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Recommendations for Prevention and Control of *Staphylococcus aureus* Infections in Neonatal Intensive Care Unit Patients.

Centers for Disease Control and Prevention
National Center for Emerging and Zoonotic Infectious Diseases
Division of Healthcare Quality Promotion

Aaron M. Milstone, MD, MHS[a], Alexis Elward, MD[b], Michael T. Brady, MD[c], Kendra Cox, MA[d], Loretta L. Fauerbach, MS, CIC[e], Judith A. Guzman-Cottrill, DO[f], Jamesa Hogges, MPH[g], W. Charles Huskins, MD, MSc[h], Kathleen L. Irwin, MD, MPH[i], Martha Iwamoto, MD, MPH[j], Gretchen Kuntz, MSW, MSLIS[k], Brian Leas, MA, MS[l], Amanda D. Overholt, MPH[g], Kristin Tansil Roberts, MSW[d], Srila Sen, MA[m], Nalini Singh, MD, MPH[n], Erin Stone, MA[n], Craig A. Umscheid, MD, MSCE[o], and Kristina Bryant, MD[p], for the Healthcare Infection Control Practices Advisory Committee[q]

[a]Johns Hopkins University School of Medicine, Baltimore, MD; [b]Washington University School of Medicine, St. Louis, MO; [c]Nationwide Children's Hospital, Columbus, OH; [d]Eagle Global Scientific, LLC, Atlanta, GA; [e]Fauerbach & Associates, LLC, Gainesville, FL; [f]Oregon Health and Science University, Portland, OR; [g]formerly Northrop Grumman Corporation, Atlanta, GA; [h]Mayo Clinic, Rochester, MN; [i]formerly Division of Healthcare Quality Promotion, National Center for Emerging and Zoonotic Infectious Diseases, Centers for Disease Control and Prevention, Atlanta, GA (now with the Agency for Healthcare Quality Research, Rockville, MD); [j]formerly Division of Healthcare Quality Promotion, National Center for Emerging and Zoonotic Infectious Diseases, Centers for Disease Control and Prevention, Atlanta, GA (now with the New York City Department of Health and Mental Hygiene, New York, NY); [k]formerly Center for Evidence-based Practice, University of Pennsylvania Health System, Philadelphia, PA (now with the University of Florida-Jacksonville, Jacksonville, FL); [l]Center for Evidence-based Practice, University of Pennsylvania Health System, Philadelphia, PA; [m]formerly Eagle Global Scientific, LLC, Atlanta, GA (now with The Bizzell Group, Lanham, MD); [n]Division of Healthcare Quality Promotion, National Center for Emerging and Zoonotic Infectious Diseases, Centers for Disease Control and Prevention, Atlanta, GA; [o]formerly Center for Evidence-based Practice, University of Pennsylvania Health System, Philadelphia, PA (now with the University of Chicago Medicine, Chicago IL); [p]University of Louisville, Louisville, KY; and [q]the Healthcare Infection Control Practices Advisory Committee

Authors are listed alphabetically, with the exception of the first two authors and the last author, based on workgroup role.

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1. Executive Summary

Recommendations for the Prevention and Control of Staphylococcus aureus *in Neonatal Intensive Care Unit Patients* provides new, evidence-based recommendations specific to the prevention and control of *Staphylococcus aureus* (*S. aureus*), including methicillin-resistant *S. aureus* (MRSA) and methicillin-sensitive *S. aureus* (MSSA), in neonatal intensive care unit (NICU) patients. This document is one section of the full *Guideline for Infection Prevention and Control in Neonatal Intensive Care Unit Patients*. This guideline will be published in a segmental manner as sections are completed. This section does not provide a comprehensive set of infection control recommendations for the prevention of *S. aureus* in NICU patients, but instead supplements other CDC guidelines. The term "*S. aureus"* includes both MSSA and MRSA. Core infection prevention and control recommendations for the prevention of *S. aureus* that apply across all healthcare settings are summarized in the Healthcare Infection Control Practices Advisory Committee (HICPAC) Core Practices document,[1] and the original recommendations can be found in the respective Centers for Disease Control and Prevention (CDC) and HICPAC Guidelines.

This document is intended for use by infection prevention staff, healthcare epidemiologists, healthcare administrators, nurses, neonatologists, other healthcare providers, and persons responsible for developing, implementing, and evaluating infection prevention and control programs for NICUs. The guideline can also be used as a resource for societies or organizations that wish to develop more detailed implementation guidance for the prevention of infection in NICU patients.

The recommendations were based on a systematic review of the best available literature through August 2019. Subject matter experts supplemented the literature search results by recommending relevant references published since August 2019. In order to provide explicit links between the evidence and recommendations, an adapted GRADE approach was used to evaluate the strength and direction of the evidence and formulate recommendations. The Methods section of this guideline provides additional detail on the development of this document. Where evidence was insufficient to formulate evidence-based recommendations, interim guidance is available to inform the delivery of healthcare in NICUs. SHEA neonatal intensive care unit (NICU) white paper series: Practical approaches to Staphylococcus aureus disease prevention | Infection Control & Hospital Epidemiology | Cambridge Core

The evidence review for *S. aureus* was guided by these Key Questions:

1. What are effective strategies for preventing *S. aureus* transmission from colonized or infected NICU patients to other patients, and do these strategies differ between MRSA and MSSA or in the setting of an outbreak?
2. If screening is conducted, which anatomic sampling sites and laboratory assays most effectively identify *S. aureus* colonization in NICU patients?
3. What are the risk factors and risk indicators for *S. aureus* infection in NICU patients, and do these factors differ between MRSA and MSSA or in the setting of an outbreak?
4. What are the risk factors and risk indicators for *S. aureus* colonization in NICU patients, and do these factors differ between MRSA and MSSA or in the setting of an outbreak?

Readers wishing to examine the primary evidence underlying the recommendations are referred to the Evidence Review in the body of this document and to the Tables in the Appendix. The Appendix contains clearly delineated search strategies, Evidence Tables containing study-level data examined, and GRADE Tables which aggregate the overall strength and direction of the evidence.

2. Summary of Recommendations

Recommendation 1.a. Perform active surveillance testing for *S. aureus* colonization in neonatal intensive care unit patients when there is an increased incidence of *S. aureus* infection or in an outbreak setting. **(Recommendation)**

- *Supporting Evidence*: The evidence consists of ten observational studies.[2-11]
- *Level of Confidence in the Evidence*: The level of confidence in this evidence is low because observational studies are considered to be at higher risk of bias than randomized controlled trials.
- *Benefits*: When there is an increased incidence of *S. aureus* infection or in an outbreak setting, the benefit of performing active surveillance testing for *S. aureus* colonization in NICU patients is a reduction in *S. aureus* infection, colonization, and transmission resulting from facility implementation of strategies targeting patients identified by active surveillance testing.
- *Risks and Harms*: Harms that could result from performing active surveillance testing in this population and setting include minor patient discomfort from performing nasal swabs or bleeding caused by trauma to the nasal mucosa. The institution of Contact Precautions has inconsistently been associated with unintended consequences, such as decreased healthcare personnel-patient contact, in other populations.[12-16] This literature search did not identify studies suggesting harm from use of Contact Precautions in NICU populations.
- *Resource Use*: Implementing active surveillance testing will result in increased human and material costs; however, it is anticipated that these costs will be less than the cost associated with invasive *S. aureus* infections in this vulnerable population that could be prevented by subsequent implementation of additional infection prevention strategies.
- *Balance of Benefits and Harms*: There is a preponderance of benefit over harm for active surveillance testing for *S. aureus.*
- *Value Judgments*: Infection prevention, patient safety, and outbreak management in this high-risk population were all considered in the formulation of this recommendation.
- *Intentional Vagueness*: The term "*S. aureus"* includes both methicillin-sensitive *S. aureus* (MSSA) and MRSA. An "increased incidence *of S. aureus* infection" may include a cluster of *S. aureus* infections or an increase in the endemic incidence of *S. aureus* infection compared to historical data from the unit or the published literature.
- *Exceptions*: There are no exceptions to this recommendation.

Recommendation 1.b. Perform active surveillance testing for methicillin-resistant *S. aureus* (MRSA) colonization in neonatal intensive care unit patients when there is evidence of ongoing healthcare-associated transmission within the unit. **(Recommendation)**

- *Supporting Evidence*: The evidence consists of five observational studies.[3,4,6-8]
- *Level of Confidence in the Evidence*: The level of confidence in this evidence is low because observational studies are considered at higher risk of bias than randomized controlled trials.
- *Benefits*: Implementation of active surveillance testing for MRSA colonization when there is evidence of ongoing healthcare-associated transmission could lead to the prompt implementation of infection control strategies that will result in a reduction of person-to person transmission and decreased incidence of MRSA colonization and infection.
- *Risks and Harms*: Harms that could result from performing active surveillance testing in this population and setting include minor patient discomfort from performing nasal swabs or bleeding caused by trauma to the nasal mucosa. The institution of Contact Precautions has inconsistently been associated with unintended consequences, such as decreased healthcare personnel-patient contact, in other

populations.[12-16] This literature search did not retrieve data suggesting harm from use of Contact Precautions in NICU populations.

