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PREVENTION OF HOSPITAL-ACQUIRED METHICILLIN-RESISTANT STAPHYLOCOCCUS AUREUS IN U.S. PEDIATRIC INPATIENTS: A SYSTEMATIC REVIEW

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PREVENTION OF HOSPITAL-ACQUIRED METHICILLIN-RESISTANT
STAPHYLOCOCCUS AUREUS IN U.S. PEDIATRIC INPATIENTS: A
SYSTEMATIC REVIEW

by

RACHEL SEE

B.S., UNIVERSITY OF GEORGIA

A Capstone Submitted to the Graduate Faculty
of Georgia State University in Partial Fulfillment of the
Requirements for the Degree

MASTER OF PUBLIC HEALTH

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APPROVAL PAGE

**PREVENTION OF HOSPITAL-ACQUIRED METHICILLIN-RESISTANT
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SYSTEMATIC REVIEW**

by

RACHEL SEE

Approved:

Committee Chair

Committee Member

Date

ACKNOWLEDGEMENTS

I would like to express my gratitude to my committee chair, Dr. Ashli Owen-Smith for her guidance and involvement with the systematic review. She dedicated a substantial amount of time and energy in order to make sure best methods were used when systematically retrieving articles. Her expertise and involvement both as a teacher and as my capstone chair were crucial to my experience in my graduate school program. It has been an absolute honor to be a student of hers as well as to work with her on this capstone. My appreciation also goes to another member of my committee, Dr. Lisa Casanova for also being a vast wealth of knowledge and support throughout my MPH program. Without Dr. Casanova's hospital infectious disease class, I would not have a solid foundation for understanding prevention and control practices. I thank you both for shaping me into the researcher I am today.

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ABSTRACT

Background: Pediatric inpatients in United States healthcare settings may be particularly vulnerable with respect to methicillin-resistant *Staphylococcus aureus* (MRSA) infection and transmission. Although infection prevention and control protocols have well been established for MRSA and for adult inpatients, there are few current guidelines available on how to address MRSA prevention and control in pediatric inpatients.

Objectives: To systematically identify, describe, and evaluate the quality of the current literature on infection prevention and control strategies for preventing the transmission of methicillin-resistant *Staphylococcus aureus* (MRSA) in United States pediatric inpatient settings.

Search methods: In June-August 2015, Campbell Collaboration Library, Cochrane Library, PubMed, MEDLINE, Biological Abstracts, CINAHL Plus, and Web of Science was searched for studies published between January of 2005 and December 2015 by using relevant key terms for pediatric patients (ex, children, infant, newborn, neonate) and prevention and control of MRSA.

Selection criteria: All primary data studies on infection prevention and control interventions for healthcare associated MRSA in United States pediatric inpatient settings were eligible for inclusion.

Data collection and analysis: Two authors independently reviewed the results of the searches. Another author was consulted for any discrepancies between categorization of articles. Data extraction was conducted by one author and was checked by a second author.

Main results: 1,619 studies were initially identified, of which 21 studies met the criteria for inclusion. Of the studies that met inclusion criteria, one was a randomized control trial, thirteen were retrospective cohort studies, four were before and after studies, two were prospective cohort studies and one was a retrospective case finding. Three studies (Song (2010), Robicsek (2009), and Gregory (2009)) found that Mupirocin or antibiotic treatment did not eradicate MRSA colonization consistently and were unsuccessful in eliminating continuing transmission of MRSA. However, the study by Delaney found that there was a significant reduction in rates of *S. aureus* infection when comparing Mupirocin prophylactic period with the control period. Another two studies (Constantini and Kjonsgaard) found that screening was not identifying all of the MRSA cases, and that HA-MRSA infection rates did not decline after implementation of ICU screening, thus proving that this method was ineffective in regards to decreasing transmission and incidence of MRSA infections.

Conclusion: There is a lack of research evaluating the effects on MRSA transmission of infection prevention and control strategies in pediatric inpatient settings. More resources should be devoted to understand the epidemiology of MRSA amongst the pediatric inpatient population as well as continued research interventions to establish prevention and control protocols for this vulnerable population.

KEYWORDS Prevention, Control, MRSA, Neonates, Infant, Pediatrics, Children,

Newborns, NICU, PICU

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The author of this capstone is:

Rachel See

9404 Whaleys Lake Trace

Jonesboro, GA 30238

The Chair of the committee for this capstone is:

Ashli Owen-Smith, PhD

School of Public Health

Georgia State University

P. O. Box 3995

Atlanta, GA 30302-3995

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Curriculum Vitae

Rachel See

9404 Whaleys Lake Trace • Atlanta, GA 30238 • 404-353-3953 • rachelesee@gmail.com

EDUCATION

Master of Public Health in Epidemiology **May 2016**
Georgia State University- Atlanta, GA

Bachelor of Science in Psychology **May 2014**
The University of Georgia- Athens, GA

PROFESSIONAL EXPERIENCE

Southside Medical Center, Atlanta, GA
HIV Clinical Coordinator **October 2015-Present**

Morehouse Choice ACO and Education System, Atlanta, GA
Intern **June-September 2015**
Developed a Balanced Scorecard for chronic conditions such as Diabetes and COPD.

Georgia State University, Atlanta, GA
Graduate Teaching Assistant **January-August 2015**
Taught SAS modules as part of Biostatistics I course and monitored and assisted with the SAS Lab weekly

Georgia State University, Atlanta, GA
Graduate Research Assistant **August -December 2014**
Conducted extensive literature review, analyzed data through various health records including HRSA, NCI, CDC, NHANES

Soliant Health, Tucker, GA
Junior Account Executive **May 2014-August 2014**
Scheduled Drug Screen Tests, compiled licensure verifications, and executed background checks for healthcare practitioners

University of Georgia, Athens, GA
Undergraduate Research Assistant **August 2012-December 2013**
Used skills for three studies:
DIVAS (sponsored by the National Cattleman's Beef Association)
EPHIT (sponsored by the Egg Nutrition Center)
Breast Cancer research (funded by UGA)
Analyzed blood vials using the centrifuge, administered phone screenings, assisted with Biodex, physical functioning, and pain stimulation tests, provided accurate data entry and analysis

Centers for Disease Control and Prevention, Atlanta, GA
Intern **March 2010**
Investigated the history of influenza outbreaks during the H1N1 outbreaks

providing background information of how influenza spreads

CAMPUS AND COMMUNITY INVOLVEMENT

Public Health Student Association, Vice President <i>Georgia State University</i>	2014-Present
Seeds of Knowledge, Vice President <i>University of Georgia</i>	2010-2014
Volunteer UGA, Liaison <i>University of Georgia</i>	2011-2014
Athens Regional Hospital, Volunteer <i>Athens, GA</i>	Fall 2011
Los Niños Primeros Camp for Children, Volunteer <i>Atlanta, GA</i>	2006-2010

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CHAPTER I. INTRODUCTION

According to the Department of Health and Human Services, about 1 in every 25 inpatients has an infection associated with hospital care, costing billions of dollars and about ten thousand lives annually (DHHS, 2015). It is therefore imperative that we treat hospital-acquired infections in order to reduce excessive expenditures and improve patient outcomes. One of the most common hospital acquired infections is methicillin-resistant *Staphylococcus aureus* (MRSA). MRSA is an opportunistic gram-positive bacteria that has in recent years become a serious healthcare as well as community threat.

