Effective Health Care Program

Future Research Needs Paper
Number 40

Screening for Methicillin-Resistant *Staphylococcus aureus* (MRSA): Future Research Needs

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Screening for Methicillin-Resistant *Staphylococcus aureus* (MRSA): Future Research Needs

Identification of Future Research Needs From Comparative Effectiveness Review No. 102

Prepared for:
Agency for Healthcare Research and Quality
U.S. Department of Health and Human Services
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This report is based on research conducted by the Blue Cross and Blue Shield Association Technology Evaluation Center Evidence-based Practice Center (EPC) under contract to the Agency for Healthcare Research and Quality (AHRQ), Rockville, MD (Contract No. 290-2007-10058-I). The findings and conclusions in this document are those of the author(s), who are responsible for its contents; the findings and conclusions do not necessarily represent the views of AHRQ. Therefore, no statement in this report should be construed as an official position of AHRQ or of the U.S. Department of Health and Human Services.

The information in this report is intended to help health care researchers and funders of research make well-informed decisions in designing and funding research and thereby improve the quality of health care services. This report is not intended to be a substitute for the application of scientific judgment. Anyone who makes decisions concerning the provision of clinical care should consider this report in the same way as any medical research and in conjunction with all other pertinent information, i.e., in the context of available resources and circumstances.

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None of the investigators have any affiliation or financial involvement that conflicts with the material presented in this report.

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Preface

The Agency for Healthcare Research and Quality (AHRQ), through its Evidence-based Practice Centers (EPCs), sponsors the development of evidence reports and technology assessments to assist public- and private-sector organizations in their efforts to improve the quality of health care in the United States. The reports and assessments provide organizations with comprehensive, science-based information on common, costly medical conditions and new health care technologies and strategies. The EPCs systematically review the relevant scientific literature on topics assigned to them by AHRQ and conduct additional analyses when appropriate prior to developing their reports and assessments.

An important part of evidence reports is to not only synthesize the evidence, but also to identify the gaps in evidence that limited the ability to answer the systematic review questions. AHRQ supports EPCs to work with various stakeholders to identify and prioritize the future research that is needed by decisionmakers. This information is provided for researchers and funders of research in these Future Research Needs papers. These papers are made available for public comment and use and may be revised.

AHRQ expects that the EPC evidence reports and technology assessments will inform individual health plans, providers, and purchasers as well as the health care system as a whole by providing important information to help improve health care quality. The evidence reports undergo public comment prior to their release as a final report.

We welcome comments on this Future Research Needs document. They may be sent by mail to the Task Order Officer named below at: Agency for Healthcare Research and Quality, 540 Gaither Road, Rockville, MD 20850, or by email to epc@ahrq.hhs.gov.

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Stakeholder Panel

The following individuals served as members of the Stakeholder Panel described in this report. Their contributions were invaluable. They were given the opportunity to review the report during the public comment period.

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Background

Methicillin-resistant *Staphylococcus aureus* (MRSA) emerged as a clinically relevant human pathogen more than 5 decades ago.[1] The virulent bacterium was first detected in hospitals and other health care facilities where vulnerable hosts, frequent exposure to the selective pressure of intensive antimicrobial therapy, and the necessity for invasive procedures created a favorable environment for dissemination. MRSA emerged as an important cause of health care-acquired infections, particularly central line-associated bloodstream infection, ventilator-associated pneumonia, and surgical site infection.

Despite the adoption of infection control measures, the incidence of MRSA infection at most hospitals in the United States (U.S.) steadily increased for many years, but is now decreasing. Routine clinical cultures may miss a large portion of patients who are silent carriers of these organisms and serve as reservoirs for further transmission. More aggressive measures have been sought to check the spread of this particularly virulent pathogen. Active surveillance screening for MRSA is receiving greater attention for its potential value in identifying carriers of MRSA to prevent further transmission.

To identify the population of colonized individuals, microbiological samples are obtained from at-risk patients even in the absence of signs or symptoms of infection. The screening strategy may use a testing modality with a rapid turnaround time (results available on the same day as the testing is performed, typically using polymerase chain reaction (PCR), intermediate turnaround time (results available next day to 2 days after testing performed) or longer turnaround time (results available greater than 2 days after testing performed, typically culture). Because screening alone is not expected to affect health outcomes, screening strategies may include screening with or without isolation and with or without attempted decolonization or eradication. By detecting the larger population of colonized individuals, at the very least conventional precautions (i.e., hand hygiene and contact isolation) can be implemented in a broader and timelier manner to interrupt horizontal transmission of MRSA. Detection of colonized patients also permits consideration of more aggressive interventions, including attempts at microbiological eradication or decolonization.

