0.21, 95% CI: 0.04-1.26), though the later was at trend level significance. Additional organisms not covered by mupirocin spectrum activity were included here, including fungi, *Propionibacterium* spp., enterococci, and *Corynebacterium* spp. We did not find any evidence of a significant increase in risk of infection when these additional, non-covered organisms were included as outcomes. Results are shown in Supplementary Figure 1.

### 5.5 Discussion

Data from this large, multicenter cohort suggest that mupirocin treatment for *S. aureus* decolonization decreases the risk of infection with select gram-positive organisms. This is consistent with other NICU studies that report reduced risk of MRSA or methicillin-sensitive *S. aureus* after mupirocin treatment.[19–21] We did not find a statistically significant increase in the risk of infection with gram-negative bacilli among MRSA-colonized NICU patients treated with mupirocin. These findings were robust to the type of sterile specimen source used to identify outcomes.

This study addresses growing concern that decolonization treatment may disrupt the microbiologic ecology of the nares and predispose to infections with other organisms. Gram-negative pathogens are of particular concern as they account for a substantial portion of HAIs in the NICU and are associated with high morbidity and mortality[1,14,22]. In the current study, we did not observe a significant increase in the proportion, rate, or hazard of gram-negative bacilli infections with mupirocin treatment. In contrast, Perez-Fontan et al.[23] previously reported an increase of gram-negative infections with nasal mupirocin use in adult peritoneal dialysis patients[23]. Similarly,
the Mupirocin Study Group[24] conducted a randomized trial of mupirocin use in peritoneal dialysis patients and noted increased occurrence of gram-negative or mixed organism infections. A meta-analysis by van Rijen and colleagues pooled data from three trials of surgical and peritoneal dialysis patients, and found an increased risk of infection with non-\textit{S. aureus} organisms in those who had received mupirocin treatment[13]. However, adult populations studied to date are likely to be highly distinct from a neonatal population in terms of risk factors, healthcare-associated and outpatient pathogen exposures, as well as microbiome development.

Our study informs distal infectious outcomes associated with mupirocin use as we observed neonates for the duration of their NICU stay, which ranged from days to months. Additional research is needed to assess the more immediate impact of topical antibiotics at the level of the microbiome in hospitalized patients, who may be more susceptible to replacement via repeated exposure to a wide range of healthcare-associated pathogens. Studies of the gut microbiome have shown that antibiotic treatment can disrupt microbial communities and place recipients at increased risk for colonization with opportunistic pathogens[25]. However, the impact of disruptions in the skin microbiome following antimicrobial use remains poorly understood[26], particularly for the relatively ubiquitous topical antibiotics. Use of triple antimicrobial ointments has been associated with \textit{Candida} colonization and infection in adult ICU patients[27]. However, a recent study of 15 adults, both outpatient and ICU patients, found that microbial richness did not differ pre- versus post-mupirocin treatment, while \textit{S. aureus} body site colonization decreased over time[28]. The assessment of this issue in neonates remains important as it is possible mupirocin-driven dysbiosis is occurring but is undetectable when clinical
infection is the outcome of interest. This may be particularly relevant as neonatal microbiomes are evolving and perturbations may impact its long-term composition and stability.

Strengths of our study include the use of data from three NICUs that utilize targeted decolonization for MRSA control. The multi-centered approach increased the capacity to identify MRSA-colonized and mupirocin-eligible neonates that could be observed for both intended and unintended infectious outcomes after mupirocin treatment. The longitudinal nature of the data allowed for estimates of individual-level risk of bacterial infections associated with mupirocin use, accounting for time at risk and establishing temporality between exposure and outcomes. In addition, we accounted for the time-varying nature of mupirocin exposure. This was important as mupirocin was not immediately administered in all cases and characterization of this time as mupirocin-exposed would have underestimated the rate of infection, and therefore, also underestimated the relative risk of infection associated with mupirocin exposure. This supports prior work demonstrating that characterization of time-varying antibiotic exposures has important implications for interpreting antimicrobial-associated infection risk[29].