Staphylococcus aureus asymptomatically colonizes the skin and anterior nares (nostrils) of approximately one-third of the human population at any given time and two out of 100 people are carriers for MRSA (CDC, 2013). Consequently, outbreaks of *S. aureus* and MRSA are extremely common as many in the population do not know that they are carriers of the bacteria (Williams, *et al.*, 2010; CDC, 2013). Unfortunately in today's society, *Staphylococcus aureus* has become resistant to common medications prescribed to treat staph infections. In order to fully understand how MRSA became resistant to several broad-spectrum antibiotics, it is important to understand the history that transformed this bacteria.

Although *Staphylococcus aureus* itself has been around for billions of years, it was the overuse of Alexander Flemmings' development of penicillin in 1928 that caused the bacteria to become resistant to antibiotics due to acquisitions of genes producing β -lactamase (Moellering, 2012). In 1959, Methicillin was introduced as a new antibiotic and within a two-year span, methicillin-resistant *Staphylococcus aureus* developed. It is

also important to note that according to Mayhall (2012), although MRSA got its name from being methicillin-resistant, MRSA is now not only resistant to anti-staphylococcal penicillins such as nafcillin and oxacillin but is also resistant to beta-lactam antibiotics from first through fourth generations of cephalosporins and carbapenems. Since 1961, MRSA has spread throughout the world, causing many healthcare, community, and livestock associated infections. According to the CDC (2013), community acquired MRSA infections are most associated with skin infections, but healthcare associated infections are associated with life-threatening bloodstream infections (or MRSA bacteremia), pneumonia, and surgical site infections. For the purpose of this systematic review, we will be focusing solely on hospital and healthcare associated infections, however it is important to note the growing prevalence of community and livestock associated infections.

Nosocomial infections (hospital acquired/healthcare associated) are those that were not present in the patient prior to hospitalization and occur usually 48-72 hours after admittance or within 10 days of discharge from the hospital (Jacobs, 2014). Healthcare associated infections (HAIs) are important to understand because they can cause life-threatening illnesses that often can be prevented if proper protocol is followed.

MRSA is a nosocomial infection that is associated with high morbidity and mortality rates. According to Boucher et al; (2008), in 2005 MRSA infections killed an estimated 19,000 hospitalized Americans, which is higher than combined AIDS, Tuberculosis, Viral hepatitis, SARS, and Avian influenza deaths in the United States. When looking at medical device related deaths, another study by Hanberger et al; (2011)

analyzed 1265 ICUs from 75 countries and found that in ICU patients, MRSA infections were independently associated with nearly 50% more hospital deaths when compared to MSSA infections of ICU patients. MRSA has been a common cause of Central Line-associated Bloodstream Infection (CLABSI), hospital-acquired pneumonia, Catheter-associated Urinary Tract Infections (CAUTIs), wound infections, and Surgical Site Infections (SSIs) (Mayhall, 2012). According to Mayhall (2012), blood stream infections caused by MRSA have mortality rates that range from 20% to more than 35%. MRSA has also been associated with longer lengths of stay, as well as increased health costs (Mayhall, 2012). Corriere & Deckner (2008) and Noskin and colleagues (2005) have shown that the length of stay for inpatients with *S. aureus* infection is three times longer than that of other patients. They also discuss that when looking at MRSA vs. Methicillin-sensitive *Staphylococcus aureus* (MSSA), the average length of stay for MRSA infections was 20.1 days longer when compared to MSSA infections, resulting in a 55% longer length of stay.

MRSA affects mostly those with compromised immune systems, those who have previously taken antibiotics, the elderly, and those with underlying diseases (CDC, 2013). Because MRSA affects mostly those with compromised immune systems, there is a higher risk associated with inpatients in the ICU, among those who recently had surgery or in those who have invasive medical devices such as catheters or intravenous lines.

According to the CDC (2013), the primary mode of transmission for hospital-acquired MRSA is through person-to-person contact, primarily through healthcare worker contact with patients or, less frequently, through patient to patient contact. Contaminated

surfaces and medical equipment are the second most common mode of transmission of MRSA. Due to the fact that MRSA is an opportunistic bacteria that most often impacts individuals with impaired immune systems, it is extremely important that prevention and control methods are standardized throughout inpatient settings in order to reduce the risk of spreading.

In addition to the risk factors discussed above, Mayhall (2012) discusses certain healthcare delivery risk factors that have been associated with an increased risk of MRSA infection in inpatient care. Mayhall (2012) found that risk of MRSA increases as the prevalence of MRSA among hospital patients increases, that risk increases among persons admitted to a hospital room in which prior room occupant was colonized or infected with MRSA, and that healthcare worker hand hygiene practices influence risk for the patient. Lastly, increased MRSA risks have been associated with staffing deficits and patient overcrowding, thus providing evidence that contact precautions and environmental cleaning are paramount to preventing hospital acquired infections (Mayhall, 2012).

Mayhall (2012) also discussed that MRSA was the cause of 56.8% of *S. aureus* healthcare-associated pneumonia, 48.6% of *S. aureus* hospital-acquired pneumonia, and 34.4% of *S. aureus* Ventilator-associated Pneumonia (VAP), although associating mortality to those who acquired *S. aureus* VAP is debatable amongst researchers. The National Healthcare Safety Network (NHSN) reported 2,045 *S. aureus* SSI cases from 2006-2007, resulting in 49% of those *S. aureus* SSI cases were due to MRSA (Calfee, 2014). Not only is MRSA highly associated with the cause of these infections, but delay

in recognizing and treating MRSA can have severe consequences such as higher mortality rates (Corrier & Deckner, 2008).

Because healthcare-associated MRSA is associated with high morbidity and mortality, MRSA is also associated with high costs of care. Jacobs (2014) found that in the United States, HAIs infect 1.7 million patients annually, account for 99,000 deaths, and cost approximately \$35.7 to \$45 billion. In order to assess how much cost was attributed per patient, a cohort study was conducted at the U.S. Department of Veterans Affairs system between 2007-2010 that analyzed inpatient as well as pharmacy costs during a year following the discharged MRSA patient (Nelson *et al.*, (2015). Nelson *et al.*, (2015) found that 3,599 of the 369,743 inpatients had positive MRSA cultures. After matching positive MRSA cultured patients to controls, patients were followed for a year and the study found that those MRSA patients had an increased post-discharge pharmacy cost average of \$776 and an increased inpatient cost average of \$12,167 (Nelson *et al.*, 2015). The study also found that MRSA patients were at an increased risk for readmission, had more prescriptions, and more inpatient days. This study provides evidence that the cost associated with MRSA patients is substantially higher than that of inpatients without MRSA. Thus, it is important to implement stricter prevention and control policies as to not only improve patient health but as to reduce extraneous spending on a national level.

According to the Active Bacterial Core Surveillance Report in 2012, the total estimated cases of MRSA infection in the United States was 75,309 with an incidence rate of 23.99 (CDC, 2012). The national metric for Healthy People 2020 and Department

of Health and Human Services Action Plan to Prevent Healthcare-Associated Infection shows that there have been 23,000 fewer cases in the United States in 2012 when compared to the baseline of 2007-2008, depicting a -30.80% change in healthcare associated infections (CDC, 2012). Another study by the National Healthcare Safety Network (NHSN) found that rates of MRSA bloodstream infections occurring in hospitalized patients fell almost 50% from 1997-2007 (CDC, 2013). A study published by the Journal of American Medical Association Internal Medicine showed that invasive MRSA hospital acquired infections declined by 54% from 2005 to 2011 as well as 9,000 fewer deaths in 2011 (CDC, 2013). The decreasing rate of infections provides evidence that there are fewer morbidities and mortalities from MRSA infections.