A Comparative Effectiveness Review (CER) was prepared by the Blue Cross and Blue Shield Association Technology Evaluation Center Evidence-based Practice Center (BCBSA TEC EPC) on Screening for Methicillin-Resistant *Staphylococcus aureus* (MRSA).[1] The objective of the CER was to synthesize comparative studies that examined the benefits or harms of screening for MRSA carriage in the inpatient or outpatient settings.[1] The review examined MRSA-screening strategies applied to all hospitalized or ambulatory patients (universal screening), as well as screening strategies applied to selected inpatient or outpatient populations (e.g., patients admitted to the intensive care unit (ICU), patients admitted for a surgical procedure, or patients at high-risk of MRSA colonization or infection such those on prolonged antibiotic therapy) and compared them to no screening or to screening of selected patient populations (targeted screening). The review evaluated MRSA-screening strategies with or without isolation and with or without attempted eradication/decolonization.

The following four Key Questions formed the basis for the CER:

Key Question 1. Among ambulatory or hospitalized patients, what are the effects of a universal screening strategy for MRSA-carriage (screen, isolate, eradicate/decolonize) – when compared with no screening?

Key Question 2. Among ambulatory or hospitalized patients, what are the effects of a universal screening strategy for MRSA-carriage (screen, isolate, eradicate/decolonize) – when compared with targeted screening?

Key Question 3.

a. Among ambulatory or hospitalized patients, what are the effects of screening ICU patients for MRSA-carriage (screen, isolate, eradicate/decolonize) – when compared with no screening?
b. Among ambulatory or hospitalized patients, what are the effects of screening surgical patients for MRSA-carriage (screen, isolate, eradicate/decolonize) – when compared with no screening?
c. Among ambulatory or hospitalized patients, what are the effects of screening high-risk patients for MRSA-carriage (screen, isolate, eradicate/decolonize) – when compared with no screening?

Key Question 4. Among ambulatory or hospitalized patients, what are the effects of an expanded screening strategy for MRSA-carriage (screen, isolate, eradicate/decolonize) – when compared with a limited screening strategy?[1]

Two analytical frameworks that guided the CER are provided in Figure A and Figure B: Figure A depicts the effects of screening for MRSA-carriage on intermediate outcomes (including MRSA acquisition) and health outcomes (including MRSA infection, morbidity and mortality); and Figure B depicts the effects of screening for MRSA carriage in detail.