- *Resource Use*: Implementing active surveillance testing for MRSA colonization will result in increased human and material costs; however, it is anticipated that these costs will be less than the cost associated with MRSA infections in this vulnerable population that could be prevented by subsequent implementation of additional infection prevention strategies.
- *Benefit-Harm Assessment*: There is a preponderance of benefit over harm for active surveillance testing for MRSA.
- *Value Judgments*: Values considered in the formulation of this recommendation include patient safety and resource considerations.
- *Intentional Vagueness*: "Healthcare-associated transmission within the unit" is suggested by an increase in cases of MRSA colonization or infection as determined by surveillance cultures or cultures obtained for clinical indications.
- *Exceptions*: This recommendation only applies to MRSA.

Recommendation 1.c. The use of active surveillance testing for methicillin-sensitive *S. aureus* (MSSA) colonization in neonatal intensive care unit patients to detect ongoing healthcare-associated MSSA transmission is an unresolved issue. **(No Recommendation)**

- *Supporting Evidence*: No evidence was retrieved evaluating the use of active surveillance testing for MSSA colonization in NICU patients to prevent transmission of MSSA.
- *Level of Confidence in the Evidence*: This criterion is not applicable.
- *Benefits*: If a facility chooses to implement active surveillance testing for MSSA, it is likely that interventions subsequently implemented to reduce MSSA transmission would result in a decrease in MSSA infections in other NICU patients.
- *Risks and Harms*: Harms that could result from performing active surveillance testing in this population and setting include minor patient discomfort from performing nasal swabs or bleeding caused by trauma to the nasal mucosa. If facilities choose to conduct active surveillance for MSSA colonization in NICU patients, there may be minor patient discomfort from performing nasal swabs.
- *Resource Use*: There would be no additional resource use if facilities chose not to conduct active surveillance for MSSA; however, if facilities chose to conduct active surveillance for MSSA to implement interventions to reduce MSSA infection and colonization, there would be increased human and material costs.
- *Benefit-Harm Assessment*: MSSA can be pathogenic and can cause invasive infections; however, benign colonization with MSSA without associated clinical signs of invasive infection is common in NICU patients. Active surveillance testing may identify infants at risk to develop MSSA infection and who may be the source for transmission of MSSA to other infants. The optimal strategies to decrease individual risk and risk to the population from MSSA-colonized infants remains unresolved.
- *Value Judgments*: Values considered in the formulation of this recommendation include the availability of evidence, patient safety, and resource considerations.
- *Intentional Vagueness*: "Healthcare-associated transmission within the unit" is suggested by an increase in cases of MSSA colonization or infection as determined by cultures obtained for clinical indications.
- *Exceptions*: This recommendation only applies to MSSA.

Recommendation 1.d. If active surveillance testing for *S. aureus* colonization is implemented for neonatal intensive care unit patients, test at regular intervals to promptly identify newly colonized patients. **(Recommendation)**

- *Supporting Evidence*: The evidence consists of ten observational studies.[2-4,6-11,17]

- *Level of Confidence in the Evidence*: The level of confidence in this evidence is low because observational studies are considered to be at higher risk of bias than randomized controlled trials.
- *Benefits*: Implementation of routine active surveillance testing for *S. aureus* colonization will enable facilities to identify colonized patients promptly and guide implementation of appropriate infection prevention and control measures to reduce person-to-person transmission.
- *Risks and Harms*: Harms that could result from performing active surveillance testing in this population and setting include minor patient discomfort from performing nasal swabs or bleeding caused by trauma to the nasal mucosa.
- *Resource Use*: The frequency of testing will directly affect costs, including human and laboratory resource costs.
- *Benefit-Harm Assessment*: There is a preponderance of benefit over harm for testing routinely for *S. aureus* colonization in NICU patients.
- *Value Judgments*: Values considered in the formulation of this recommendation include patient safety and resource considerations.
- Intentional Vagueness:
    - The frequency of active surveillance testing is noted as "at regular intervals" to allow facilities to sample weekly, or more or less frequently, depending upon the facility's baseline rates of colonized and infected patients or as unit epidemiology changes.
    - The addition of admission testing to testing at regular intervals is best determined by the individual facility or health system.
- Exceptions: There are no exceptions to this recommendation.

Recommendation 1.e. If active surveillance testing for *S. aureus* colonization in neonatal intensive care unit patients is implemented, consider testing outborn infants or infants transferred from other newborn care units on admission to promptly identify newly admitted colonized patients. **(Conditional Recommendation)**

- *Supporting Evidence*: The evidence consists of four observational studies.[2,8-10]
- *Level of Confidence in the Evidence*: The level of confidence in this evidence is low because observational studies are considered to be at higher risk of bias than randomized controlled trials. Additionally, three of the four studies were conducted in the same facility, potentially limiting the generalizability of their results.
- *Benefits*: If outborn infants or infants transferred from other newborn care units are tested on admission for *S. aureus* colonization, a reduction in *S. aureus* colonization and infection could be seen due to potentially higher endemic rates in the outborn neonatal population.
- *Risks and Harms*: If facilities chose to conduct active surveillance for *S. aureus* colonization in NICU patients, there could be minor patient discomfort from performing nasal swabs or bleeding caused by trauma to the nasal mucosa.
- *Resource Use*: Performing testing for *S. aureus* colonization on outborn infants or infants transferred from other newborn care units on admission would result in increased material and human resource costs. However, it is anticipated that these costs will be less than the cost of invasive *S. aureus* infections in this vulnerable population that could be prevented by subsequent implementation of additional infection prevention strategies.
- *Benefit-Harm Assessment*: There is a preponderance of benefit over harm for testing outborn infants or those transferred from other newborn care units. Relatively minor risks and harms, including discomfort from performing nasal swabs and the costs of testing, are outweighed by the potential benefits of preventing *S. aureus* colonization and infection. The likelihood of benefit increases in settings in which outborn and transferred infants have higher *S. aureus* colonization rates.

- *Value Judgments*: Values considered in the formulation of this recommendation include patient safety and economic and human resource costs.
- *Intentional Vagueness*:
    - Benefit has also been seen in the literature in testing all neonates on admission. The recommendation specifies outborn infants or transferred infants because the literature showed a higher colonization prevalence in this population compared to newborns admitted from labor and delivery units. Units can consider their own unique epidemiologic needs when determining the optimal population to test on admission.
    - The term "*S. aureus"* includes methicillin-resistant *S. aureus* (MRSA) and methicillin-sensitive *S. aureus* (MSSA).
- *Exceptions*: There are no exceptions to this recommendation.

Recommendation 1.f. If active surveillance for *S. aureus* colonization in neonatal intensive care unit patients is performed, either culture-based or polymerase chain reaction detection methods are acceptable. **(Recommendation)** (See Implementation Considerations - Page 19).

- *Supporting Evidence*: The evidence consists of three diagnostic studies.[18-20]
- *Level of Confidence in the Evidence*: The level of confidence in this evidence is moderate due to imprecision in the estimate of effect.
- *Benefits*: If this recommendation is followed, facilities will be able to select the assay that best fits facility considerations and the needs at hand. While polymerase chain reaction (PCR) testing offers marginally increased sensitivity over culture for detecting *S. aureus*, culture has the advantage of having isolates available for molecular typing and susceptibility tests.
- *Risks and Harms*: PCR is more sensitive for the detection of *S. aureus* and offers a small additional benefit over culture. PCR can have a more rapid turnaround, depending on laboratory capabilities; however, PCR has a lower specificity for detecting methicillin-resistant *S. aureus* (MRSA). While culture is not likely to miss detecting a large number of *S. aureus*-colonized infants, the possibility exists that the use of culture-based methods may result in a small number of *S. aureus*-colonized infants not being identified. PCR does not yield organisms that can undergo strain typing, which is a disadvantage in an outbreak investigation.
- *Resource Use*: PCR is more expensive than culture-based methods.
- *Benefit-Harm Assessment*: There is a benefit to using PCR versus culture-based methods to detect *S. aureus* colonization, but this benefit is offset by important considerations. The sensitivity of PCR is slightly higher, but facilities can balance performance characteristics of the test, clinical management considerations, susceptibility testing, facility volume, outbreak identification, and test turnaround time when choosing an assay, as outlined above.
- *Value Judgments*: Values considered in the formulation of this recommendation include test characteristics and availability, outbreak management, unit volume, economic considerations, need for a full susceptibility panel, speed of test turnaround, and resource utilization.
- *Intentional Vagueness*: The term "*S. aureus"* incudes MRSA and methicillin-sensitive *S. aureus* (MSSA).
- *Exceptions*: There are no exceptions to this recommendation.

Recommendation 1.g. If active surveillance for *S. aureus* colonization of neonatal intensive care unit patients is performed, collect samples from at least the anterior nares of neonatal intensive care unit patients. **(Recommendation)** (See Implementation Considerations - Page 19).

- *Supporting Evidence*: The evidence consists of two diagnostic studies.[21,22]
- *Level of Confidence in the Evidence*: The level of confidence in this evidence is moderate due to inconsistent results across studies.