However, the University of Chicago Medicine (UCM) and the University Healthcare Consortium (UHC) published data in 2012 that estimated that the rates of MRSA in U.S. academic medical centers from 2003-2008 had actually doubled (David, et al., 2012). Jacobs (2014) discusses that this difference between the UCM and UHC study and the CDC data could possibly be due to the fact that the CDC only looks at invasive infections, which excludes skin infections that were included in the UCM and UHC study. Another study conducted by Jarvis et al., (2012) surveyed all U.S. Association for Professionals in Infection Control and Epidemiology, members in order to assess the prevalence of MRSA from August 1 to December 30, 2010 for all inpatients. The study found that the overall MRSA prevalence rate was 66.4 per 1,000 inpatients, which was higher than rate reported in their 2006 study, which used the same methodology. Thus, it appears that there is a decrease in MRSA invasive infections but an increase in the overall prevalence of MRSA in inpatients.

Although there is an improvement due to the decrease in the severity of and risk of mortality as a result of infections, healthcare associated MRSA infections were not significantly reduced among pediatric populations from 2005-2010, indicating that there needs to be further research as to why there is an overall improvement among adults but not for pediatric inpatients (Iwamoto et al., 2013). It is important to study pediatric populations because according to Milstone et al., (2011) 8.5% of pediatric patients that were colonized with MRSA on admission developed a MRSA infection. Even more staggering is the fact that 47% of patients who became colonized with MRSA in the pediatric ICU developed MRSA infections (Milstone *et al.*, 2011). In comparison, Hudson et al., (2012) found that the rates of MRSA carriage to be 6-12% in general hospital patients and 9-24% in ICUs. MRSA is a common bacterial infection amongst children, especially in the NICU due to their susceptibility to infections. Various strategies for prevention and eradication have been used with various rates of success, but implementation of standardized prevention methods needs to be developed specifically for pediatrics.

Guidelines for prevention of healthcare associated MRSA (HA-MRSA) currently exist from the Center for Disease Control and Prevention, but there is limited evidence about best practices implementation for MRSA prevention for pediatrics. The purpose of this study was to conduct a systematic review in order to evaluate the current state of the science with respect to MRSA interventions in order to reduce the transmission and incidence of MRSA infections in pediatric inpatient settings in the United States. This systematic review included literature found from 2005-2015 and specifically focused on inpatient pediatrics. This study aimed to

1. Identify interventions for the prevention of hospital-acquired MRSA in pediatrics in the United States
2. Explore which prevention interventions appear to be most effective as defined by decrease in transmission or incidence of infection
3. Develop informed suggestions to policy makers regarding current hospital-acquired MRSA prevention protocols for pediatrics

CHAPTER II. LITERATURE REVIEW

Numerous strategies to reduce MRSA colonization and invasive infections have been published, but very few of these have focused on pediatric patients. This is problematic due to the fact that we cannot generalize results from adult studies to the pediatric patients due to the fact that pediatric patients cannot take the same dosages, they have weaker immune systems, and are often more susceptible to infections. The article released in 2014 by Nelson et al., titled “*One size does not fit all: why universal decolonization strategies to prevent methicillin-resistant Staphylococcus aureus colonization and infection in adult intensive care units may be inappropriate for neonatal intensive care units*” is important to note because it articulates why it is not necessarily appropriate to apply strategies used with adult populations to pediatric populations. The article discusses the recently published REDUCE MRSA TRIAL, a large multicenter, randomized controlled trial that compared the efficacy of three surveillance and decolonization strategies for reducing MRSA colonization and infection in adult ICUs (Nelson et al., 2014). Some of the results of the trial that were intended for adult ICU patients only has trickled down to the pediatric ICU patient population. Nelson (2014) discussed that many prevention control procedures (such a Chlorohexidine) that have been implemented in adult settings have not been studied in pediatric populations, or worse are shown to have serious health implications (Nelson et al., 2014).

Because this systematic review is concerned with prevention and control interventions of MRSA in the pediatric inpatient population, it is important to review current policies of prevention or control of MRSA in this populations. Another important aspect that warrants review is the prevalence and cost of MRSA infections in the

pediatric inpatient population in order to assess the magnitude of the issues and lastly review current prevention methods for this population. Because the REDUCE MRSA TRIAL influenced protocols published by the AHRQ and CDC, it is important to next review these protocols and discuss the gaps in the literature.

In this section, current guidelines and published protocols by the Center for Disease Control and Prevention and the Department of Health and Human Services will be discussed. More specifically, the Agency for Healthcare Research and Quality (AHRQ) provides two guidelines that will be reviewed. Although all of these guidelines make suggestions related to MRSA prevention/control among pediatric inpatients, none of these guidelines are specific to this population and prevention of MRSA, providing evidence that there is a gap in guidelines specifically intended for pediatric inpatients.

The first guideline from AHRQ titled “Diagnosis and management of complicated intra-abdominal infection in adults and children: guidelines by the Surgical Infection Society and the Infectious Disease Society of America” by Solomkin et al., (2010) is important to discuss because MRSA is associated with surgical site infections (SSIs). The guideline provides regimens for healthcare associated infections including MRSA therapy. The author searched through both primary and secondary sources as well as electronic databases in order to develop recommendations. The guidelines are based on evidence from randomized clinical trials from 2002-2008, which used antimicrobials for the treatment of intra-abdominal infection. A panel of experts in the infectious diseases, surgery, pharmacology, and microbiology prepared these guidelines for the IDSA (Infectious Disease Society of America).

The guidelines suggest that those who are known to be colonized with MRSA or are at risk of having an infection due to prior treatment failure and antibiotic exposure should receive empiric antimicrobial coverage (Solomkin et al., 2010). Also, Vancomycin is recommended for treatment of suspected or positive identified MRSA infection for intra-abdominal infections. However, routine use of broad-spectrum agents are not indicated for all pediatric inpatients with low suspicion or complication of infection.

For pediatrics, the guidelines discuss that selection of specific antimicrobial therapy with infection should be based on community vs. healthcare-associated infection source, severity of illness, and the safety of antimicrobial agents in specific pediatric age groups. For neonates, broad-spectrum antibiotics may be used with vancomycin being the primary antibiotic used for MRSA control. However, the guideline also suggest that therapy for pediatric patients with intra-abdominal infection is constrained by safety concerns and that some forms of antibiotics such as tetracyclines and parenteral fluorquinolones are not recommended when other alternatives exist. This shows that there is no clarity of when broad-spectrum antibiotics use is appropriate when treating neonates. In conclusion, the guideline did not mention prevention or control of MRSA in pediatrics, and in fact it provides very limited information with respect to the treatment of MRSA amongst pediatric patients.

The second guideline from AHRQ “Clinical practice guidelines by the Infectious Diseases Society of America for the treatment of methicillin-resistant *Staphylococcus aureus* infections in adults and children” (Liu et al., 2011) discusses key prevention and

control guidelines for preventing, controlling, and treating of MRSA. This guideline provides details about the management of MRSA in skin and soft-tissue infections (SSTIs), the management of recurrent MRSA SSTIs, bacteremia, MRSA pneumonia, MRSA bone and joint infections, and MRSA central nervous system infections. An expert panel reviewed and synthesized the evidence published between 1961 and 2010. Literature searches of PUBMED of the English-language literature were performed from using terms “methicillin-resistant *Staphylococcus aureus*” or “MRSA”.

The results of this review suggest that, for pediatrics, almost all MRSA infections are controlled and treated with Vancomycin; however, there is limited data about the dosage efficacy, and safety of antibiotic usage. Consequently, the guideline suggests that additional studies should be conducted. Current literature does suggest that in neonates and young infants, topical treatments as an implementation of control methodology is standard. The guideline recommends that for more-extensive diseases or in premature or very-low birth weight, vancomycin or clindamycin should be used. For SSTIs, antibiotic therapy is only recommended for the cohorts associated with extremes of age (ex. pediatrics and elderly), but topical treatment is best approach.