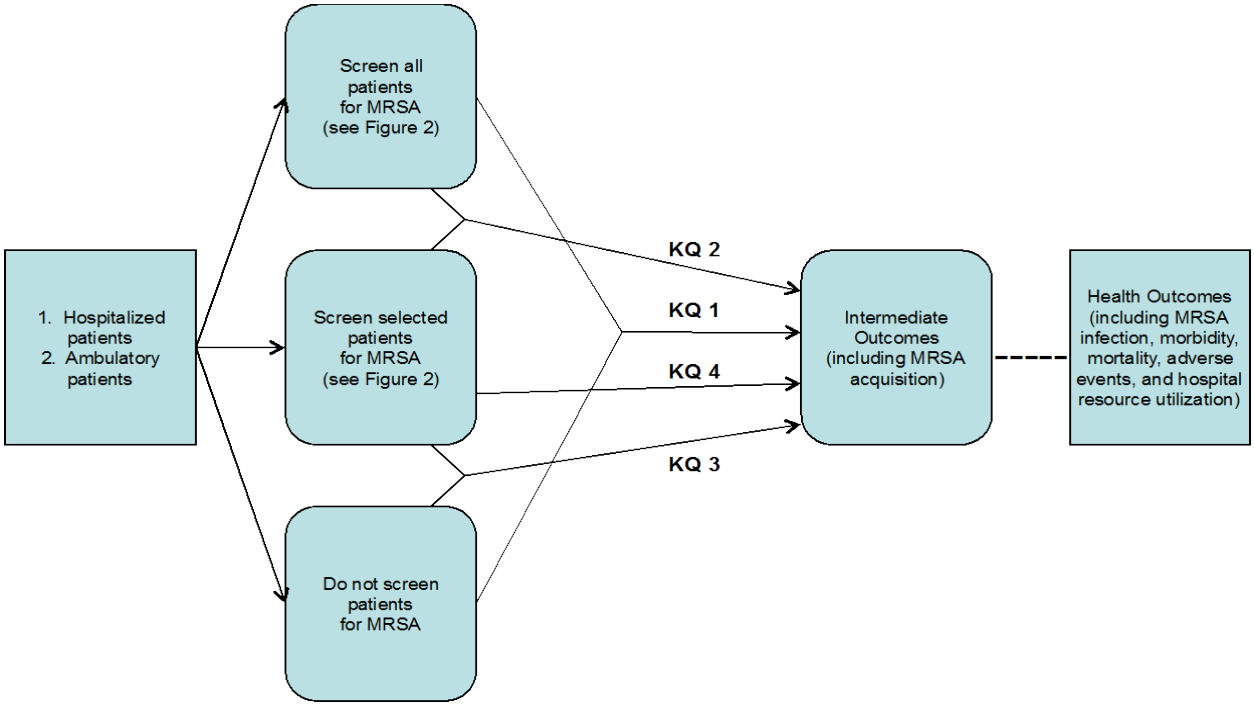
Four different screening strategies were evaluated: (1) universal screening compared with no screening; (2) universal screening compared with targeted screening of selected patient populations; (3) targeted screening of selected patient populations compared with no screening; and (4) expanded screening compared with limited screening. The draft CER found insufficient evidence to determine the comparative effectiveness of MRSA screening on MRSA acquisition, infection, morbidity, mortality, harms and resource utilization.

The draft CER identified evidence gaps related to the effectiveness of MRSA screening. The context in which screening is implemented (e.g., prior multidrug resistance organism control programs and the safety culture of the health care institution) lacked consistent and transparent documentation making it difficult to assess the full impact of screening. Knowledge of epidemiologic trends and inconsistency in the definition, application and measurement of the interventions commonly bundled together with MRSA screening limited interpretation of the available evidence. It is possible that a single component of a MRSA screening strategy, for example the decolonization of patients found through screening to be MRSA-positive, may produce an independent, clinically significant benefit, but the influence of other important factors such as the testing strategy (e.g., PCR vs. culture) and knowledge of its corresponding test turn-

around time, management of patients before screening test results are known, and the use of concomitant infection prevention strategies and treatments could not be determined.