Our study has several limitations. First, as this was an observational study, we cannot rule out residual confounding. Though we were not aware of any systematic causes for withheld mupirocin-based decolonization treatment, we attempted to address this issue by comparing only MRSA-colonized neonates at the same time from identification of colonization to maximize comparability between exposure groups. Models were adjusted to control for potential confounders. In particular, adjustment for
gestational age, calendar time, and site served to address unit CHG use, secular trends in infection control practice over the study period, and variation in practice by site. Though notable confounding by these variables was not observed, results nevertheless should be interpreted in the context of ongoing, unit-based infection control practices. Post-mupirocin infection risk may vary in settings where these practices are not in use. A second limitation is the reliance on clinical culture proxy to define clinically apparent infection outcomes. We limited outcomes to positive sterile site cultures to improve confidence that we were measuring true infection, but this was not verified by chart review. Recognizing that coagulase-negative staphylococci culture positives may, in some cases, reflect skin colonization as opposed to infection, we performed sensitivity analyses focusing on *S. aureus* alone and found a significant decrease in overall rate of *S. aureus* between exposure groups, suggesting that the observed effect was not entirely driven by decreased occurrence of coagulase-negative staphylococci. Third, we continued to observe neonates that had a gram-positive cocci or gram-negative bacilli positive clinical culture prior to study entry for the occurrence of remaining species of outcome organisms. We did so to avoid inclusion of infections that originated prior to the beginning of observation, but also because an early infection with one organism would not necessarily preclude subsequent risk of overgrowth and infection by another organism. In doing so, we reduce outcome possibilities in neonates with organisms of interest prior to study entry; however, given that we did not observe a significant decrease in the number of events in this subset, we believe this limitation is outweighed by the risk of excluding a potentially high risk group. Moreover, findings were consistent irrespective of the inclusion or exclusion of these neonates. Finally, the absence of a
significant finding for mupirocin-associated gram-negative bacilli infection risk does not itself demonstrate absence of an effect. To address this issue, we conducted a post-hoc power analysis using effect sizes obtained from the Mupirocin Study Group[24]. Given a higher proportion of infection with gram-negative or mixed organisms in the mupirocin group (20 [15%] of 134 vs. 7 [5%] of 133, p=0.01 by Fisher’s exact test)[24] and our sample size of 522 neonates, we would have 87% power to detect a similar effect. Further research is required to elucidate the short- and long-term impact of topical antimicrobials in a neonatal population. Studies that evaluate outcomes associated with decolonization therapy should consider reporting the overall incidence of infections with any organism to assess for unintended consequences.

In this study, we report the risk of bacterial infections following mupirocin decolonization in a NICU population. Our analysis suggests that mupirocin-based decolonization treatment does not facilitate infection with organisms not directly targeted by the approach, but does appear to be working as intended by reducing risk of infection with gram-positive organisms.
Table 1. Study site description

<table>
<thead>
<tr>
<th>Site</th>
<th>Calendar Time</th>
<th>Bed size</th>
<th>Admissions</th>
<th>MRSA-colonized neonates</th>
<th>Person-time (Analysis 1)</th>
<th>Person-time (Analysis 2)</th>
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<td>5,653</td>
<td>233</td>
<td>9,523</td>
<td>9,308</td>
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<td>Site 2 (Louisville, KY)</td>
<td>Aug 2009-Nov 2013</td>
<td>100</td>
<td>4,303</td>
<td>185</td>
<td>5,649</td>
<td>5,932</td>
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<tr>
<td>Site 3 (Baltimore, MD)</td>
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<td>45</td>
<td>6,188</td>
<td>104</td>
<td>3,009</td>
<td>3,111</td>
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<tr>
<td>Total</td>
<td>--------------------</td>
<td>----------</td>
<td>------------</td>
<td>--------------------------</td>
<td>--------------------------</td>
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</tr>
</tbody>
</table>

Calendar time refers to the time period during which targeted decolonization was in place for each site. Admissions reflects neonate admissions during the calendar time period. MRSA-colonized neonates identified during the relevant calendar time that had at least one day of follow up were included in the analytic population. Analysis 1 is a survival analysis of time to gram-positive cocci infection and Analysis 2 is a survival analysis of time to gram-negative bacilli infection.
Table 2. Characteristics of study population