- *Benefits*: The anterior nares have the highest yield for identifying *S. aureus* colonization. Collecting samples from the axilla, rectum, and umbilicus can increase the yield. The yield from collecting samples from additional sites offers an incremental increase in sensitivity. During outbreaks with a highly virulent strain, sampling additional sites might provide greater benefit.
- *Risks and Harms*: Harms that could result from performing active surveillance testing in this population and setting include minor patient discomfort from performing nasal swabs or bleeding caused by trauma to the nasal mucosa. Further, if neonates are not colonized in the anterior nares and only the nares are sampled, then colonization at another anatomic sites may be missed.
- *Resource Use*: There could be increased costs associated with running multiple assays for multiple sites, including time, financial, human, and material resources. However, samples could be combined and processed as a single test to yield a composite result, limiting increased costs associated with sampling multiple sites.
- *Benefit-Harm Assessment*: There is a preponderance of benefit over harm for sampling at least the anterior nares, which is the most sensitive anatomic site for identifying NICU patients colonized with *S. aureus.* However, some infants are colonized at sites other than the anterior nares, and those infants would be missed if only the nares were sampled. No patient-level harm is associated with sampling the axilla, rectum, or umbilicus: only additional resource utilization and cost. While collecting samples from additional sites increases sensitivity, it is not clear that the additional samples will have a meaningful impact on outcomes, or that the additional costs are warranted. The benefit of testing additional sites may be greater in periods in which increased sensitivity is needed, such as during an outbreak.
- *Value Judgments*: Values considered in the formulation of this recommendation include test characteristics and resource utilization.
- *Intentional Vagueness*: The term "*S. aureus"* includes methicillin-resistant *S. aureus* (MRSA) and methicillin-sensitive *S. aureus* (MSSA). "At least" is intentionally vague to allow providers to determine alternate sampling sites.
- *Exceptions*: There are no exceptions to this recommendation.

Recommendation 2.a. Consider targeted decolonization for *S. aureus*-colonized neonatal intensive care unit patients in addition to the implementation of, and adherence to, appropriate infection prevention and control measures in an outbreak setting, or when there is ongoing healthcare-associated transmission, or an increase in the incidence of infection. **(Conditional Recommendation)**

- *Supporting Evidence*: The evidence consists of four observational studies.[9-11,23]
- *Level of Confidence in the Evidence*: The level of confidence in this evidence is low because observational studies are considered to be at higher risk of bias than randomized controlled trials. Two of these studies were performed in a single center NICU population.
- *Benefits*: Implementing targeted decolonization could result in a reduction in the *S. aureus* colonization rate of NICU patients, which then may result in a reduction in *S. aureus* transmission and infection in NICUs.
- *Risks and Harms*: If targeted decolonization were conducted for *S. aureus* colonized NICU patients, harms could include systemic absorption of decolonizing agents, increased resistance to the decolonizing agent, and adverse skin reactions. Application of nasal ointment can be technically challenging in a very low birth weight infant. There could be minor patient discomfort from the application of intranasal ointment, which could partially occlude small nares and accumulate in the prongs of nasal cannula used to deliver oxygen.
- *Resource use*: Conducting targeted decolonization will result in increased material and human resource costs.

- *Benefit-Harm Assessment*: The potential reduction in *S. aureus* colonization resulting from the implementation of targeted decolonization is balanced by concern for the development of antimicrobial resistance, antiseptic tolerance, cross-resistance, and safety concerns due to systemic absorption of decolonization agents seen in this population.
- *Value Judgments*: Values considered in the formulation of this recommendation include patient safety, antimicrobial stewardship and resistance concerns, federal regulatory approvals, and resource utilization.
- *Intentional Vagueness*:
  - While *S. aureus* colonized NICU patients are the most frequently targeted population for decolonization, the optimal population to target is left for the facility to determine.
  - "Healthcare-associated transmission within the unit" is suggested by an increase in cases of *S. aureus* colonization or infection as determined by cultures obtained for clinical indications.
  - The term "*S. aureus"* includes methicillin-resistant *S. aureus* (MRSA) and MSSA.
- *Exceptions*: There are no exceptions to this recommendation.

Recommendation 2.b. The use of universal decolonization for *S. aureus*-colonized neonatal intensive care unit patients is an unresolved issue. **(No Recommendation)**

- *Supporting Evidence*: The evidence consists of two observational studies.[11,17]
- *Level of Confidence in the Evidence*: The level of confidence in this evidence is low because observational studies are considered to be at higher risk of bias than randomized controlled trials.
- *Benefits*: The implementation of universal decolonization for *S. aureus* colonized NICU patients could lead to a reduction of *S. aureus* colonization and infection rates.
- *Risks and Harms*: Harms associated with implementing universal decolonization in this population include systemic absorption of decolonizing agents and adverse events from the agent chosen for decolonization. Resistance is more likely to develop if decolonization is indiscriminate in its application.
- *Resource Use*: If universal decolonization were implemented, resource use would shift from lab costs to decolonization costs, which in some cases may increase or decrease overall resource use.
- *Benefit-Harm Assessment*: Universal decolonization may be more feasible and easier to implement than targeted decolonization, but its additional benefit is unclear.
- *Value Judgments*: Values considered in the formulation of this recommendation include patient safety, antimicrobial stewardship and resistance concerns, federal regulatory approvals, and resource utilization.
- *Intentional Vagueness*: There is no intentional vagueness in this recommendation.
- *Exceptions*: There are no exceptions to this recommendation.

Recommendation 2.c. The optimal decolonization agent or combination of agents remains an unresolved issue. **(No Recommendation)**

- *Supporting Evidence*: The evidence consists of approved labels from the US Food and Drug Administration (FDA) and five observational studies.[9-11,17,23]
- *Level of confidence in evidence*: The level of confidence in this evidence is low because observational studies are considered to be at higher risk of bias than randomized controlled trials, and additional evidence is regulatory.
- *Benefits*: A reduction is seen in *S. aureus* infection and colonization when intranasal decolonization is implemented (alone or in combination with antiseptic) in addition to the implementation of core infection prevention and control practices.
- *Risks and Harms*: The safety and efficacy of intranasal mupirocin is not established in patients aged less than 12 years. Additionally, in neonates and premature infants, systemic absorption occurs following

intranasal administration, but it remains uncertain whether this absorption causes adverse health consequences in neonates. *S. aureus* may exhibit resistance to mupirocin; increased use of the agent may contribute to increased rates of resistance. The application of a nasal ointment can be technically challenging in a very low birthweight infant and there could be minor patient discomfort from the application of intranasal ointment, which could partially occlude small nares and accumulate in the prongs of nasal cannula used to deliver oxygen. The FDA indication for topical chlorhexidine (CHG) is for use "with care" in premature infants or infants under 2 months of age. The potential harms of CHG in the NICU population retrieved by this review include adverse skin reactions, including chemical burns; systemic absorption of uncertain clinical significance; and the development of tolerance to the agent used, or cross-resistance to other agents.

- *Resource Use*: Implementation of decolonization would result in increased material and human resource costs.
- *Benefit-Harm Assessment*: The balance of benefits and harms of decolonization agents, which include significant systemic absorption, the development of tolerance to the agent used or cross-resistance to other agents, and topical reactions, is unclear.
- *Value Judgments*: Values considered in the formulation of this recommendation include federally approved labels, patient safety, antimicrobial stewardship and resistance concerns, and resource utilization.
- *Intentional Vagueness*: This recommendation does not specify a specific decolonization agent or agents because no FDA-approved decolonization agent has been consistently proven effective and safe in this population.
- *Exceptions*: There are no exceptions to this recommendation.

Recommendation 3. Appropriate procedures to allow discontinuation of Contact Precautions for individual neonatal intensive care unit patients who have a history of colonization or infection with methicillin-resistant *S. aureus* (MRSA) is an unresolved issue. **(No Recommendation)**

- *Supporting Evidence*: No evidence was retrieved that could be used to formulate a recommendation regarding appropriate procedures to allow discontinuation of Contact Precautions for individual NICU patients who have a history of colonization or infection with MRSA.
- *Level of Confidence in the Evidence*: This criterion is not applicable.
- *Benefits*: For patients with a history of *S. aureus* colonization or infection, continuing Contact Precautions for the duration of hospitalization can prevent transmission of *S. aureus* from patients with recurrent colonization.
- *Risks and Harms*: Even after decolonization, neonates can have recurrent *S. aureus* colonization. Early discontinuation of Contact Precautions for patients with a history of colonization or infection can contribute to increased transmission of *S. aureus*. Implementation of Contact Precautions has inconsistently been associated with unintended consequences, such as decreased healthcare personnel contact, in other populations.[12-16] This literature search did not retrieve data suggesting harm from the use of Contact Precautions in NICU populations.
- *Resource Use*: Implementation of Contact Precautions contributes to increased material and human resource costs.
- *Benefit-Harm Assessment*: This literature search retrieved no data to support a specific protocol by which to discontinue Contact Precautions (e.g., discontinue after multiple negative cultures).
- *Value Judgments*: Values considered in the formulation of this recommendation include patient safety, familial bonding, the individual facility's baseline colonization and infection rates, and economic and human resource considerations.

- *Intentional Vagueness*: There is no intentional vagueness in this recommendation.
- *Exceptions*: There are no exceptions to this recommendation.