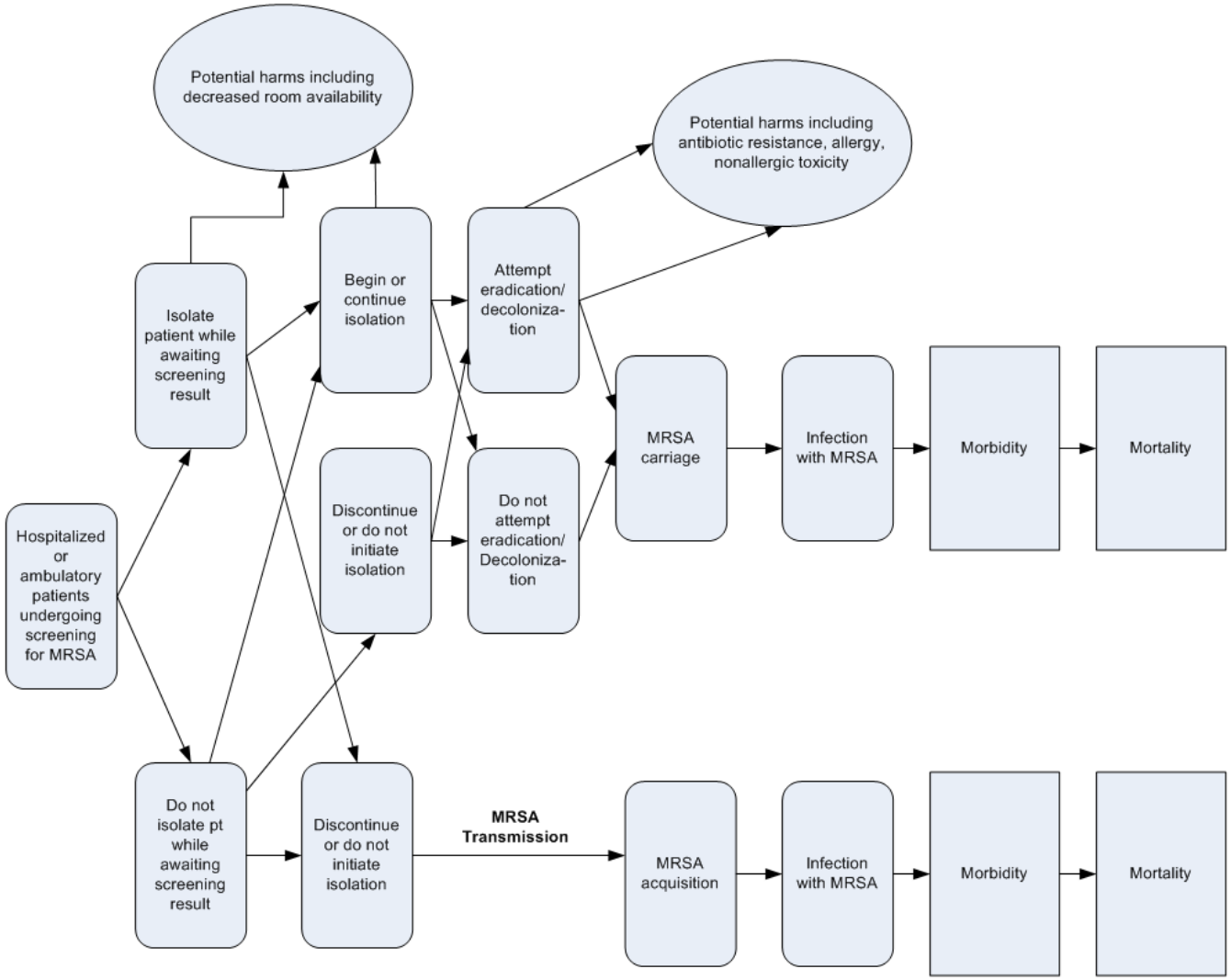
Precise estimates of the comparative effectiveness of screening for MRSA-carriage on morbidity and mortality are lacking. Studies failed to enroll sufficient numbers of patients to be adequately powered to detect the effect of screening for MRSA-carriage compared with no screening or to screening of selected patient populations on morbidity and mortality. Perhaps most importantly, the harms of screening were not clearly delineated, particularly in the outpatient setting. Since community-dwelling residents may develop health-care acquired MRSA infection and hospitalized patients may develop community-acquired MRSA infection, understanding both the benefits and harms of screening for MRSA is of increasing importance. However, the evidence in the draft CER focused largely on the benefits of screening, thereby presenting an incomplete picture of the full impact of screening for MRSA-carriage.

Figure A. Analytic framework for MRSA screening



KQ = Key Question; MRSA = methicillin-resistant *Staphylococcus aureus*

Figure B. Detailed analytic framework for MRSA screening



KQ = Key Question; MRSA = methicillin-resistant *Staphylococcus aureus*

Methods

First, evidence gaps were identified through the BCBSA TEC EPC CER. The literature search was updated and clinicaltrials.gov was searched to identify any ongoing or recently published research studies that might address the evidence gaps. A group of 10 stakeholders (Stakeholder Panel) was convened, representing diverse clinical perspectives including methodological/research expertise, clinical experience, and consumer and payer representation. The Stakeholder Panel prioritized each research need and corresponding research questions using an online survey tool called SurveyMonkey®.

The project team modified the Effective Health Care (EHC) Program Selection Criteria to be applicable to primary research rather than to systematic reviews of original research. The Stakeholder Panel used the modified selection criteria to prioritize both research needs and corresponding research questions. We compiled a final list, taking the Panel members' comments into consideration and paying particular attention to areas where ongoing efforts might overlap with prioritized research questions. The research questions were characterized using the PICOTS framework consisting of the population(s) (P), interventions (I), comparators (C), outcomes (O), timing (T), and settings (S). The project team then evaluated potential study designs to address each of the prioritized research questions in accordance with the recent Future Research Needs methods report authored by the RTI-UNC Evidence-based Practice Center (EPC) commissioned by the Agency for Healthcare Research and Quality (AHRQ).[2] The Stakeholder Panel provided insight into how future research agendas and proposed studies to address the research needs fit within these pre-specified criteria.