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<th>No mupirocin treatment n=142 (%)</th>
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<tr>
<td>Streptococcus spp.</td>
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<td>1 (6)</td>
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</tr>
<tr>
<td>Previous gram-positive cocci</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No previous gram-positive cocci</td>
<td>55 (14)</td>
<td>28 (20)</td>
<td>0.15</td>
</tr>
<tr>
<td>Event specimen types</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Blood</td>
<td>6 (27)</td>
<td>2 (29)</td>
<td>1.00a</td>
</tr>
<tr>
<td>Urine</td>
<td>16 (73)</td>
<td>5 (71)</td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td></td>
</tr>
<tr>
<td>Event organisms</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Acinetobacter spp.</td>
<td>1 (5)</td>
<td>0 (0)</td>
<td>1.00a</td>
</tr>
<tr>
<td>Enterobacteriaceae</td>
<td>19 (86)</td>
<td>6 (86)</td>
<td></td>
</tr>
<tr>
<td>Pseudomonas spp.</td>
<td>2 (9)</td>
<td>1 (14)</td>
<td></td>
</tr>
<tr>
<td>Previous gram-negative bacilli</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No previous gram-negative bacilli</td>
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<td>6 (4)</td>
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<tr>
<td>Event specimen types</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Blood</td>
<td>18 (26)</td>
<td>17 (31)</td>
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</tr>
<tr>
<td>Urine</td>
<td>30 (9)</td>
<td>32 (10)</td>
<td>0.20b</td>
</tr>
<tr>
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<td>50 (36)</td>
<td>0.06</td>
</tr>
<tr>
<td>Event organisms</td>
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<tr>
<td>Acinetobacter spp.</td>
<td>180 (47)</td>
<td>53 (37)</td>
<td></td>
</tr>
<tr>
<td>Enterobacteriaceae</td>
<td>127 (33)</td>
<td>58 (41)</td>
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<tr>
<td>Pseudomonas spp.</td>
<td>73 (19)</td>
<td>31 (22)</td>
<td></td>
</tr>
</tbody>
</table>

Analysis 2: Time to gram-negative bacilli infection

<table>
<thead>
<tr>
<th>Mupirocin-treated n=384</th>
<th>No mupirocin treatment n=138</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gram-negative bacilli event</td>
<td></td>
<td></td>
</tr>
<tr>
<td>No event</td>
<td>22 (6)</td>
<td>7 (5)</td>
</tr>
<tr>
<td>Event specimen types</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Blood</td>
<td>6 (27)</td>
<td>2 (29)</td>
</tr>
<tr>
<td>Urine</td>
<td>16 (73)</td>
<td>5 (71)</td>
</tr>
<tr>
<td>Other</td>
<td>0 (0)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Event organisms</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Acinetobacter spp.</td>
<td>1 (5)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Enterobacteriaceae</td>
<td>19 (86)</td>
<td>6 (86)</td>
</tr>
<tr>
<td>Pseudomonas spp.</td>
<td>2 (9)</td>
<td>1 (14)</td>
</tr>
<tr>
<td>Previous gram-negative bacilli</td>
<td></td>
<td></td>
</tr>
<tr>
<td>No previous gram-negative bacilli</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Event specimen types</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Blood</td>
<td>18 (26)</td>
<td>17 (31)</td>
</tr>
<tr>
<td>Urine</td>
<td>30 (9)</td>
<td>32 (10)</td>
</tr>
<tr>
<td>Other</td>
<td>183 (48)</td>
<td>50 (36)</td>
</tr>
<tr>
<td>Event organisms</td>
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</tr>
<tr>
<td>Acinetobacter spp.</td>
<td>180 (47)</td>
<td>53 (37)</td>
</tr>
<tr>
<td>Enterobacteriaceae</td>
<td>127 (33)</td>
<td>58 (41)</td>
</tr>
<tr>
<td>Pseudomonas spp.</td>
<td>73 (19)</td>
<td>31 (22)</td>
</tr>
</tbody>
</table>