3. Introduction

The first *Staphylococcus aureus* (*S. aureus*) outbreak in infants in hospital nurseries was reported in the literature in the late 1800s.[24] This organism is now the most commonly reported healthcare-associated infection (HAI) pathogen in United States neonatal intensive care units (NICUs).[25] Rates of invasive *S. aureus* infections are high in neonates, especially in preterm and low birthweight infants.[26] Methicillin-resistant *S. aureus* (MRSA) infections in the neonatal population have been described since the early 1980s,[27] and numerous outbreaks in NICUs have been reported.[6,28-39] Although outbreaks of *S. aureus* among patients, especially MRSA, pose significant challenges for NICUs,[40] *S. aureus* is endemic in the NICU as well,[21] giving rise to the need for prevention strategies in both outbreak and endemic settings. While MRSA has long been the focus of prevention efforts due to the difficulty in treating and eradicating it, recent studies have demonstrated that methicillin-sensitive *S. aureus* (MSSA) has morbidity and mortality equal to MRSA and occurs more frequently in NICU patients.[26,40]

When work on this Guideline effort began in 2009, the draft recommendations focused only on MRSA. At that time, the literature base for MSSA in NICUs was sparse and deemed insufficient to support a full literature review on the topic. Since then, studies have been published demonstrating the burden of MSSA disease and prevention in the NICU. While MRSA remains epidemiologically significant and a priority pathogen, MSSA infections far exceed MRSA infections in the NICU, so prevention strategies for *S. aureus* as a whole are needed.

Neonates who acquire *S. aureus* colonization are at increased risk of *S. aureus* infection.[21] The ultimate goal driving efforts to prevent and control *S. aureus* transmission in NICUs is the prevention of disease in vulnerable neonates. Any neonatal infection can be associated with long-term sequelae, including negative long-term neurocognitive outcomes and poor prognosis. In practice, NICU patients with MRSA, and in some cases MSSA, are decolonized with the intent of preventing progression to invasive diseases and limiting further transmission. Limited evidence about optimal decolonization regimens exists in this population, and new drugs and alternative therapies for decolonization are rarely studied in neonates and are unlikely to achieve approval for widespread implementation. Strategies to mitigate risk when colonization occurs are urgently needed, but in the meantime, efforts to prevent transmission and subsequent colonization should therefore be prioritized.

This document is based on current understanding of the transmission dynamics of *S. aureus* in the NICU setting.[41,42] New laboratory methods, including whole genome sequencing (WGS), suggest that related strains account for the largest proportion of transmission events in NICUs, presumably from patient-to-patient spread via indirect contact transmission, but multiple unrelated strains may be transmitted concurrently in parallel and new, unrelated strains are introduced frequently.[43-46] The reservoirs for new and existing strains are incompletely understood. Infection prevention measures targeting spread from healthcare personnel and the hospital environment - the focus of this document - may not be sufficient to prevent all transmission. Specifically, parents are a known reservoir from which neonates can acquire *S.* aureus colonization, and an intervention targeting parents may reduce transmission.[47] Further studies are needed to determine when strategies to interrupt transmission from parents, such as hand hygiene educational intervention or decolonization, can prevent neonatal *S. aureus* disease.

This document makes specific recommendations about interventions to be implemented when there is evidence of ongoing transmission of *S. aureus*, an increased incidence of *S. aureus* infection, or in an outbreak setting. However, no discrete benchmark or threshold for *S. aureus* or MRSA infection rates indicates when additional

efforts are required. It is necessary for healthcare facilities to use their own data to determine when to add interventions and where to target prevention efforts when infections are occurring. As part of a comprehensive infection prevention and control strategy, facilities can employ a quality improvement framework to maximize efficiency in reducing infections. Tools such as CDC's Targeted Assessment for Prevention (TAP) Strategy Toolkit[48] enable hospitals to target locations within facilities, assess gaps, and implement interventions to prevent and control *S. aureus*.

This Guideline was developed to provide evidence-based recommendations for the prevention of *S. aureus* in this vulnerable population. For important topics where evidence was insufficient to formulate evidence-based recommendations, companion guidance is available to inform the delivery of healthcare in NICUs *[link to SHEA Companion Document]*. Additionally, guidance is available elsewhere regarding the management of multidrug-resistant organisms (MDROs) in healthcare settings (https://www.cdc.gov/infectioncontrol/guidelines/mdro/index.html), including limiting MRSA outbreaks.[49]

4. Methods

This guideline is based on a targeted systematic review of the best available evidence on the prevention and control of infections in NICUs.

4.a. Development of Key Questions

In order to inform the development of the *Staphylococcus aureus* (*S. aureus*) Key Questions, electronic searches were conducted to retrieve existing relevant guidelines and to identify gaps and areas where new evidence may have been published. The strategies used for the guideline searches and results can be found in the *Appendix (https://www.cdc.gov/infectioncontrol/pdf/guidelines/NICU-saureus-Appendix-508.pdf).*(Appendix, Section 1.) The results of this initial review informed the development of a preliminary list of Key Questions. Clinical experts were surveyed at national infectious disease society meetings to provide feedback on potential Key Questions and to identify additional topics of interest. Key Questions were finalized after vetting them with HICPAC.

4.b. Literature Search

A list of search terms was developed to identify the literature most relevant to the Key Questions. The terms were incorporated into search strategies, and these searches were performed in MEDLINE, EMBASE, CINAHL, and the Cochrane Library.

At the outset of this effort in 2011, the literature base was deemed insufficient to formulate evidence-based recommendations for methicillin-sensitive *Staphylococcus aureus* (MSSA). Therefore, databases were searched through December 2011 for studies addressing methicillin-resistant *Staphylococcus aureus* (MRSA). When the MRSA-specific literature search was updated with results from December 2011 to August 2019, the MSSA literature base was deemed sufficient for review. The additional search encompassed *S. aureus* and included MSSA. The detailed search strategies for identifying primary literature and the search results are provided in the *Appendix (https://www.cdc.gov/infectioncontrol/pdf/guidelines/NICU-saureus-Appendix-508.pdf).* (Appendix Section 1.B.) Subject matter experts supplemented the literature search results by recommending relevant references published since August 2019.

4.c. Study Selection

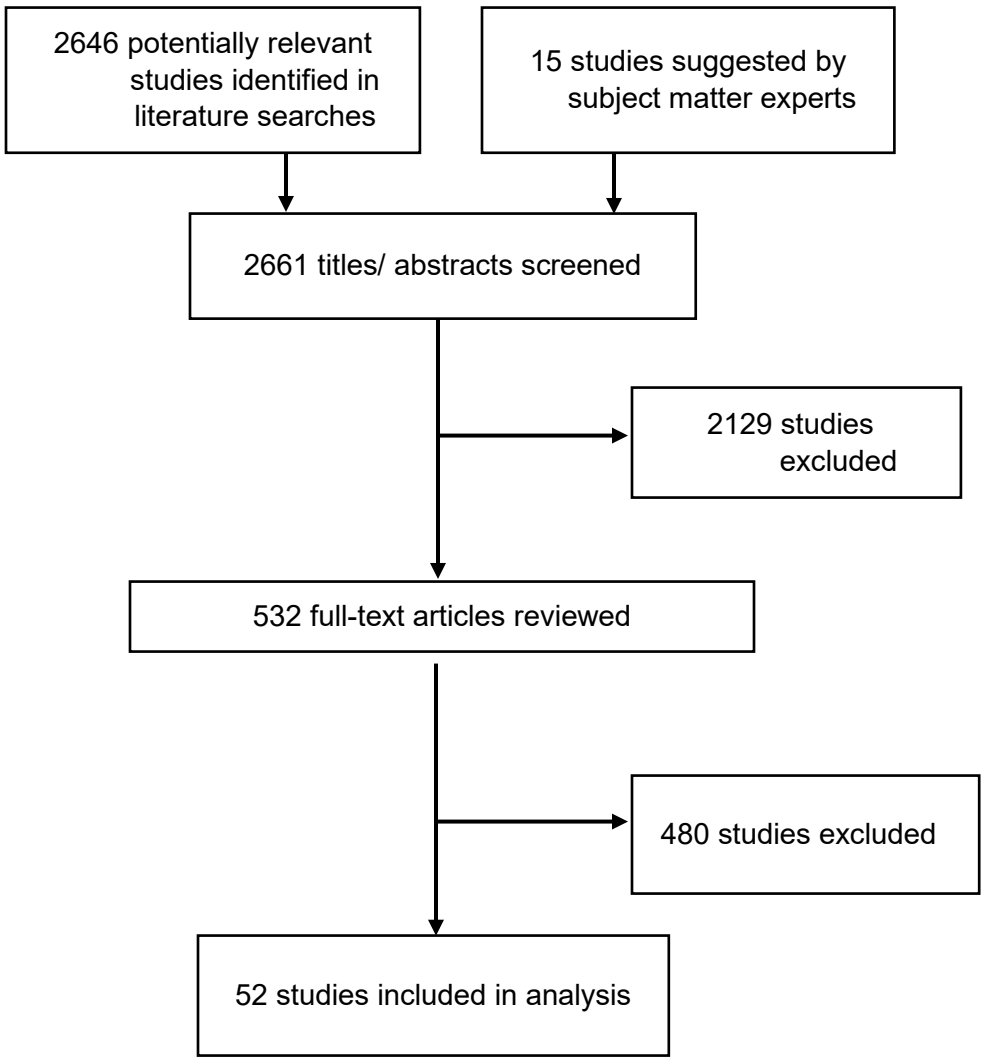
Titles and abstracts from references were screened by dual review (M.D., A.E., C.H., J.H., K.I., M.I., A.D.O., K.T.R., S.S., or E.C.S.). Full-text articles were retrieved if they were:

1. Relevant to one or more Key Question;

2. Primary research, systematic reviews, or meta-analyses; and
3. Written in English.

The *Appendix (https://www.cdc.gov/infectioncontrol/pdf/guidelines/NICU-saureus-Appendix-508.pdf)* presents the full list of exclusion criteria. (Appendix Section 2.) The full texts of selected articles were then screened by two independent reviewers, and disagreements were resolved by discussion (K.B., M.D., A.E., L.F., J.H., W.C.H., K.I., M.I., A.M., A.D.O., K.T.R., S.S., N.S., or E.C.S.). After the full-text screening was complete, a bibliography of the articles selected for inclusion was vetted with subject matter experts. Additional studies suggested by the subject matter experts were screened for inclusion as described above. The results of the study selection process are depicted in *Figure 1.*

Figure 1. Results of the Study Selection Process



4.d. Data Extraction and Synthesis

Data and results of clinically relevant outcomes from the studies meeting inclusion criteria were extracted into standardized evidence tables. Data and analyses were extracted as presented in the studies. For the purposes of this review, statistical significance was defined as $p \leq 0.05$.