Results

A total of seven research needs were identified through a combination of the CER findings and conversations with the Stakeholder Panel. These research needs are stated in Table A (in order of priority).

Table A. Prioritized list of research needs

1. What are the central components of a MRSA screening strategy?
2. Who may benefit from MRSA screening?*
3. What outcomes should be considered for evaluations of MRSA screening?*
4. What are the most effective tests for MRSA screening?
5. What factors could influence MRSA test results (e.g., when to screen, which sites to swab)?
6. What are the appropriate comparators for MRSA screening?
7. From which perspective(s) should evaluations of MRSA screening be conducted (e.g., societal, hospital, emergency room, patient, payer)?

MRSA = methicillin-resistant *Staphylococcus aureus*
*Both questions received equal votes.

These seven research needs were considered priorities because the information at present is insufficient or imprecise and precludes conclusions about the effectiveness of, and need for, MRSA screening. While acknowledging that the research needs are interrelated, their ranking reflected the major issues the Stakeholder Panel felt needed to be addressed to understand the context in which MRSA screening may be effective. The Stakeholder Panel then generated and prioritized a list of potential research questions that incorporated the research needs. The research questions included the patient populations the Panel members felt would most likely

benefit from MRSA screening. They are surgical admissions, general medical inpatients and intensive care populations. The final prioritized list of research questions are presented in Table B.

Table B. Prioritized list of research questions

1.	For surgical admissions, what is the most effective strategy for reducing MRSA acquisition and infection rates and improving morbidity, mortality, patient flow and resource use?
2.	For surgical admissions what factors are associated with increased risk of MRSA acquisition and infection?
3.	For intensive care populations, what is the most effective strategy for reducing MRSA acquisition and infection rates and improving morbidity, mortality, patient flow and resource use?
4.	For the neonatal intensive care setting, what is the most effective strategy for reducing MRSA acquisition and infection rates and improving morbidity, mortality, patient flow and resource use?
5.	For intensive care populations, what factors are associated with increased risk of HA-MRSA acquisition and infection?
6.	For general medical inpatients, what is the most effective strategy for reducing MRSA acquisition and infection rates and associated morbidity, mortality, patient flow and resource use?
7.	For general medical inpatients, what factors are associated with increased risk of HA-MRSA acquisition and infection?

HA = hospital acquired; MRSA = methicillin-resistant *Staphylococcus aureus*

For the assessment of study designs, the project team evaluated the appropriateness of various designs for each prioritized research question and incorporated Stakeholder Panelists' considerations for future research into PICOTS (populations, interventions, comparators, outcomes, timing, and settings) elements. For questions 2, 5, and 7 epidemiological studies offer the most valid and practical approaches to quantifying the relationship between factors associated with the increased risk of MRSA acquisition and infection. They are: cohort studies; nested case-control or case-control studies; and cross-sectional studies. These prioritized research questions along with PICOTS elements are presented in Table C.

On the other hand, for questions 1, 3, 4 and 6 that address the effectiveness of MRSA screening, experimental designs are needed to determine the causal effect of MRSA screening strategies on patient outcomes. The optimal design would allow the researcher to address multiple research needs by manipulating one or more variables and controlling and measuring their effects on other variables, while balancing the feasibility and practicality of carrying out the design. The project team proposed the following study designs: cluster randomized controlled trials; quasi-experimental (before-after) studies; and modeling. These prioritized research questions are accompanied with PICOTS elements in Table D.

Discussion and Conclusions

This Future Research Needs project was developed to address important evidence gaps identified in the BCBSA TEC EPC CER. A multidisciplinary Stakeholder Panel of 10 participants used an 11-step process to identify and prioritize research needs and key research questions across the selected research needs. The final research questions reflect the research needs in the evidence related to the key populations identified in the CER and by the Stakeholder Panel.

We used multiple techniques to engage stakeholders, including individual interviews, online surveys and conference calls. The literature search update allowed for more informed decisions in selecting topics that were not duplicative with current ongoing trials and to which further research would add the greatest value.