Characteristics of study population shown by receipt of mupirocin. Event specimen type and organism show distribution of composite outcomes. Other sites refer to sterile sites other than blood and urine, including cerebrospinal fluid, abscess fluid, and pleural fluid. Previous gram-positive cocci and gram-negative bacilli variables refer to the occurrence of positive culture with any outcome organisms prior to study entry. \(^a\) P value obtained by Fisher’s exact test, \(^b\) P value obtained by Kruskal-Wallis test. Abbreviations: coNS, coagulase-negative staphylococci; LOS, length of stay; d, days; g, grams; IQR, interquartile range.
Table 3a. Clinical characteristics associated with risk of gram-positive cocci infection among MRSA-colonized neonates eligible for mupirocin treatment (Analysis 1)

<table>
<thead>
<tr>
<th>Variable</th>
<th>HR</th>
<th>95% CI</th>
<th>aHR</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>mupirocin treatment</td>
<td>0.43</td>
<td>0.21-0.86</td>
<td>0.36</td>
<td>0.17-0.76</td>
</tr>
<tr>
<td>LOS prior to study entry (days)</td>
<td>0.99</td>
<td>0.98-1.01</td>
<td>0.98</td>
<td>0.97-1.00</td>
</tr>
<tr>
<td>Calendar year</td>
<td>0.94</td>
<td>0.80-1.10</td>
<td>1.00</td>
<td>0.85-1.18</td>
</tr>
<tr>
<td>Previous gram-positive cocci in culture</td>
<td>1.03</td>
<td>0.47-2.26</td>
<td>0.93</td>
<td>0.40-2.17</td>
</tr>
<tr>
<td>Birth weight (g)</td>
<td>1.00</td>
<td>0.99-1.00</td>
<td>1.00</td>
<td>0.99-1.00</td>
</tr>
<tr>
<td>Gestational age (weeks)</td>
<td>0.94</td>
<td>0.88-1.02</td>
<td>0.89</td>
<td>0.76-1.02</td>
</tr>
<tr>
<td>Site</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Site 1</td>
<td>0.86</td>
<td>0.45-1.65</td>
<td>0.72</td>
<td>0.30-1.72</td>
</tr>
<tr>
<td>Site 2</td>
<td>0.79</td>
<td>0.38-1.64</td>
<td>0.79</td>
<td>0.24-2.58</td>
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<tr>
<td>Site 3 (Ref)</td>
<td>-</td>
<td>-</td>
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</tbody>
</table>

Table 3b. Clinical characteristics associated with risk of gram-negative bacilli infection among MRSA-colonized neonates eligible for mupirocin treatment (Analysis 2)

<table>
<thead>
<tr>
<th>Variable</th>
<th>HR</th>
<th>95% CI</th>
<th>aHR</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>mupirocin treatment</td>
<td>1.13</td>
<td>0.47-2.76</td>
<td>1.05</td>
<td>0.42-2.62</td>
</tr>
<tr>
<td>LOS prior to study entry (days)</td>
<td>1.00</td>
<td>0.99-1.01</td>
<td>0.99</td>
<td>0.98-1.01</td>
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<tr>
<td>Calendar year</td>
<td>1.01</td>
<td>0.84-1.21</td>
<td>1.04</td>
<td>0.87-1.26</td>
</tr>
<tr>
<td>Previous gram-negative bacilli in culture</td>
<td>1.53</td>
<td>0.95-4.86</td>
<td>1.63</td>
<td>0.53-4.98</td>
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<tr>
<td>Birth weight (g)</td>
<td>1.00</td>
<td>0.99-1.01</td>
<td>1.00</td>
<td>0.99-1.00</td>
</tr>
<tr>
<td>Gestational age (weeks)</td>
<td>0.91</td>
<td>0.83-1.00</td>
<td>0.90</td>
<td>0.74-1.10</td>
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<tr>
<td>Site</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Site 1</td>
<td>0.95</td>
<td>0.37-2.43</td>
<td>0.94</td>
<td>0.34-2.66</td>
</tr>
<tr>
<td>Site 2</td>
<td>0.56</td>
<td>0.18-1.75</td>
<td>0.62</td>
<td>0.14-2.67</td>
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<tr>
<td>Site 3 (Ref)</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