4.e. Grading of the Evidence

The risk of bias associated with each study was assessed using scales developed by the University of Pennsylvania Center for Evidence-based Practice, and scores were recorded in the evidence tables. The *Appendix (https://www.cdc.gov/infectioncontrol/pdf/guidelines/NICU-saureus-Appendix-508.pdf)* includes the questions used to assess the quality of each study design. (Appendix, Section 4.) The quality of the evidence base was then assessed using methods adapted from the Grading of Recommendations Assessment, Development and Evaluation (GRADE) Working Group, which considers randomized controlled trials (RCTs) the gold standard. The GRADE approach[50,51] was applied to provide explicit links between the available evidence and the resulting recommendations.

The literature retrieved to answer Key Questions 3 and 4 did not include interventional studies that might target higher-risk NICU patients. As the literature retrieved for this question was insufficient to formulate recommendations for the prevention of *S. aureus* in NICU patients, the evidence for this Key Question was not assessed using GRADE. Rather, a qualitative summary of the results of these studies is included in the narrative.

4.f. Formulating Recommendations

The criteria used to formulate the strength of each recommendation are described in the *HICPAC Update to the Recommendation Categorization Scheme* (https://www.cdc.gov/hicpac/workgroup/recommendation-scheme-update.html), and in the *Appendix (https://www.cdc.gov/infectioncontrol/pdf/guidelines/NICU-saureus-Appendix-508.pdf)*. (Appendix Section 5.) The recommendation justification tables for each recommendation outline the factors weighed when determining the recommendation's strength. The draft recommendations were cross-checked with the guidelines identified in the systematic literature search.

4.g. Reviewing and Finalizing the Guideline

A draft of the Guideline, including narrative evidence reviews, recommendations, GRADE tables, and evidence tables, was presented to HICPAC for review and input at public meetings in November 2017, May 2018, and November 2018. Following further revisions, the Guideline was in the *Federal Register* for a period of public comment from September 2 – November 4, 2019. The literature search was updated, and results of the updated search and the public comments received were reviewed at a HICPAC meeting on November 15, 2019. The draft was revised accordingly and finalized and is posted to CDC's Infection Control Guidelines website.

4.h. Updating the Guideline

Future revisions to this Guideline will be guided by new research and technological advancements for preventing and managing infectious disease outbreaks in the NICU setting.

5. Evidence Summaries

5.a. Interventions to prevent transmission of *S. aureus* in NICUs

Key Question 1. What are effective strategies for preventing *S. aureus* transmission from colonized or infected NICU patients to other patients, and do these strategies differ between MRSA and MSSA or in the setting of an outbreak?

Key Question 2. If active surveillance is conducted, which anatomic sampling sites and laboratory assays most effectively identify *S. aureus* colonization in NICU patients?

To address these questions, studies were considered that examined interventions for the prevention of transmission of *S. aureus*, including methicillin-resistant *S. aureus* (MRSA) or methicillin-sensitive *S. aureus* (MSSA), from colonized or infected NICU patients to other patients. The search strategy predominantly identified studies describing multiple infection prevention and control strategies implemented simultaneously or sequentially. In multi-intervention studies, it is not possible to distinguish the effectiveness of individual interventions, and it is likely that a combination of interventions led to any reported reductions in healthcare-associated transmission of *S. aureus*. The interventions described in these studies include core infection prevention and control strategies, institution of preemptive Contact Precautions, changes in hand hygiene protocols, use of polymerase chain reaction (PCR) compared to conventional culture for testing, active surveillance testing, and decolonization of NICU patients.

The benefits weighed in evaluating the evidence included the outcomes of reduction in *S. aureus* infection, colonization, and transmission (a composite measure including both infection and colonization), attributable mortality, and length of stay. Harms included the outcomes of antimicrobial resistance and product-related adverse events. The outcome deemed critical to decision-making was reduction in *S. aureus* infections. For the purposes of this analysis, healthcare-associated transmission within the NICU is suggested by an increase in cases of *S. aureus* colonization or infection as determined by cultures obtained for clinical indications or surveillance purposes.

The evidence for these questions consisted of 20 observational studies.[2-9,11,17,23,32,38,52-58] The findings of the evidence review and the grades for all critical and important outcomes are provided in the *Appendix (https://www.cdc.gov/infectioncontrol/pdf/guidelines/NICU-saureus-Appendix-508.pdf)*. (Appendix Section 3.)

5.a.1. Multi-intervention Strategies

The search identified 12 observational studies[2-5,7,8,11,32,54-56,58] that implemented multiple infection prevention and control strategies simultaneously to prevent and control *S. aureus* transmission. Nine studies[3-8,32,55,56] implemented multi-intervention strategies to prevent MRSA: 2 in the outbreak setting,[3,6] and 7 in the non-outbreak setting.[4,5,7,8,32,55,56] One study[54] implemented multi-intervention strategies to prevent MSSA in the non-outbreak setting, and 2 non-outbreak studies[2,58] implemented these strategies to reduce *S. aureus* transmission. For the purposes of this analysis, multi-intervention infection prevention and control strategies included a combination of the following interventions:

- General Infection Prevention and Control Interventions
    - Hand hygiene
    - Standard Precautions
    - Contact Precautions
    - Patient isolation
    - Patient cohorting
    - Education and training
- Environmental Interventions
    - Cleaning and disinfection
    - Dedicated equipment
    - Other environmental and equipment interventions
- Healthcare Personnel interventions
    - Staffing ratios

    - Staff cohorting
    - Screening
    - Decolonization
    - Work restrictions or removal of colonized personnel
- Active Surveillance Testing
- Patient Decolonization

All studies retrieved in this analysis implemented a combination of some or all of these interventions. The independent effect of each of these interventions cannot be determined due to the concurrent implementation of the measures.

The evidence suggests a benefit to implementing multiple infection prevention and control strategies to reduce *S. aureus* transmission. This conclusion is based on overall reductions in *S. aureus* infections[2,8,10,32,54,56] and the composite outcome of transmission, which included both infected and colonized infants.[6] The benefit of implementing multi-intervention strategies to reduce *S. aureus* colonization as a sole outcome measure could not be determined due to inconsistency in results across studies[4,5,32,55]; however, the results of one study[4] suggesting no benefit in the endemic setting were likely confounded by the emergence of an outbreak strain. The overall quality of this evidence was rated as low. The harms data reported in these studies was limited. One study[7] reported no difference in unadjusted length of stay and attributable mortality. (Appendix Section 3.A.1.a., Table 11)

Three studies[3,6,8] suggest a benefit to implementing multi-intervention strategies to reduce MRSA transmission. However, the evidence suggests mixed results regarding the benefit of implementing multi-intervention strategies to reduce MRSA infections and colonization.[4,5,7,8,32,56,58] It is notable that 2 of the 3 studies reporting the outcome of MRSA transmission were conducted in the outbreak setting, and both of these studies[3,6] reported a reduction of transmission. Again, data were limited on harms, and only one study[7] reported no change in unadjusted length of stay and attributable mortality. A reduction in MRSA transmission was seen in 2 studies[3,6] conducted in the outbreak setting. The combination of interventions implemented in the outbreak and non-outbreak setting were similar. (Appendix Section 3.A.1.a., Table 12)

Multi-intervention strategy data are limited for MSSA, with only one study[54] suggesting a reduction in MSSA bacteremia following the implementation of multiple infection prevention and control strategies. No harm outcomes were reported for this comparison. (Appendix Section 3.A.1.a., Table 13)

The optimal combination of infection prevention and control strategies could not be determined because all studies implemented different combinations of infection prevention and control strategies in both the endemic and outbreak settings and reported heterogeneous outcome measures. It is notable that all 7 studies[2,8,10,32,54-56] that reported a reduction in *S. aureus*, MRSA, or MSSA infections included the intervention of infant decolonization. In these studies, infant decolonization was frequently implemented after other infection prevention and control strategies were not successful in controlling transmission. The added implementation of Contact Precautions for MRSA, versus Standard Precautions alone for MSSA, is the primary difference in the infection prevention and control strategies implemented between studies.