The guidelines also have found that preventive educational messages on personal hygiene and appropriate wound care are recommended for all patients with SSTIs. Also environmental hygiene measures should be considered, with a focus cleaning efforts on high-touch surfaces (i.e. surfaces that come into contact with people’s bare skin such as door knobs, toilet seats). This recommendation is congruent with findings reported by Giannini et al., (2009) which found that in a children’s cancer hospital, alcohol wipes on

toilet seats prior to use resulted in a 50-fold reduction in mean daily bacterial counts and eliminated MRSA, thus providing additional evidence that environmental decontamination is key to avoiding spread of MRSA in pediatric patients. Lastly, decolonization should be considered in selected cases based on severity of infection, recurrence of MRSA despite implementing wound care and hygiene measures. In conclusion, the guidelines published by Liu et al., (2011) did provide some information on control and preventive measures, but in general the guidelines were more focused on the adult inpatient population rather than on pediatric inpatient populations.

Another guideline that is important to discuss is the recent “Strategies to Prevent Methicillin-Resistant *Staphylococcus aureus* Transmission and Infection in Acute Care Hospitals: 2014 Update” by Calfee et al., (2014). The development of this guideline was sponsored by the Society for Healthcare Epidemiology of America (SHEA) and was a product of collaboration from the Infectious Disease Society of America, the American Hospital Association, the Association for Professionals in Infection Control and Epidemiology, and The Joint Commission. It is one of the most comprehensive guidelines to date with respect to MRSA prevention and treatment in inpatient settings. The guideline’s main purpose is to highlight practical recommendations for implementing and prioritizing MRSA prevention efforts. The authors suggest that basic practices for preventing MRSA transmission and infection are recommended for all acute care hospitals and that active surveillance testing should be implemented when basic practices are insufficient.

Calfee and colleagues suggest that basic prevention practices include conducting a MRSA risk assessment, educating healthcare personnel regarding MRSA, ensuring compliance with hand hygiene recommendations, ensuring proper cleaning and disinfection of equipment and environment, ensuring compliance with contact precautions for MRSA-colonized and infected patients, and implementing a MRSA monitoring program. If these steps are insufficient, compliance with basic practices needs to be assessed. If compliance with basic practices is met and MRSA is not effectively controlled, the guidelines suggest instituting one or more special approaches. The list of special approaches include conducting active surveillance testing for MRSA colonization among patients, implementing MRSA decolonization therapy, implementing universal gowns and gloves, continuing to monitor MRSA rates, and continuing a MRSA reporting and accountability system.

These are the general guidelines for prevention and control of MRSA among acute inpatient facilities. However, the guidelines indicate that, in pediatric populations, there needs to be more research on prevention protocols. For example, the guideline reports that limited data are available on use of chlorohexidine for routine patient cleansing for prevention of MRSA outside of the adult ICU setting (Rupp et al., 2012). Also, when universal decolonization is suggested, the guidelines report that a few quasi-experimental single-center studies in the neonatal ICUs have shown a benefit of universal decolonization with topical mupirocin in control of MRSA outbreaks and endemic MRSA disease (Hitomi et al., 2000 and Delaney et al., 2013).

The guidelines continue to report the fact that outside of neonates, universal decolonization has not been studied in hospitalized children. Lastly, the guidelines report that the neonatal ICU has a number of unique characteristics that should be considered when an AST program is being implemented such as the size of the NICU, the number of beds per pod, if any neonates such as twins share beds, etc. (Calfée *et al.*, 2014). The census after reading the guidelines from Calfée *et al.*, (2014) suggest that there needs to be more research conducted in the area of prevention and control of MRSA in pediatric inpatients.

Echoing this information is the information published in the *National Action Plan to Prevent Health Care-Associated Infections: Road Map to Elimination* published in April of 2013. The National Action Plan is a product of the Federal Steering Committee for the Prevention of Health Care-Associated Infections, which was established in 2008. The steering committee's members include clinicians, scientists, and public health leaders from the Department of Defense, the Department of Health and Human Services, the U.S. Department of Labor, and the U.S. Department of Veterans Affairs. The purpose of the Steering Committee is to accelerate progress toward national infection reduction goals.

In the National Action Plan of 2013, the Steering Committee stated that in 2005, there was an estimated 94,000 invasive MRSA infections in the U.S. which were associated with nearly 18,000 deaths. Of these invasive infections, 86% were associated with health care delivery (Kallen *et al.*, 2010). Fortunately, rates of invasive health care-associated MRSA infections have decreased, but the optimal strategy for preventing and controlling health care-associated MRSA has not been fully reached. In their discussion

about the current gaps in knowledge and practice, the Steering Committee suggest the need to understand the epidemiology of MRSA outside the adult ICU, especially in the pediatric population. The committee also discussed the need to facilitate an understanding of the role of various prevention strategies in reducing transmission of MRSA. Also an important issue that is discussed is the need to translate accepted prevention practices to areas outside the adult ICU, thus providing evidence that more research needs to be conducted in order to adequately represent the pediatric population.

After review all current MRSA prevention and control guidelines, there is a consensus that there needs to be more research conducted for prevention and control of MRSA in pediatric inpatient settings. Now that we have a knowledge basis of current guidelines, it is important to review the prevalence of MRSA in pediatric inpatient settings in order to understand the magnitude of the problem.

The article by Kallen *et al.*, (2010) surveyed 9 metropolitan areas covering a population of approximately 15 million persons. Their main objective was to describe changes in rate of invasive health care-associated MRSA infections from 2005-2008. Kallen *et al.*, (2010) found that there were 21,503 episodes of invasive MRSA infections, 17,508 were healthcare associated and that the rate of hospital-onset invasive MRSA infections was 1.02 per 10,000 in 2005 and decreased 9.4% per year (95% confidence interval [CI], 14.7% to 3.8%; P = .005). Although this shows vast improvement in our healthcare settings, it is important to focus on data available for pediatric populations in order to see if any improvements have been achieved there.

Song *et al.*, (2013) published an article that discusses the incidence of MRSA infection in a children's hospital in the Washington metropolitan area from 2003 - 2010. They found that in 2004 there were 0.93 per 1,000 patient-encounter MRSA infections, then dramatically increased to 5.34 per 1,000 patient-encounter MRSA infections in 2007 and decreased to 3.77 per 1,000 patient-encounters by the end of 2010 (Song *et al.*, 2013). Another study conducted by Gerber *et al.*, (2010) performed a retrospective, observational study using the Pediatric Health Information System from more than 40 US children's hospitals. The study used discharge codes during the period of January 2002 to December 31st, 2007 and found that there was a significant increase in cases of MRSA infection (from 6.7 cases per 1,000 admissions in 2002 to 21.1 cases per 1,000 admissions in 2007). This research shows that there is a need for prevention protocol development at children's hospitals across the nation. Next, we will focus more specifically at the trends in incidence of MRSA in the NICU.