Estimates obtained via Cox proportional hazards regression. Infection outcomes as measured by novel occurrence of positive sterile site culture with any of specified organisms. Abbreviations: HR, hazard ratio; aHR, adjusted hazard ratio; CI, confidence interval; LOS, length of stay; g, grams.
Supplementary Figure 1: Heatmap for unadjusted hazard ratios from individual Cox proportional hazards models

Heatmap for unadjusted hazard ratios from individual Cox proportional hazards models. Organisms not covered by mupirocin’s spectrum of activity shown in top portion of figure (dark gray label). Organisms covered by mupirocin are depicted in the bottom portion (black label). Color of cells reflective of numeric distance from other cells in map. Figure demonstrates consistency of effect measures according to whether organisms are covered or non-covered by mupirocin irrespective of how outcome was constructed. Other sterile sites include cerebrospinal fluid, abscess fluid, and pleural fluid. Abbreviations: GNB, gram-negative bacilli; GNB&F, gram-negative bacilli or fungi; GNB&F + Other, gram-negative bacilli, fungi, or other organisms not within mupirocin’s spectrum of activity (*Propionibacterium* spp., enterococci, *Corynebacterium* spp.); SA, *Staphylococcus aureus*; Staph spp., *Staphylococcus aureus* or coagulase-negative staphylococci; GPC, gram-positive cocci (staphylococci & streptococci).
5.6 References


CHAPTER 6

Conclusions

Infants in the neonatal intensive care unit are particularly vulnerable to the acquisition of healthcare-associated pathogens[1]. Infections at this critical stage can be devastating. *S.aureus* infections have been associated with mortality of 5%-18% the NICU[2]. Active surveillance culture (ASC) and decolonization strategies have been proposed to reduce individual-level risk of *S.aureus* disease as well as to reduce unit-based transmission. In this work, we show that ASC and decolonization is an effective strategy to reduce transmission risk from colonized patients and reduce risk of gram-positive infection in colonized individuals in the NICU. In addition, we show that mupirocin-based does not appear to facilitate infections with organisms not targeted by the approach.

This research supports the growing body of evidence that ASC and decolonization is a safe and effective approach to *S.aureus* control in the NICU. The strategy employs multiple infection prevention elements, each of which have high biologic plausibility of effectiveness in reducing patient-to-patient transmission. First, the “active” component of the approach involves the identification of MRSA-colonized neonates. Detection alone may promote healthcare worker compliance with hand hygiene and other basic unit infection prevention measures. In addition, detected neonates are placed on contact precautions, requiring healthcare workers to wear gowns and gloves when in contact with colonized patients. Finally, MRSA-colonized neonates are treated with topical antimicrobials (e.g. mupirocin) to eliminate the carriage state. This combination of healthcare worker awareness, contact precautions, and decolonization treatment provides
multi-faceted prevention against the spread of MRSA in hospital settings, each component conferring protection should the others fail. This is important as healthcare workers face numerous challenges in the care of critically ill patients. Though perfect compliance with all infection prevention is the goal, it is often not plausible in these settings. Our work supports this multi-faceted approach as detection (and the use of contact precautions) was itself highly protective against transmission. This protection was also seen in those decolonized and isolated.

ASC and decolonization strategies are targeted in the sense that prevention strategies are focused on MRSA-colonized neonates. This strikes an important balance between the need to eliminate pathogen carriage with judicious antimicrobial use. In the era of emerging antimicrobial resistance[3], it is becoming increasingly important to preserve the antibiotics we have available through appropriate use. Recently, researchers have suggested expanding the use of decolonization to all unit patients, irrespective of carriage status. This would eliminate the need for costly and time-intensive weekly surveillance screening. In doing so, asymptomatic MRSA-carriers would no longer be placed on contact precautions[4]. This approach may indeed be cost saving, but resistance to decolonizing agents such as mupirocin has been shown to emerge with increased use in in-patient settings[5]. In addition, in the NICU setting, detection and contact precautions may play a larger role in prevention when compared to adult settings, where these strategies have failed to impress[6]. Additional research is needed to assess if universal decolonization strategies would be safe and successful in the NICU setting[7].