Recommendations on strategies considered foundational to infection prevention and control across healthcare settings can be found in the Core Infection Prevention and Control Practices for Safe Healthcare Delivery in All Settings – Recommendations of the HICPAC (2017) [PDF - 15 pages] document (https://www.cdc.gov/hicpac/pdf/core-practices.pdf).[1]

5.a.2. Preemptive Contact Precautions

In the setting of endemic MRSA, there is limited evidence of benefit to implementing preemptive Contact Precautions for outborn infants until their colonization status is confirmed as negative. A decrease in MRSA transmission rate was observed after implementation of preemptive Contact Precautions; however, this evidence consisted of one study[52] which also reported a 25% increase in hand hygiene compliance during the intervention period, likely confounding the results. This study did not report adjusted morbidity or attributable mortality. (Appendix Section 3.A.1.b., Table 14)

5.a.3. Hand Hygiene Protocol

Evidence from one study[53] suggests benefit to implementing a new hand hygiene protocol which incorporated multiple policy changes, including implementing universal glove use and changing the cleansing agent from a chlorhexidine hand wash to a chlorhexidine-alcohol hand rub. This study[53] found a decrease in the incidence of MRSA septicemia with the institution of this new hand hygiene protocol. No changes in either mean length of stay or infection-related mortality were associated with the implementation of the interventions associated with this policy. (Appendix Section 3.A.1.c., Table 15)

5.a.4. Active Surveillance Testing

5.a.4.1. Implementing Active Surveillance Testing

Active surveillance testing of NICU patients to identify newly-colonized infants to guide implementation of infection prevention and control measures, such as Contact Precautions or decolonization, has been shown to be of benefit in the context of an outbreak, increased incidence of infection, or ongoing healthcare-associated transmission.[2,4,5,8-11,58] Observational studies report decreased incidence of infection and colonization. In most studies, the anterior nares were sampled; the umbilicus, rectum, axilla, and groin were also sampled. (Appendix Section 3.A.1.d.)

The evidence retrieved suggests that implementation of active surveillance testing to guide implementation of infection control strategies results in a reduction in *S. aureus* infection[2,4,7-11] and transmission.[3,6] The evidence of benefit was inconsistent for the outcome of *S. aureus* colonization.[2,4,5,58] The quality of evidence for these outcomes was rated as low. (Appendix Section 3.A.1.d., Table 16)

There was evidence of reduction in MRSA transmission after using active surveillance testing to guide implementation of multiple infection prevention and control strategies. Two of the 3 studies[3,6] reporting this outcome were conducted in the outbreak setting. The evidence suggests no reduction in MRSA infections with the implementation of active surveillance testing. Two studies reported the outcome of MRSA colonization, and the results were inconsistent.[4,58] (Appendix Section 3.A.1.d., Table 17)

Two non-outbreak studies[9,11] employed active surveillance to guide the implementation of infection prevention and control measures to prevent MSSA. One study[9] implemented decolonization of MSSA-colonized infants, and the other study[11] provided decolonization to very low birthweight infants with central venous or peripheral catheters. Both reported reductions in composite MSSA infections[9] or MSSA bloodstream infection (BSI) and pneumonia.[11] (Appendix Section 3.A.1.d., Table 18)

5.a.4.2. Frequency of Active Surveillance Testing

Thirteen studies reported varying frequencies of active surveillance testing to detect *S. aureus* colonization in NICU infants. In these studies, active surveillance testing was performed: 1) on admission only[3]; 2) on admission and every 2 weeks for all infants[7]; 3) on admission and at weekly intervals for all infants[2,17]; 4) on admission for

new outborn infants and at weekly intervals for all infants[8-10]; and 5) on all patients at a weekly interval.[4,6,11] One study[32] implemented routine surveillance on a monthly basis, and one tested all intubated patients weekly and added admission screening for "increased burden."[58] The interventions implemented for patients following results of surveillance cultures also varied among the studies, which affects the interpretability of the results. (Appendix Section 3.A.1.e.)

Five studies found a reduction in *S. aureus* infection from implementing active surveillance testing on admission and weekly thereafter. Two of these studies[2,17] conducted admission screening for all infants, and 3 conducted admission screening for outborn infants only.[8-10] One non-outbreak study[7] implementing active surveillance testing on admission and weekly for all infants found no reduction in MRSA infections. The choice of the optimal target population for conducting active surveillance testing can be guided by epidemiology in the facility and unit. (Appendix Section 3.A.1.e., Tables 19 – 22)

The interpretability of the impact of conducting weekly surveillance testing is limited due to inconsistent results in the outcomes of infection and colonization across studies.[4,11,58] These studies were conducted in the non-outbreak setting; however, one study[4] saw reductions in MRSA colonization that were not sustained during a period of overcrowding and the introduction of a new MRSA strain. One outbreak study[3] suggested a benefit to implementing admission screening for all infants in the outbreak setting. (Appendix Section 3.A.1.e., Tables 21 – 25)

5.a.5. Optimal Testing Method and Anatomic Site

To address this question, studies providing test characteristics for the detection of *S. aureus* were critically reviewed. The available data on detection of *S. aureus* examined the characteristics of tests and the choice of anatomical sites for sampling for active surveillance testing for *S. aureus*. Laboratory methods available to detect *S. aureus* colonization included culture-based methods and molecular testing methods. The evidence consists of one diagnostic study examining *S. aureus* colonization[19] and 5 diagnostic studies examining MRSA colonization.[18,20-22,57] (Appendix Section 3.A.1.f. – 3.A.1.g.)

5.a.5.1. Laboratory Assays

One diagnostic study[19] compared assays to detect *S. aureus* and reported higher sensitivity and negative predictive value for real-time PCR than for culture-based methods using broth enrichment techniques. Results for specificity and positive predictive value to detect *S. aureus* were the same for PCR and culture. In this study, culture-based methods were used as the reference standard upon which the results were calculated. While this study conducted susceptibility testing, results were reported in aggregate for *S. aureus*, and not for MRSA or MSSA. (Appendix Section 3.A.1.f., Table 26)

Evidence from 2 diagnostic studies[18,20] suggests high sensitivity, specificity, and negative predictive value of PCR for detecting MRSA. However, evidence from both studies suggested that the positive predictive value of PCR was low. In the study finding a positive predictive value of 41%,[18] 7 PCR-positive results were negative on culture: 5 of the 7 cultured positive for MSSA via nasal swabs. In these studies, culture-based methods were used as the reference standard upon which the results were calculated. (Appendix Section 3.A.1.f., Table 27)

One observational outbreak study[38] found a benefit to changing from culture-based testing methods to real-time PCR testing to analyze active surveillance samples during an MRSA outbreak. This study reported a decrease in both the MRSA infection rate and the MRSA transmission rate. This study also reported moderate compliance with hand hygiene protocols and Contact Precautions and did not assess any adverse events. (Appendix Section 3.A.1.f., Table 28)

Implementation Considerations

Although PCR may have higher sensitivity, multiple considerations influence which test a facility may use to screen for *S. aureus* colonization. These include, but are not limited to, outbreak identification; turnaround time; performance characteristics of the test; use in clinical management; the number of specimens combined with the capabilities of the laboratory providing the service; and resource utilization. Depending on laboratory capacity, molecular diagnostic testing methods such as PCR may be more useful in circumstances such as identifying an outbreak when there may be an increased volume of cultures to process and a faster turnaround time is needed. However, culture-based methods provide the benefit of lower cost and the ability to assess pathogen susceptibility patterns to guide patient treatment, and to assess genetic relatedness of other strains for outbreak detection. Either PCR or culture-based methods are acceptable, and facilities and providers can balance these situation-specific needs to select the assay that best benefits their NICU patients.

5.a.5.2. Anatomic Sampling Site

Evidence from 3 diagnostic studies[21,22,57] demonstrated that swabs taken from the nares had higher sensitivity and negative predictive value for MRSA than swabs taken from the umbilical and rectal areas. While one study[22] concluded that nasal cultures are sufficient to detect MRSA in the majority of colonized neonates, another study[21] suggested that sampling from 2 sites would increase sensitivity. (Appendix Section 3.A.1.g., Table 29)

The literature search did not reveal studies that provided test characteristics for the detection of MSSA; data on the appropriate target populations; or the ideal timing or frequency for active surveillance testing for *S. aureus*. The literature search did not reveal studies examining the optimal anatomical site for detection of *S. aureus* or MSSA.

Implementation Considerations

The available evidence suggests that the nares samples will yield high sensitivity when screening NICU patients for MRSA and that other sites can be sampled to optimize sensitivity of screening strategy. Although evidence on performance of various biologic samples for detecting MSSA and *S. aureus* is not available, it is likely that evidence for MRSA applies due to biologic similarities. In general, testing and sampling strategies that apply to MRSA also apply to MSSA; however, future research may provide greater insight into this issue.

5.a.6. Infant Decolonization and Active Surveillance Testing

Eliminating the carrier state was associated with decreases in infections and colonization in the NICU when there was evidence of ongoing healthcare-associated transmission and when there was increased incidence of infection.[9-11,18] No studies retrieved by this literature search examined these interventions as a stand-alone strategy in outbreak settings. In 5 studies,[9-11,17,23] all colonized infants received decolonization. Two of these studies[9,10] were conducted in the same facility at different time periods and found this strategy was associated with reductions in *S. aureus* infections. One study[10] observed reductions in infections, but not reductions in colonization of other NICU patients. One study[11] that provided prophylactic decolonization and chlorhexidine bathing only to very low birthweight (VLBW) infants with central venous and peripheral venous catheters found reductions in *S. aureus* infections in all infants in the NICU. Two studies[9,10] that provided all NICU patients mupirocin decolonization, regardless of colonization status, found reductions in *S. aureus* infections in all NICU patients. (Appendix Section 3.A.1.h.)

5.a.6.1. Optimal Decolonization Strategy

The literature search did not retrieve studies that compared different decolonization strategies or regimens in NICU patients.