According to the National Nosocomial Infection Surveillance System, incidence of late-onset MRSA infections in NICUs increased from 0.7 to 3.1 infection per 10,000 patient days from 1995-2004, showing an increase of 308% late-onset infections (Lessa *et al.*, 2009). This information is important because prevention methods will have to be altered to specifically address late-onset MRSA infections. A better picture of the colonization in neonatal and pediatric ICUs can be seen in the meta-analysis conducted in 2014 by Zervous *et al.* The meta-analysis identified 18 articles that were clinical studies on MRSA colonization published from 2006-2013. The prevalence of colonization of MRSA among NICU patient on admission was 1.5% (95% CI 0.9%-2.2%) compared to the 3.0% (95% CI 1.9%-4.5%) among PICU patients. According to Zervous *et al.*,

(2014), “the acquisition rate was 4.1% (95% CI 1.2%–8.6%) among the neonatal and pediatric population, whereas among the neonatal population alone, 6.1% (95% CI 2.8%–10.6%) of patients acquired MRSA during the NICU stay”. This supports all other research discussed where steps need to be taken to prevent and control MRSA in the vulnerable pediatric population. This population should be treated differently than the adult population and should have specific protocols dedicated to pediatric inpatient facilities. More research needs to be conducted in order to assess current incidence rates and trends in MRSA pediatric inpatients as well as to deduce which prevention and control policy has quantitatively shown a reduction in MRSA infection rates in pediatric inpatients.

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CHAPTER III. MANUSCRIPT

PREVENTION OF PEDIATRIC HOSPITAL-ACQUIRED METHICILLIN- RESISTANT STAPHYLOCOCCUS AUREUS IN U.S. PEDIATRIC INPATIENTS: A SYSTEMATIC REVIEW

Rachel See, MPH, Georgia State University

Veronica Mahathre, MPH, Georgia State University

Ashli Owen-Smith, PhD, Emory University

Prevention of hospital-acquired methicillin-resistant staphylococcus aureus in U.S. pediatric inpatients: a systematic review

R. See, V. Mahathre, A. Owen-Smith

ABSTRACT

Background: The vulnerability of the pediatric inpatient population in United States healthcare settings establish a perfect environment for the acquisition and spread of methicillin-resistant *Staphylococcus aureus* (MRSA). Although infection prevention and control protocols have well been established for MRSA and for adult inpatients, there is a gap in literature in current guidelines on how to address MRSA prevention and control in pediatric inpatients.

Objectives: To determine the effects of infection prevention and control strategies for preventing the transmission of methicillin-resistant *Staphylococcus aureus* (MRSA) in United States pediatric inpatient settings.

Search methods: In June-August 2015, we searched Campbell Collaboration Library, Cochrane Library, PubMed, MEDLINE, Biological Abstracts, CINAHL Plus, and Web of Science for studies published between January of 2005 and December 2015 by using relevant key terms for pediatric patients (ex, children, infant, newborn, neonate) and prevention and control of MRSA.

Selection criteria: All primary data studies on infection prevention and control interventions for healthcare associated MRSA in pediatric inpatient settings were eligible for inclusion.

Data collection and analysis: Two review authors independently reviewed the results of the searches. Another review author was consulted for any discrepancies between categorization of articles. Data extraction was conducted by one review author and was checked by a second review author.

Main results: 1,619 studies were initially identified, of which 21 studies met the criteria for inclusion. Of the studies that met inclusion criteria, one was a randomized control trial, thirteen were retrospective cohort studies, four were before and after studies, two were prospective cohort studies and one was a retrospective case finding. Three studies (Song (2010), Robicsek (2009), and Gregory (2009)) found that Mupirocin or antibiotic treatment did not eradicate MRSA colonization consistently and were unsuccessful in eliminating continuing transmission of MRSA. However, the study by Delaney found that there was a significant reduction in rates of *S. aureus* infection when comparing Mupirocin prophylactic period with the control period. Another two studies (Constantini and Kjonogaard) found that screening was not identifying all of the MRSA cases, and that HA-MRSA infection rates did not decline after implementation of ICU screening, thus proving that this method was ineffective in regards to decreasing transmission and incidence of MRSA infections.

Conclusion: There is a lack of research evaluating the effects on MRSA transmission of infection prevention and control strategies in pediatric inpatient settings. More resources should be devoted to understand the epidemiology of MRSA amongst the pediatric inpatient population as well as continued research interventions to establish prevention and control protocols for this vulnerable population.

KEYWORDS Prevention, Control, MRSA, Neonates, Infant, Pediatrics, Children, Newborns, NICU, PICU

MRSA is an opportunistic gram-positive bacteria that has in recent years become a serious healthcare as well as community threat. In particular, MRSA is a common bacterial infection amongst children,

especially in the NICU due to their susceptibility to infections. Iwamoto et al., (2013) found that although there is an improvement due to the decrease in the severity of and risk of mortality as a result of infections, healthcare associated

MRSA infections were not significantly reduced among pediatric populations from 2005-2010. This indicates that there needs to be further research as to why there is an overall improvement among adults but not for pediatric inpatients. It is important to study pediatric populations because according to Milstone *et al.*, (2011) 8.5% of pediatric patients that were colonized with MRSA on admission developed a MRSA infection. Even more staggering is the fact that 47% of patients who became colonized with MRSA in the pediatric ICU developed MRSA infections (Milstone *et al.*, 2011). In comparison, Hudson et al; (2012) found that the rates of MRSA carriage to be 6-12% in general hospital patients and 9-24% in ICUs. Various strategies for prevention and eradication have been used with various rates of success. However, implementation of standardized prevention methods has yet to be developed specifically for pediatrics, even though there is a clear need for such protocols.

Guidelines for prevention of healthcare associated MRSA (HA-MRSA) currently exist from the Center for Disease Control and Prevention, but there is limited evidence about best practices with respect to implementation for MRSA prevention among pediatric populations. The purpose of this study was to conduct a systematic review in order to evaluate the current state of the science with respect to MRSA interventions in pediatric inpatient settings in the United States.

Specifically, this study aimed to:

1. Identify interventions for the prevention of hospital-acquired MRSA in pediatrics in the United States

2. Explore which prevention interventions appear to be most effective as defined by a decrease in transmission or incidence of MRSA infections
3. Develop informed suggestions to researchers and policy makers in regards to current hospital-acquired MRSA prevention protocols for pediatrics

METHODS

This systematic review included literature found from 2005-2015 and specifically focused on inpatient pediatrics.

Search Strategy

With the help of the university librarian, the first author conducted scientific literature searches using the Campbell Collaboration Library, Cochrane Library, PubMed, MEDLINE, Biological Abstracts, CINAHL Plus, and Web of Science for studies published between January of 2005 and December 2015 by using relevant key terms for pediatric patients (ex, children, infant, newborn, neonate) and prevention and control of MRSA. All studies that were not in the English language were excluded for this systematic review. From this original search, we identified a total of 1,619 articles. After compiling all sources and removing duplicate articles we had a total of 698 original articles.

Study Selection

Studies were required to meet the following criteria in order to be included in the review:

1. Conducted in the United States
2. Evaluated the impact of an intervention for prevention and/or control of MRSA
3. Included children age 0-17 years old
4. Implemented in an inpatient setting

Studies that did not collect primary data such as reviews, opinion articles, and letters to editors were excluded.

The first round of review was based on screening titles and abstracts against the inclusion and exclusion criteria. Two researchers who were blinded by each other's categorization conducted this assessment. Then after each researcher completed the first assessment, categorizations were compared and quality of categorization was measured by percent agreed upon (89%). The articles that were not agreed upon were set aside and were included in the full text review.

The second round of review was based on reading the full article in order to review any unclear abstracts. During the second round of assessment, a third researcher was brought in to settle any discrepancies between those studies that were not agreed upon for categorization in the first round. Also any articles that were met inclusion criteria were reviewed again in the second round to verify they fit criteria for inclusion. After the second round of assessment, 21 articles met all criteria for inclusion.

Validity assessment

In order to assess the quality of all included studies, the first author completed the quality assessment form

included in the article by Zara et al., (2000). Parameters included in the assessment of study quality were based on six categories of common problems including descriptions, sampling, measurement, analysis, results, and other.