There are numerous challenges associated with the study of hospital-based pathogen acquisition. Here, we address several of these. First, we account for the highly
dependent nature of the acquisition outcomes by measuring the impact of exposure to colonized neonates as well as by the explicit representation of the infectious process in analytic models. In addition, we account for the interval-censored nature of weekly surveillance screening, imputing the most likely date of conversion to MRSA positive to inform daily acquisition risk. Finally, we account for the time-varying nature of exposures of interest. A remaining challenge in the science of infection prevention is the disentanglement of concurrently implemented strategies. In the current work, we attempted to isolate the effect of detection and contact precautions, but our estimates for transmissibility of decolonized neonates should be interpreted as a joint effect of multiple infection prevention components. Though these estimates demonstrate a reassuring absence of transmissibility in treated neonates, the independent effect of decolonization remains elusive due to concurrency of contact isolation and other standard unit infection prevention (e.g. environmental decontamination and hand hygiene). Cluster randomized trials are needed to elucidate how these multi-faceted components may perform in isolation.

Decolonization treatment reduces the risk of progression to infection in treated MRSA carriers. This, in and of itself, is a meaningful clinical impact of this approach. Much of the work we present here suggests that an ASC and decolonization approach also has a significant impact on transmission risk in the NICU. Patient-to-patient transmission is clearly an important part of NICU MRSA acquisition in the NICU, as evidenced by notable transmission risk associated with exposure to MRSA-colonized neonates who have not yet been detected by surveillance culture. Improving time-to-detection may be an important intervention point to further reduce unit-based MRSA
transmission. However, this dissertation also emphasizes that at least one third of unit-based MRSA acquisition could not be attributed to patient-to-patient transmission. The importance of non-patient *S. aureus* reservoirs has been demonstrated in other inpatient settings[8]. It is likely that other sources of MRSA-acquisition are an important driver of MRSA-endemicity in the NICU setting. These sources could include introduction from parents or visitors, prolonged colonization of healthcare workers, or contact with hospital locations outside of the NICU (e.g. radiology, operating room). MRSA elimination will likely not be possible until these reservoirs are better understood and intervened upon. Given the complex nature of MRSA acquisition in this setting, prioritizing unit-based prevention approaches will be essential.

References


PROFESSIONAL LICENSES
District of Columbia RN License, Active
Maryland RN License, Active

EDUCATION
Expected Aug 2017  Doctor of Philosophy (Ph.D.) in Epidemiology
Johns Hopkins Bloomberg School of Public Health  Baltimore, MD
Track: Infectious Diseases
Dissertation: Infectious outcomes associated with mupirocin-based
decolonization treatment in the NICU.
Advisors: Dr. Aaron Milstone, Dr. Justin Lessler

May 2015  Certificate in Healthcare Epidemiology & Infection Prevention &
Control
Johns Hopkins Bloomberg School of Public Health  Baltimore, MD

May 2012  Master of Science in Public Health Microbiology & Emerging
Infectious Diseases
The George Washington University School of Public Health & Health
Services  Washington, DC
Thesis: Sexual risk behaviors in emergency department patients:
Associations with potentially modifiable factors and prioritization of
future interventions.

May 2009  Critical Care Internship
The George Washington University Hospital

Dec 2008  Bachelor of Science in Nursing
University of Pennsylvania School of Nursing  Philadelphia, PA
Senior Inquiry: Evidence for cocaine-induced disruptions in maternal
behavior: Animal and human models.

May 2007  Pre-Health Post-Baccalaureate Program
University of Pennsylvania  Philadelphia, PA

May 2006  Bachelor of Arts in Psychology
Boston College  Boston, MA
Honors Thesis: The experience of emotion: Evidence for a
psychological constructivist model of emotion.

SCHOLARSHIPS
2015-2016  The Lillian Hiss–Ethel Crosby Scholarship for public health nurse
graduate students, JHSPH
2015-2016 Ruth Freeman Memorial Award for outstanding continuing nurse doctoral students, JHSPH

2015 Scholarship to attend the Summer Institute in Statistics and Modeling in Infectious Diseases, University of Washington, School of Public Health

2014-2015 Teaching Assistantship in Epidemiologic Methods, JHSPH Department of Epidemiology

2014-2015 Ruth Freeman Memorial Award for outstanding continuing nurse doctoral students, JHSPH