Four studies[9-11,23] examined the implementation of decolonization of colonized infants, and all found reductions in *S. aureus* infections. Two of these studies[9,10] were performed in a single center NICU population and examined the impact of infant decolonization on MSSA[9] and on *S. aureus* as a whole.[10] One study[23] found no difference in MRSA colonization between the group that was decolonized and the group that was not decolonized. The fourth study[11] found reductions in MSSA-attributable infections after implementing surveillance and decolonization of only MSSA-colonized infants with IVs. All of these studies were conducted in non-outbreak settings. (Appendix Section 3.A.1.h., Tables 30 – 32)

Two studies[11,17] examined prophylactic use of decolonization agents. One[11] targeted VLBW infants with central and peripheral lines with intranasal decolonization and chlorhexidine bathing, and one[17] decolonized all infants in the NICU every 5 weeks with intranasal mupirocin. Both found a reduction in *S. aureus* infections; however, the prophylactic decolonization regimens and choice of agents were too dissimilar to determine the optimal prophylactic strategy. (Appendix Section 3.A.1.h., Table 33)

Decolonization regimens varied across the studies and included intranasal mupirocin[17]; mupirocin ointment applied to the nares and umbilicus[23] or to the nares, umbilicus, eroded skin, and wounds[2]; intranasal mupirocin with chlorhexidine bathing for select patients[9,10]; and intranasal mupirocin and octenidin washes.[11] Octenidin is not approved by the US Food & Drug Administration (FDA) for use in US healthcare settings. All studies suggested reductions in *S. aureus* infection and transmission. (Appendix Section 3.A.1.h., Tables 30 – 33)

5.a.6.2. Harms

Two studies[11,23] examined adverse events associated with the decolonization protocols, and found none. Safety concerns exist, however, for the 2 most commonly utilized decolonizing agents. The FDA has not determined the safety and effectiveness for intranasal mupirocin in children younger than 12 years of age. Specifically, the FDA-approved drug label states that pharmacokinetic data in neonates and premature infants suggests that significant systemic absorption can occur following intranasal administration of mupirocin. Additionally, chlorhexidine bathing products may be used “with care” in premature infants or infants under 2 months of age. These products may cause irritation or chemical burns in these patients. (Appendix Section 3.A.1.h., Tables 30 – 33)

Four studies[2,9,17,23] examined *S. aureus* isolates for increased antimicrobial resistance to the decolonizing agent during the study period. Two studies[9,23] examined resistance after the implementation of targeted decolonization of colonized infants and found no increase in resistance associated with targeted decolonization. Two studies[2,17] examined resistance after the implementation of a universal decolonization strategy that prophylactically decolonized all NICU infants. One study[2] reported no resistance, and the other[17] reported a small increase in mupirocin resistance associated with universal decolonization. The studies that reported mupirocin resistance evaluated the development of resistance over shorter periods of time. There is greater concern regarding the evolution of harms, such as resistance to the decolonizing agent, if it is applied broadly to an entire population in a unit. (Appendix Section 3.A.1.h., Tables 30 – 33)

There are concerns that decolonization can have farther-reaching effects than resistance and can alter the microbiome of NICU patients. One study reported that while the authors could not exclude the possibility of pathogen replacement, they found no changes in either the central line-associated bloodstream infection (CLABSI) rate or the pathogen distribution contributing to CLABSIs among infants who were decolonized with mupirocin.[17] (Appendix Section 3.A.1.h., Tables 30 – 33)

5.b. Risk Factors and Risk Indicators for *S. aureus* in NICU Patients

Key Question 3. What are the risk factors and risk indicators for *S. aureus* infection in NICU patients, and do they differ between MRSA and MSSA or in the setting of an outbreak?

Key Question 4. What are the risk factors and risk indicators for *S. aureus* colonization in NICU patients, and do they differ between MRSA and MSSA or the setting of an outbreak?

These Key Questions were asked to identify modifiable risk factors and risk indicators to formulate actionable recommendations to prevent *S. aureus* transmission. For the purposes of this effort, risk factors and risk indicators were defined as characteristics, attributes, or exposures confirmed by temporal sequence, which if present, may be associated with an increased probability of *S. aureus* colonization or infection.[59] The majority of the risk factors and risk indicators described in the evidence are considered non-modifiable from the perspective of NICU patient care, e.g., low birthweight; age at first positive culture or diagnosis; administration of maternal antibiotics; prior admission to the NICU; and pre-colonization or infection length of stay, among others. Without studies examining modifiable risk factors and risk indicators, actionable recommendations cannot be formulated.

The evidence retrieved for non-modifiable risk factors and risk indicators consists of 29 observational studies. Many of the studies reported differences in the presence of these characteristics between *S. aureus*-positive and *S. aureus*-negative infants; however, these results were not statistically significant. Additionally, many possible risk factors and risk indicators were assessed in only one study, which precludes drawing conclusions as to their importance. Several studies reported composite outcomes of colonization or infection rather than reporting colonization and infection rates separately, which hinders the ability to assess the association of risk factors and risk indicators with each specific outcome. A summary of the evidence on risk factors and risk indicators analyzed in at least 2 studies follows. The findings of the evidence review and the summary of potential risk factors and risk indicators across studies are provided in the *Appendix*. (Appendix Section 3.B.)

5.b.1. Risk factors and risk indicators for *S. aureus* infection

Lower birthweight[2,33,60-62] and younger gestational age[2,33,60] were reported to be significantly associated with *S. aureus* and MRSA infection in NICU patients. An association was reported between prior colonization and *S. aureus* infection,[2,23] while sex[2,61-63] was not associated with *S. aureus* infection; one of these studies[62] analyzed a composite outcome that included colonization. Inconsistent results across studies suggest an unclear association between race[60,62] and multiple gestation[33,60] for *S. aureus* and MRSA infection. Data were limited to formulate any conclusions regarding risk factors and risk indicators for MSSA infection; however, 3 studies[26,30,64] compared risk factors and risk indicators for MRSA and MSSA infection. These studies found a significantly higher incidence of MSSA infections in older infants; however, gestational age was not different between these infants, suggesting that a longer length of stay may affect an infant's likelihood of acquiring MSSA infections when compared with MRSA infections. Only one study[33] examined risk factors and risk indicators for MRSA infections in the outbreak setting, which was insufficient to formulate conclusions regarding the differences between risk factors and risk indicators for infection between the endemic and the outbreak settings. (Appendix Section 3.B.1., Tables 42 - 45)

5.b.2. Risk factors and risk indicators for *S. aureus* colonization

Multiple gestation[33,60,65] and administration of antibacterial therapy[65,66] were significantly associated with MRSA colonization. It is notable that administration of antibacterial therapy is a potentially modifiable risk factor to prevent MRSA colonization; however, infants in the NICU are severely ill, and administration of these antibiotics is necessary and likely unavoidable. The literature search did not retrieve any studies demonstrating the optimal duration of antibiotic therapy to prevent MRSA colonization; thus, no recommendation can be formulated to guide practitioners on the duration of systemic antibacterial therapy that may prevent MRSA colonization. (Appendix Section 3.B.1.b., Table 46)

As with MRSA infection, lower birthweight was associated with MRSA colonization[21,23,33,38,41,60,62,65,67]; it should be noted that 3 of these studies[38,62,67] analyzed composite outcomes that included infection. Age at NICU admission,[21,23,62,65,68] delivery method,[4,45,66,68,69] sex,[21,23,41,45,60,62,66-74] race,[62,67-69,73,74] maternal age,[68,69] malformation,[4,65] the presence of a central venous catheter or endotracheal intubation,[63,66,68,70] and occurrence of surgical procedures[66,68] were not associated with MRSA colonization. Due to conflicting results across studies, there was unclear association between MRSA colonization status and gestational age,[4,21,23,33,41,45,60,65,66,68-71,74] inborn status,[4,21,23,41,45,60,65,66,74,75] Apgar score,[4,65,69,70] retinopathy of prematurity,[68,71] length of NICU stay,[65,66,73] and healthcare personnel hand hygiene[68,76] compliance. Lower birthweight[33,38,67] is the only risk factor found in the literature for MRSA colonization in the outbreak setting. This association may be confounded because 2 of these studies[38,67] analyzed composite outcomes that included infection. (Appendix Section 3.B.1.b., Table 46 - 52)

No risk factors or risk indicators for MSSA colonization in NICU patients were found in the literature. Younger gestational age,[77,78] birthweight,[68,78] delivery method,[68,77] sex,[68,78] healthcare personnel hand hygiene compliance,[68,77] presence of central venous catheter,[20,74] and occurrence of surgical procedure[63,64] were not associated with MSSA colonization in the available evidence. There was an unclear association between Apgar score[77,78] and MSSA colonization due to conflicting results across studies. Data were limited to confer any difference in risk factors and risk indicators for MSSA colonization status between the endemic and outbreak settings. (Appendix Section 3.B.1.c., Table 53 - 58). Additional studies would elucidate modifiable risk factors and risk indicators for *S. aureus* transmission and infection to test novel interventions to prevent *S. aureus* disease.