Data abstraction and synthesis

By using standardized extraction forms produced by Zara et al., (2000), the first author independently extracted all data. The third and first author reviewed results of data abstraction form in order to summarize for systematic review. Discrepancies were discussed and resolved by consensus.

RESULTS

Description of Studies

We followed the Preferred Reporting Items for Systematic Reviews (PRISM) guidelines (Moher, Liberati, Tetzlaff, Altman, & The PRISMA Group, 2010) in order to conduct this systematic review to best standards and to report results systematically.

1,619 studies were originally identified, of which 21 studies met the criteria for inclusion. Of the studies that met inclusion criteria, one was a randomized control trial, thirteen were retrospective cohort studies, four were single-group pre-posttest studies, two were prospective cohort studies and one was a retrospective case finding. The study identification and data abstracting process is outlined in Figure 1.

Eleven out of twenty one studies took place in the NICU, five were in a children's hospital, three were at the entire hospital, and two were in hospital systems. Most studies reported MRSA colonization or infection as a percentage;

some studies reported patient-days at risk while others reported attack rates.

Methodological quality of included studies

Very few studies measured pre-intervention MRSA incidence. This is a major flaw in the studies analyzed in the fact that there is no comparison before intervention to see if the intervention plays a key role in MRSA transmission reduction. Also, few studies actually measured hospital worker-related outcomes in order to see if healthcare practitioners adhered to interventions. Again, most studies did not assess pre-intervention hand hygiene compliance rates, surveillance rates, or contact precaution adherence rates. Another important aspect of the studies included that should be addressed is the fact that none of the studies separated each intervention piece. Every study included multiple intervention types, so there is no way of separating interventions in order to see if individual intervention components would be effective on its own.

Only one study was a randomized control trial, most were observational studies, and in most of the studies key details on the population demographics were not described. Through detailed team discussion we were able to identify key results and the intervention types that we felt were most important, thus allowing us to classify studies based on intervention type and summarize the results.

Hospital Worker-Related Outcome

Six studies identified healthcare workers as being colonized with MRSA and thus decolonized the healthcare worker effectively. Three studies

identified successful increase in hand hygiene compliance. The study by Song *et al;* (2013) noted that sustaining hand hygiene at 80% or higher was associated with a 48% further reduction of MRSA in comparison with the study by Holzmann-Pazgal *et al;* (2011) that found significant improvement in hand hygiene compliance was not independently associated with reduction in MRSA transmission. This shows that there is still some discrepancy in the results as to the effectiveness of worker-related outcomes in relation to decrease in transmission and incidence of MRSA infections.

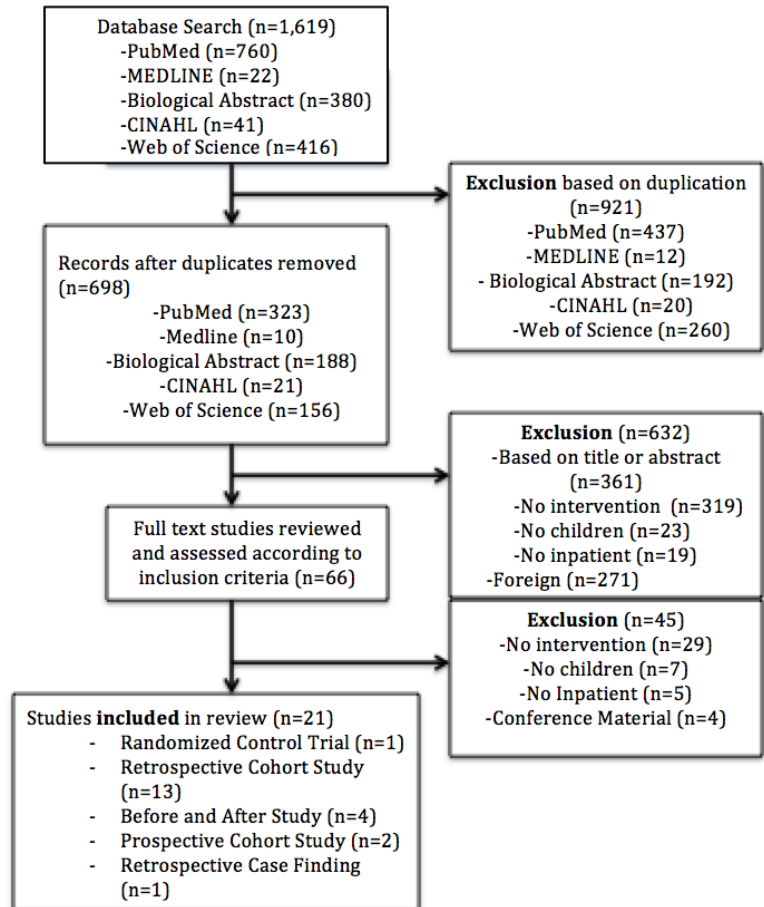


Figure 1 Inclusion Flow Diagram.

Patient-Related Outcome

Colonization rates varied amongst all studies with Murillo (2009) finding 9.3% of babies were colonized, Song (2010) found 7% that were colonized/infected, Khoury (2005) found 21.4% colonized, and Kaushik (2014) found 57% were colonized at admission.

Three studies (Song (2010), Robicsek (2009), and Gregory (2009)) found that Mupirocin or antibiotic treatment did not eradicate MRSA colonization consistently and were unsuccessful in eliminating continuing transmission of MRSA. However, the study by Delaney found that there was a significant reduction in rates of *S. aureus* infection when comparing Mupirocin prophylactic period with the control period.

Another two studies (Constantini and Kjonegaard) found that screening was not identifying all of the MRSA cases, and that HA-MRSA infection rates did not decline after implementation of ICU screening, thus proving that this method was ineffective in regards to decreasing transmission and incidence of MRSA infections.

DISCUSSION

Strengths of review

This study has several strengths including an extensive, thorough search of current literature of which two blinded reviewers categorized articles in order to reduce misclassification bias. Another strength found in this review is that each article that met inclusion criteria also went through a quality assessment in order to rank articles by best methods. Another strength of this review is that the focus on the study population is very precise, thus allowing the results to be directly applied to children in inpatient settings.

Limitations of review

Publication bias is always an important bias to address in systematic reviews. Publication bias is when studies that have statistically significant results are more likely to be published in comparison to those whose results are not statistically significant. Thus for the purpose of this review, we must address the fact that we were only able to collect articles that were published in journals, thus excluding all research that did not make it to journal acceptance.

Another bias that that needs to be addressed is the chance of misclassification bias due to researcher misclassifying articles by inclusion criteria.

This study also has limitations in the fact that it cannot be generalized to outpatients or adult MRSA patients.

Implications for health policy, clinical care, and future research

This systematic review has shown that there is much research that is still needed in order to find a solution to reduce transmission of MRSA in pediatric inpatient settings. The implications that this systematic review has are limited since the majority of the studies included were observational and tested multiple intervention components simultaneously.

Given the heavy reliance on Mupirocin as the topical antibiotic of choice when treating MRSA, more research needs to be conducted on the efficacy of treatment among this subpopulation. More research also needs to be conducted to investigate whether decolonization is effective and cost-effective in preventing transmission of MRSA amongst pediatric inpatients.

The article by Kho on implementing an email alert system in hospital systems seems to be a very effective approach that allows for cohorting infected or colonized patients immediately when they are admitted, thus reducing transmission. More research should be conducted to see if this system is effective in high MRSA incidence areas.

One suggestion for future research would be to separate NICU patients and pediatrics, as NICUs have different practices (such as bed sharing with twins) and are at higher risk due to their compromised immune systems in comparison to those pediatric inpatients.