2014-2015 Abe Lilienfeld Scholarship for exceptional students in the area of professional epidemiology, JHSPH Department of Epidemiology

2007 Janssen Scholarship, American Psychiatric Nurses Association

2004 -2006 Undergraduate Research Fellowships, Boston College (Consecutive)

TEACHING EXPERIENCE

Mar-May 2016 Teaching Assistant, Department of Epidemiology
Problems in the Design of Epidemiologic Studies: Proposal Critique and Review (Enrollment: 25 students)
Johns Hopkins Bloomberg School of Public Health

Sep-Dec 2015 Teaching Assistant, Public Health Studies Program
Senior Undergraduate Honors Thesis in Public Health (Enrollment: 18 students)
Johns Hopkins University

Mar-May 2015 Teaching Assistant, Department of Epidemiology
Methodologic Challenges in Epidemiologic Research (Enrollment: 100 students)
Johns Hopkins Bloomberg School of Public Health

Jan-Mar 2015 Lead Teaching Assistant, Department of Epidemiology
Epidemiologic Methods III (Enrollment: 200 students)
Johns Hopkins Bloomberg School of Public Health

Oct-Dec 2014 Lead Teaching Assistant, Department of Epidemiology
Epidemiologic Methods II (Enrollment: 264 students)
Johns Hopkins Bloomberg School of Public Health

Sep-Oct 2014 Teaching Assistant, Department of Epidemiology
Epidemiologic Methods I (Enrollment: 276 students)
Johns Hopkins Bloomberg School of Public Health

Jan-Mar 2014 Teaching Assistant, Department of Epidemiology
Epidemiologic Methods III (Enrollment: 194 students)
Johns Hopkins Bloomberg School of Public Health
Oct-Dec 2013  Teaching Assistant, Department of Epidemiology  
*Healthcare Epidemiology* (Enrollment: 17 students)  
Johns Hopkins Bloomberg School of Public Health  
*Epidemiologic Methods II* (Enrollment: 220 students)  
Johns Hopkins Bloomberg School of Public Health

Oct-Dec 2012  Teaching Assistant, Department of Epidemiology  
*Epidemiology of Infectious Diseases* (Enrollment: 56 students)  
Johns Hopkins Bloomberg School of Public Health

2010-2012  Charge RN  
Emergency Department 
Led Emergency Department RN Orientation  
Led Annual Competencies Review & Testing  
The George Washington University Hospital

2011-2012  Infection Preventionist, Infection Control Department  
Taught New Staff Orientation Course: Introduction to Infection Control and Prevention  
The George Washington University Hospital  
Taught New Graduate RN Course: Clinical Practice & Infection Control and Prevention  
The George Washington University Hospital

PROFESSIONAL EXPERIENCE

Oct 2015-Present  Infection Control Practitioner, Department of Infection Control, Johns Hopkins Hospital (Intrastaff)  
Conducted surveillance for surgical site infections; worked with multiple electronic health record systems to extract data necessary for national reporting.

Jan 2013-Dec 2014  Research Coordinator, Department of Epidemiology & Department of Hospital Epidemiology & Infection Control  
Johns Hopkins Bloomberg School of Public Health  
Baltimore, MD  
Johns Hopkins Hospital  
Working with Dr. Derek Cummings and Dr. Trish Perl to conduct a multi-site study on risk factors for healthcare-associated *Staphylococcus aureus* and *Pseudomonas aeruginosa* infection to inform potential therapeutics.

Feb 2012-Aug 2012  Infection Preventionist, Department of Infection Control  
The George Washington University Hospital  
Washington, DC  
Served as one of two hospital epidemiologists conducting facility-wide surveillance for multi-drug resistant organisms, healthcare-associated infections (HAIs), and infection control practice compliance; Prepared and coordinated infectious outbreak response; Collaborated with local hospitals and state health departments; Led the implementation of a hand hygiene improvement initiative, MRSA screening program, Surgical Site Infection Prevention Bundle, and visitor education program; Authored and implemented Infection Control Policies & Procedures Manual;
Provided educational in-services and infection prevention recommendations for clinical staff and hospital departments.