6. References

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7. Contributors

Healthcare Infection Control Practices Advisory Committee (HICPAC)

HICPAC Members: Hilary M. Babcock, MD, MPH, Washington University School of Medicine; Judene Bartley, MS, MPH, CIC, VP Epidemiology Consulting Services, Inc.; Dale W. Bratzler, DO, MPH, The University of Oklahoma Health Sciences Center; Patrick J. Brennan, MD, University of Pennsylvania Health System; Vickie M. Brown, RN, MPH, WakeMed Health & Hospitals; Kristina Bryant, MD, University of Louisville School of Medicine; Lillian A. Burns, MT, MPH, Greenwich Hospital; Ruth M. Carrico, PhD, RN, CIC, University of Louisville School of Medicine; Sheri Chernetsky Tejedor, MD, Emory University School of Medicine; Vineet Chopra, MBBS, MD, MSc, FACP, FHM, The University of Michigan Health System; Elaine Dekker, Priscilla Chan and Mark Zuckerberg San Francisco General Hospital & Trauma Center; Daniel J. Diekema, MD, University of Iowa Carver College of Medicine; Alexis Elward, MD, Washington University School of Medicine; Jeffrey Engel, MD, North Carolina State Epidemiologist; Loretta L. Fauerbach, MS, CIC, Fauerbach & Associates, LLC; Neil O. Fishman, MD, University of Pennsylvania Health System; Ralph Gonzales, MD, MSPH, University of California, San Francisco; Mary K. Hayden, MD, Rush University Medical Center; Michael D. Howell, MD, MPH, Google Research, Google; Susan Huang, MD, MPH, University of California Irvine School of Medicine; W. Charles Huskins, MD, MSc, Mayo Clinic College of Medicine; Lynn Janssen, MS, CIC, CPHQ, California Department of Public Health; Tammy Lundstrom, MD, JD, Providence Hospital; Lisa Maragakis, MD, MPH, The Johns Hopkins University School of Medicine; Yvette S. McCarter, PhD, University of Florida Health Science Center; Denise M. Murphy, MPH, RN, CIC, Main Line Health System; Russell N. Olmsted, MPH, St Joseph Mercy Health System; Stephen Ostroff, MD, US Food and Drug Administration; Jan Patterson, MD, University of Texas Health Science Center, San Antonio; David A. Pegues, MD, David Geffen School of Medicine at UCLA; Peter J. Pronovost, MD, PhD, The Johns Hopkins University; Gina Pugliese, RN, MS, Premier Healthcare Alliance; Keith M. Ramsey, MD, The Brody School of Medicine at East Carolina University; Selwyn O. Rogers Jr, MD, MPH, The University of Chicago; William P. Schecter, MD, University of California, San Francisco; Kurt Brown Stevenson, MD, MPH, The Ohio State University Medical Center; Tom Talbot, MD, MPH, Vanderbilt University Medical Center; Michael L. Tapper, MD, Lenox Hill Hospital; and Deborah S. Yokoe, MD, MPH, University of California, San Francisco.

HICPAC *ex officio* Members: William B. Baine, MD, Agency for Healthcare Research and Quality; Elizabeth Claverie-Williams, MS, US Food & Drug Administration; Nicole Haynes, MD, Health Resources & Services Administration; David Henderson, MD, National Institutes of Health; Stephen Kralovic, MD, MPH, US Department of Veterans Affairs; Dan Mareck, MD, Health Resources & Services Administration; Jeannie Miller,

RN, MPH, Centers for Medicare & Medicaid Services; Melissa Miller, BSN, MD, MS, Agency for Healthcare Research and Quality; Paul D. Moore, PhD, Health Resources & Services Administration; Sheila Murphey, MD, US Food & Drug Administration; Tara Palmore, MD, National Institutes of Health; Gary Roselle, MD, US Department of Veterans Affairs; Daniel Schwartz, MD, MBA, Centers for Medicare & Medicaid Services; Judy Trawick, RN, BSN, Health Resources & Services Administration; Kim Willard-Jelks, MD, MPH, Health Resources & Services Administration; Rebecca Wilson, MPH, Health Resources & Services Administration.

HICPAC Liaison Representatives: Kathy Aureden, MS, MT(ASCP), SI, CIC, Association of Professionals of Infection Control and Epidemiology, Inc.; Elizabeth Bancroft, MD, Council of State and Territorial Epidemiologists; Nancy Bjerke, BSN, RN, MPH, CIC, Association of Professionals of Infection Control and Epidemiology, Inc.; Joan Blanchard, RN, BSN, Association of Perioperative Registered Nurses; Debra Blog, MD, MPH, Association of State and Territorial Health Officials; William A. Brock, MD, Society of Critical Care Medicine; Michelle Cantu, MPH, National Association of County and City Health Officials; Darlene Carey, MSN, RN, CIC, NE-BC, FAPIC, Association of Professionals of Infection Control and Epidemiology, Inc.; Holly Carpenter, BSN, RN, American Nurses Association; Paul Conway, American Association of Kidney Patients; Craig Coopersmith, MD, FACS, FCCM, Society of Critical Care Medicine; Barbara DeBaun, MSN, RN, CIC, Association of Professionals of Infection Control and Epidemiology, Inc.; Elaine Dekker, RN, BSN, CDC, America's Essential Hospitals; Louise M. Dembry, MD, MS, MBA, Society for Healthcare Epidemiology of America; Kathleen Dunn, BScN, MN, RN, Public Health Agency of Canada; Kris Ehresmann, RN, MPH, Association of State and Territorial Health Officials; Beth Feldpush, PhD, American Hospital Association; Sandra Fitzler, RN, American Health Care Association; Scott Flanders, MD, Society of Hospital Medicine; Janet Franck, RN, MBA, CIC, DNV Healthcare, Inc.; Diana Gaviria, MD, MPH, National Association of County and City Health Officials; Jennifer Gutowski, MPH, BSN, RN, CIC, National Association of County and City Health Officials; Lisa Grabert, MPH, American Hospital Association; Valerie Haley, PhD, Association of State and Territorial Health Officials; Lori Harmon, RRT, MBA, Society of Critical Care Medicine; Patrick Horine, MHA, DNV Healthcare, Inc.; Michael D. Howell, MD, MPH, Society of Critical Care Medicine; W. Charles Huskins, MD, MSc, Infectious Diseases Society of America; Marion Kainer, MD, MPH, Council of State and Territorial Epidemiologists; Lilly Kan, DrPH, MA, National Association of County and City Health Officials; Alan Kliger, MD, American Society of Nephrology; Evelyn Knolle, American Hospital Association; Jacqueline Lawler, MPH, CIC, CPH, National Association of County and City Health Officials; Chris Lombardozzi, MD, America's Essential Hospitals; Emily Lutterloh, MD, MPH, Association of State and Territorial Health Officials; Lisa Maragakis, MD, Society for Healthcare Epidemiology of America; Michael McElroy, MPH, CIC, America's Essential Hospitals; Lisa McGiffert, Consumers Union; Jennifer Meddings, MD, MSc, Society of Hospital Medicine; Richard Melchreit, MD, Council of State and Territorial Epidemiologists; Sharon Morgan, MSN, RN, NP-C, American Nurses Association; Silvia Muñoz-Price, MD, America's Essential Hospitals; Dana Nguyen, BSN, RN, CIC, National Association of County and City Health Officials; Shirley Paton, RN, MN, Public Health Agency of Canada; Kelly Podgorny, DNP, MS, CPHQ, RN, Joint Commission; Michael Anne Preas, RN, CIC, Association of Professionals of Infection Control and Epidemiology, Inc.; Mark E. Rupp, MD, Society for Healthcare Epidemiology of America; Mark Russi, MD, MPH, American College of Occupational and Environmental Medicine; Sanjay Saint, MD, MPH, Society of Hospital Medicine; Robert G. Sawyer, MD, Surgical Infection Society; Andi Shane, MD, MPH, Pediatric Infectious Disease Society; Roslyne Schulman, MHA, MBA, American Hospital Association; Barbara M. Soule, RN, MPA, CIC, The Joint Commission; Kathryn Spates, The Joint Commission; Linda Spaulding, RN, CIC, DNVGL Healthcare; Lisa Spruce, RN, DNP, ACNS, ACNP, ANP, Association of PeriOperative Registered Nurses; Rachel Stricof, MPH, Advisory Council for the Elimination of Tuberculosis; Sheri Chernetsky Tejedor, MD, Society of Hospital Medicine; Donna Tiberi, RN, MHA, Healthcare Facilities Accreditation Program; Margaret VanAmringe, MHS, The Joint Commission; Valerie Vaughn, MD, Society of Hospital Medicine; Stephen Weber, MD, Infectious Diseases Society of America; Elizabeth Wick, MD, American

College of Surgeons; Robert Wise, MD, The Joint Commission; Amber Wood, MSN, RN, CNOR, CIC, CPN, Association of PeriOperative Registered Nurses.

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8. Acronyms and Abbreviations

Abbreviation	Expansion
BSI	Bloodstream Infection
CDC	Centers for Disease Control and Prevention
CLABSI	Central Line-Associated Bloodstream Infection
FDA	Food and Drug Administration
GRADE	Grading of Recommendations Assessment, Development and Evaluation
HICPAC	Healthcare Infection Control Practices Advisory Committee
IV	Intravenous
MDRO	Multidrug-Resistant Organism
MRSA	Methicillin-Resistant *Staphylococcus aureus*
MSSA	Methicillin-Sensitive *Staphylococcus aureus*
NICU	Neonatal Intensive Care Unit
PCR	Polymerase Chain Reaction
RCT	Randomized Controlled Trial
S. aureus	*Staphylococcus aureus*
TAP	Targeted Assessment for Prevention
VLBW	Very Low Birthweight
WGS	Whole Genome Sequencing