CONCLUSION

This systematic review provides some evidence that Mupirocin decolonization is not effective in reducing transmission of MRSA amongst pediatric inpatients. Another key report is that universal surveillance may not be as effective as originally thought, and thus mixed method prevention interventions should be instituted in order to have the best patient outcome. However, much research is needed on the pediatric population in order to develop guidelines in order to prevent transmission of MRSA amongst pediatric inpatients.

Table 1 Characteristics of included studies

Study	Setting	Intervention Type	Study Design	Relevant Outcomes	Process evaluation	Outcome Evaluation
Song et al; (2010)	NICU-LII/III	- Behavioral-Professional - Legislation/Regulation/ Enforcement - Clinical	RCS	- AS-N - CP - E - HH - D - SCH - En - C	- Active screening identified 67% infants with MRSA - Hand hygiene compliance rate 65-80% - Contact precaution adherence 61-78% - HCW screening- 3 colonized	- 218 (7%) patients admitted to NICU colonized/infected with MRSA - Overall- 2.8 per 1,000 p-d-at-risk; 5.2 per 1,000 p-d-at-risk during outbreak - 33.8% developed 1 or more infections - Mupirocin decolonization was unsuccessful in eliminating continuing transmission of MRSA
Khoury et al; (2005)	NICU-LIII/IV 18 beds	- Behavioral-Professional - Legislation/Regulation/ Enforcement - Clinical - Public health/medical - Environmental	RCS	- AS-P - CP - E - HH - D - En	- 6/110 (5.5%) HCW colonized	- 6 colonized (21.4%) out of 28 screened, 12 infected - Original attack rate 5.3% - Increased attack rate of 21.2% - Transmission rate: 3.97 in 2001 vs. 0.46 in 2000 with relative risk= 8.59 [95% CI: 1.99, 37.00 p=0.0005] - 42% developed 1 or more infections
Gans et al; (2013)	Children's Hospital	- Behavioral-Professional - Legislation/Regulation/ Enforcement - Clinical	PCS	- AS-P - NA	NA	- 3/87 patients developed SSI- 2 cases of nonvancomycin sensitive Enterobacter and 1 Vancomycin-sensitive MRSA - Application of local powder Vancomycin during spine deformity correction had no clinically significant effect on Creatinine levels
Kaushik et al; (2014)	Tertiary Care Hospital LIII 50 beds	- Behavioral-Professional - Legislation/Regulation/ Enforcement - Clinical	BAS	- AS-N - CP - C	NA	- 43% colonized during hospitalization - 57% colonized at admission - Cohorting colonized & infected infants needed to prevent spread of infection
Robicsek et al; (2009)	Hospital System (3 hospitals) 850 bed hospitals	- Behavioral-Professional - Legislation/Regulation/ Enforcement - Clinical	RCS	- AS-N - D	NA	- 69% of initial uninfected patients developed at least 1 MRSA infection - At time of readmission, 144 (47.8%) of 301 patients who received any quantity of Mupirocin were still colonized in contrast to 67 (63.2%) of 106 patients who did not receive Mupirocin p=0.007 - High levels of Mupirocin resistance in a MRSA isolate predicted continued colonization. OR 4.1 [95% CI: 1.6, 10.7]

Table 1 Characteristics of included studies

Study	Setting	Intervention Type	Study Design	Relevant Outcomes	Process evaluation	Outcome Evaluation
Holzmann-Pazgal et al; (2011)	PICU 20 beds	- Behavioral- Professional - Legislation/Regulation/ Enforcement - Clinical	BAS	- AS-N - CP - HH	- Significant improvement in hand hygiene compliance p<0.001, not independently associated with reduction in MRSA transmission	- Admission prevalence: 20/730 (2.7%) in 2006, 23/784 (2.9%) in 2007, 40/756 (5.3%) in 2008, 69/827 (8.3%) in 2009, significantly increased between 06-08 p=0.01, between 07-08 p=0.02, '08-'09 p=0.02
Kho et al; (2013)	Healthcare System-17 hospitals	Public health/medical care system interventions	PCS	- Other	- June 2007-June 2010-12,748 email alerts on 6,270 unique patients delivered	- Only 10.9% (2595) of cohort age <18 - 1.9% cultured both MRSA and VRE - 23% admissions of patients with previous history of MRSA identified at different hospitals from admitting hospital (range 19-30% of admissions each year during 3 years)
James et al; (2007)	Hospital 178 beds	- Behavioral- Professional - Legislation/Regulation/ Enforcement - Clinical	RCS	- AS-N - CP - HH - SCHW - En	- 2/135 (1.5%) of HCW screened identified as being nasal MRSA carriers, and 9 (6.7%) colonized with MSSA	- Of 432 peripartum women, 40 (6.9%) and 10 (2.3%) were colonized with MSSA in the nares and vagina, but no MRSA detected - MSSA isolated from nares of 14/399 (3.5%) newborns and 1 MRSA (0.3%) case was identified
Myers et al; (2011)	NICU-LIIID 71 beds	- Behavioral- Professional - Legislation/Regulation/ Enforcement - Clinical	RCS	- AS-N	NA	- Of the 447 inborn and 167 outborn infants, 1.6% and 3.6% were MRSA screen positive (p=0.0004, fishers exact test) - Of inborn, none developed infection but among outborn 50% had subsequent MRSA infection
Maraqa et al; (2011)	NICU-LIII 48 beds	- Behavioral- Professional - Legislation/Regulation/ Enforcement - Clinical	RCS	- AS-N - CP - E - HH - D - C	NA	- Colonization detected in 138 (6.74%) infants - Of colonized detected 30/138 (21.74%) infected-9/44 in 2004, 14/56 in 2005, 7/38 in 2006, overall 41 (2%) infected, 11/1,910 noncolonized infants (0.58%) infected - 119/1,616 (7.36%) inborn infants developed MRSA colonization RR 1.67 [95:1.04, 2.69] compared with 19/432 (4.4%) outborn infants p=0.03 - Annual incidence per 1,000 PD 0.915 in '04, 1.169 in '05, 0.893 in '06 - Relative risk of MRSA for colonized patients is 37.75 (95:19.335,73.69) p<.001 compared to noncolonized patients - Infection prevalence 0.997 (0.692-1.302), colonization prevalence 3.356 (3.043, 4.205) p<0.001, no difference in year