Feb 2011-Feb 2012  **Infection Control Nurse**, Department of Infection Control  
The George Washington University Hospital  
Washington, DC  
Conducted surveillance for multi-drug resistant organisms, healthcare-associated infections (HAIs), and infection control practice compliance; Served as liaison from clinical hospital staff to infection control department and the infection control committee; Performed in-services and staff education on infection control topics and HAI prevention.

Sep 2011-May 2012  **Co-investigator & Data Analyst**, Medical Faculty Associates  
Department of Emergency Medicine  
The George Washington University Hospital  
Washington, DC  
Served as co-investigator in clinical research within the Emergency Department to investigate the prevalence and demography of acute *Helicobacter pylori* infection in abdominal pain patients. Obtained experience in proposal and manuscript writing, study design, analysis using SAS/GIS, and follow up methodologies.

Feb 2009-Feb 2012  **Registered Nurse**, Emergency Department  
The George Washington University Hospital  
Washington, DC  
Served as emergency department charge nurse managing all MDs, RNs, and technicians to effectively direct patient care; Cared for critically ill patients in Level 1 trauma environment; Mentored new nurses and new nurse graduates in Critical Care Internship Program; Designed triage flow sheets for identification of infectious diseases to promote rapid identification and isolation as necessary; Authored and implemented MRSA screening program in Emergency Department; Participated in hazmat/emergency preparedness drills, including readiness for large scale outbreaks and infectious exposures; Performed a range of nursing skills (e.g. peripheral IV insertion, arterial blood draw, EKG interpretation, extensive patient education).

May 2004-May 2005  **Residential Life Skills Instructor**  
Germaine Lawrence Diagnostic Center  
Arlington, MA  
Germaine Lawrence specializes in clinical treatment of adolescent girls with eating disorders, substance abuse, oppositional and defiant disorders, and those with a history of aggression and/or fire-starting; Responsible for building therapeutic relationships with facility residents; Trained in general counseling procedures (PEM- corrective behavior management system) to encourage the development of skills that apply to life outside of the diagnostic center; Trained in CPI (non-violent crisis intervention) restraint techniques to ensure resident and staff safety.

Boston College  
Chestnut Hill, MA  
Participated in research on the neurobiology of motivation, emotion, and social behavior; specifically neurobiology of parental behavior in rodents.
and the effects of hormones and experience on the relevant hypothalamic, limbic, and striatal circuits.

Sep 2003-May 2006 Emotion Experience Advanced Research Assistant and Study Lead, Feldman Barrett Laboratory
Boston College Chestnut Hill, MA
Completed 2 years of independent study work as a research assistant/study lead and a final year completing a Psychology Honors Thesis on the perceived neural and cognitive structure of the human emotional experience.

HONORS AND AWARDS
May 2004 Phi Beta Kappa Honor Society (Sophomore Entry), Boston College
May 2006 Summa Cum Laude graduate, Boston College
December 2008 Summa Cum Laude graduate, University of Pennsylvania
August 2010 Service Excellence Award, George Washington University Hospital

PUBLICATIONS


PRESENTATIONS


PROFESSIONAL SKILLS
Computer Skills: Proficient in R, STATA, SAS, ArcGIS, Epi Info
Database Management Experience: Redcap, Access
Electronic Health Record & Surveillance Systems Experience: CERNER, EPIC, IBEX, OPUS, Sunrise, Theradoc

ACADEMIC SERVICE
2015-2017 Surveillance and Outbreak Response Team (SORT) Member, Department of Epidemiology Johns Hopkins Bloomberg School of Public Health

Responsibilities: Serve the state and local health departments as needed to assist with outbreak response, data analysis, literature reviews, data collection, and study protocol preparation.

2015-2016 Teaching Assistant Student Chair, Department of Epidemiology Johns Hopkins Bloomberg School of Public Health

2013-2014 Student Co-Representative to the Curriculum Committee, Department of Epidemiology Johns Hopkins Bloomberg School of Public Health

2013-2014 Student Co-Coordinator of Infectious Disease Epidemiology Journal Club, Department of Epidemiology Johns Hopkins Bloomberg School of Public Health

2015 Reviewer: American Journal of Epidemiology
Ad hoc Reviewer: Infection Control and Hospital Epidemiology (Primary Reviewer: Aaron Milstone)