Table 1 Characteristics of included studies

Study	Setting	Intervention Type	Study Design	Relevant Outcomes	Process evaluation	Outcome Evaluation
Murillo et al; (2009)	NICU-LIV 47 beds	- Behavioral-Professional - Legislation/Regulation/Enforcement - Clinical - Public health/medical	RCS	- AS-N - CP - E - HH - D - SCHW - En	- 6 of 175 health care workers (3.4%) were also positive colonized	- (9.3%) 23/248 babies colonized - Jan-Dec 2005- infection rate of 2.14 infections per 100 admissions (0.99 infections per 1,000 patient-days) - Early MRSA infection rates in 2002, 2003, and 2004 were 1.69, 1.35, and 1.16 per 100 admissions and 0.93, 0.58, and 0.56 per 1000 patient-days respectively - In 21 babies (91.3%) MRSA was eradicated after 7 days of topical treatment but two babies (8.7%) required an, additional 7 days of treatment
Chiu et al; (2011)	2 tertiary care NICUs LIHB 50 bed LIHC 18 bed	- Behavioral-Professional - Legislation/Regulation/Enforcement - Clinical	BAS	- AS-P NA		- There was a significant decrease in use of Vancomycin with the number of Vancomycin starts was reduced by 35% to 62% and the number of infants treated with Vancomycin per 1,000 patient days was reduced by 40% to 49% (P<0.05) - Implementation of guideline and sustainably reduced Vancomycin use in NICUs with low prevalence of MRSA infection
Song et al; (2013)	Children's hospital 303 beds NICU LIII C 54 beds	- Behavioral-Professional - Legislation/Regulation/Enforcement - Clinical	RCS	- AS-N - CP - HH - En	- HH compliance rate increased from 50.3% pre to 84.0% post intervention (relative risk [RR], 1.7; 95% [95%CI]: 1.6-1.9) - Compliance among physicians & nurses increased from 48.6% to 87.0% (RR, 1.4; 95% CI: 1.3-1.6) and from 46.5% to 77.9% (RR, 1.3; 95% CI: 1.2-1.4), respectively - Sustaining HH at 80% or higher was associated with a 48% further reduction of MRSA acquisition (incident rate ratio, 0.52; 95% CI: 0.31 to 0.90) in a unit that had comprehensive MRSA prevention measures	- Overall hand hygiene compliance rate and MRSA acquisition rate in the unit was 81.0% (n 1/4 501; N 1/4 627) and 1.7 per 1,000 patient-days, respectively - When hand hygiene compliance increased from poor (<60%) to excellent (!90%), each level of improvement was associated with a 24% reduction in risk of MRSA acquisition (IRR, 0.76; 95% CI: 0.55-1.05) - When comparing hand hygiene compliance rates above 80% with rates below 80%, MRSA acquisition risk decreased significantly by 48% (IRR, 0.52; 95% CI: 0.31-0.90) - Averaged 2.4 MRSA acquisitions/ month, the 48% reduction in acquisition risk represented preventing 1.3 MRSA acquisitions each month

Table 1 Characteristics of included studies

Study	Setting	Intervention Type	Study Design	Relevant Outcomes	Process evaluation	Outcome Evaluation
Bertin et al; (2006)	NICU LIII	- Behavioral-professional - Legislation/Regulation/Enforcement - Environmental - Clinical	RCS	- AS-N - CP - E - HH - D - SCHW - En - C	- Identification of strain to HCW and cases, led to nasal Mupirocin treatment to and work restrictions for HCW, unsuccessfully treated first time - Retreated and successfully decolonized with nasal Mupirocin and 0.1% hydrocortisone butyrate topical ear solution	- Attack rate: 75% (9/12 neonates) - In 2004, 6 colonized
Volk et al; (2011)	Perinatal ward in 571 bed tertiary care academic setting	- Behavioral-Professional - Legislation/Regulation/Enforcement - Clinical	RCS	- AS-N	NA	- 4 (0.2%) of the 2,110 infants had nasal MRSA colonization upon screening - Strong association between maternal nasal colonization and that of new infants - Universal surveillance of maternal and newborn may not be warranted
Delaney et al; (2012)	NICU LJIB 60 beds	- Behavioral-Professional - Legislation/Regulation/Enforcement - Clinical	RCS	- AS-N - CP - HH - D - C	NA	- Active screening identified 77 colonized infants in 2008 - 2004- incidence 1.88 per 1,000 PDAR in pre-Mupirocin time, rate decreased to 0.40 per 1,000pdar after implementation of intranasal Mupirocin in august 2004; discontinued Mupirocin 2005- incidence rate 1.42 per 1,000pdar, implemented infection control and Mupirocin rate decreased to 0.33 per 1,000 PDAR - Overall, when comparing Mupirocin prophylactic period with control period, significant reduction in rate of s. aureus infection (p<0.0001) with a number needed to treat of 49 and incidence rate ratio of 0.29 (95%: 0.166, 0.512)
Popoola et al; (2014)	NICU LIII 45 beds	- Behavioral-Professional - Legislation/Regulation/Enforcement - Clinical	RCS	- AS-N - CP - E - HH - D - SCHW - C	- All HCW (204) screened -7 (3.4%) colonized - All decolonized, 4 (80%) recurrent colonization and again decolonized	- 74/3,536 neonates (2.0%) culture grow MRSA - 19/74 (26%) had a MRSA infection, 11/66 (17%) colonized - Mean quarterly incidence of NICU-onset MRSA infection was 0.3 per 1,000 patient days [95%: 0.0,0.8] - MRSA transmission continued despite increases in hand hygiene compliance (p<0.001)

Table 1 Characteristics of included studies

Study	Setting	Intervention Type	Study Design	Relevant Outcomes	Process evaluation	Outcome Evaluation
Gregory et al; (2009)	NICU LIIIB	- Behavioral-Professional - Legislation/Regulation/ Enforcement - Clinical	RCS	- AS-N - CP - C	NA	- 87 (85.3%) of 102 colonized - 15 (14.7%) of 102 invasive infection - 7997 infants admitted to NICU-> 102 MRSA + (1.3%) - 1.79 cases per 1,000 patient days [95%: 1.19, 2.49] in 20000 0.15 cases per 1,000 patient days [95%: 0.15, 0.44] in 2005 Poisson regression analysis revealed a 31% decrease in incidence per year over this period p<0.0001 - However, sharp increase in first 8 months of 2007 with 1.26 cases per 1,000 patient days [95%: 1.03, 2.42]-> showing poison regression increase of 250% annual increase in incidence for this time p<0.0001 - Antibiotic treatment did not eradicate MRSA colonization consistently; 1/6 infants with BSI and 8/9 infants with SSTI remained colonized with MRSA after treatment, did not decolonize other infants, only infected infants
Thomson et al; (2011)	Pediatric center 123 beds	- Behavioral-Professional - Legislation/Regulation/ Enforcement - Clinical	RCS	- AS-N - CP	NA	- 234/3934 (5.7%) pediatric patients colonized and 99 (2.4%) had culture-proven MRSA infection - Colonization of infants less than a year old was 8.4% when compared to those older than one at 5.2% (p=0.004) - MRSA infection also more prevalent in children under 5 (3.6%) vs. children older than 5 (1%) p=0.002 - Only 54% of those with MRSA infection had a positive nasal screen
Costantini et al; (2013)	Pediatric cardiac surgery patients	- Behavioral-Professional - Legislation/Regulation/ Enforcement - Clinical	RCR	- AS-N - AS-P - D	NA	- The overall rate of colonization with MRSA and MSSA was 4.2% and 29.1%, respectively - Screening of only the nose would have failed to detect 28.6% of the MRSA cases - Of the 102 patients, 85 had a groin swab (three positive) for MRSA, 9 had a perianal swab (zero positive), & 8 had an umbilical swab (zero positive) - Overall, 7 6.9% of the 102 dually screened patients tested positive for MRSA at least in one site
Kjonegaard et al; (2013)	MICU- 24 bed SICU- 15 bed	- Behavioral-Professional - Legislation/Regulation/ Enforcement Clinical	BAS	- AS-N - AS-P - CP	NA	- HA-MRSA infection rates did not decline after implementation of ICU screening - The mean number of hospital admissions per month was 2,235 with a range from 2,081 to 2,459. An average of 2.4 HA-MRSA infections per month was identified (range, 0-7)

RCS, Retrospective Cohort Study; RCF, Retrospective case findings; PCS, prospective cohort study; BAS, Before & After study; RCT, Randomized control trial.; RCR, Retrospective Chart Review.
LII/III, Level II/III.
AS-N, Active Surveillance Nasal Cultures; AS-P, Active Surveillance swab other than nares; CP, Contact Precaution; E, Education; HH, Hand Hygiene; D, Decolonization; SHCW, Screening Healthcare worker; En, Environment; C, Cohorting MRSA Patients.
PD, Patient-Days; PDAR, Patient Days At Risk

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