It should be noted that the Stakeholder Panel brought forth research needs that were outside the scope of the original review, such as the need to address methicillin-susceptible *Staphylococcus aureus* (MSSA). Strategies found to be effective in reducing hospital-acquired (HA) MRSA infection would likely reduce HA MSSA. Future study designs could pre-specify MRSA and MSSA as different subgroups. Panel members emphasized the need for further basic epidemiological investigation to identify groups at high-risk for MRSA infection which would help target and design appropriate interventions. The Stakeholder Panel suggested that two questions ranked as lower priorities might also be considered as future research needs. First, in terms of burden of infection and high public health impact, the question addressing the most effective strategy for preventing MRSA infection among carriers after discharge from the hospital would benefit from further research to address the appropriate prevention strategy in this population. Second, determining the most effective anatomical-site screening protocol for detecting MRSA and MSSA carriage especially in high-risk surgical patients is presently an "under-studied" area in need of further research.

One of the major challenges we encountered in our process was the various ways to combine/categorize many of the proposed topics; there was overlap among the various research needs and key underlying research questions given their inter-relatedness. In addition, it was important to maintain the focus on the research needs in the evidence (and scope) addressed in the CER. A limitation of this process was that the Stakeholder Panel was presented with the draft results of the CER during the prioritization process; the conclusions did change between the draft and the final version, and thus the impact of these changes on the rankings of the research needs is unknown.

Table C. Prioritized list of risk factor research questions with PICOTS information

Research Question	Population(s)	Interventions	Comparators	Outcomes	Timing	Settings
2. For surgical admissions what factors are associated with increased risk of MRSA acquisition and infection?	Full or representative sample of surgical admissions: • Ambulatory care/ED admissions • Surgical unit admissions • Elective admissions	• MRSA screening/culture • Surveillance of potential risk factors for MRSA acquisition or infection (e.g., interview, questionnaire, database)	• No screening • Surveillance of potential risk factors for MRSA acquisition or infection (e.g., interview, questionnaire, database)	• MRSA surgical site infection rate • MRSA acquisition rates • Risk factors for MRSA acquisition • Risk factors for MRSA infection	• On admission (e.g., in the ED or surgical unit) • Pre-admission • At discharge • At followup visit	• Inpatient • Outpatient • Non-outbreak setting
5. For intensive care populations, what factors are associated with increased risk of HA-MRSA acquisition and infection?	Full or representative sample of intensive care admissions with the potential to acquire MRSA. May come from: • Ambulatory care/ED • General inpatient population	• MRSA screening/culture • Surveillance of potential risk factors for MRSA acquisition or infection (e.g., interview, questionnaire, database)	• No screening • Surveillance of potential risk factors for MRSA acquisition or infection (e.g., interview, questionnaire, database)	• MRSA acquisition • Risk factors for MRSA acquisition • MRSA infection • Risk factors for MRSA infection	• On admission (e.g., in the ED or ICU)	• Inpatient • Non-outbreak setting
7. For general medical inpatients, what factors are associated with increased risk of HA-MRSA acquisition and infection?	Full or representative sample of general medical admissions with the potential to acquire MRSA. May come from: • Ambulatory care/ED • Elective admissions	• MRSA screening/culture • Surveillance of potential risk factors for MRSA acquisition or infection (e.g., interview, questionnaire, database)	• No screening • Surveillance of potential risk factors for MRSA acquisition or infection (e.g., interview, questionnaire, database)	• MRSA acquisition • Risk factors for MRSA acquisition • MRSA infection • Risk factors for MRSA infection	• On admission (e.g., in the ED or to the ward)	• Outpatient (for elective admissions) • Inpatient • Non-outbreak setting

ED = emergency department; HA = hospital acquired; ICU = intensive care unit; MRSA = methicillin-resistant Staphylococcus aureus; PICOTS = population(s), interventions, comparators, outcomes, timing, settings

Table D. Prioritized list of effectiveness research questions with PICOTS information

Research Question	Population(s)	Interventions	Comparators	Outcomes	Timing	Settings
1. For surgical admissions, what is the most effective strategy for reducing MRSA acquisition and infection rates and improving morbidity, mortality, patient flow and resource use?	• Broad range of risk categories (low, medium, high) for universal screening strategies or • High risk populations for targeted screening strategies	• Screening-based strategy (e.g., screening and decolonization) + standard care precautions Types of MRSA screening tests to be considered: • Multiplex PCR • Culture Site(s) of MRSA screening: • Nares, throat, axilla, groin, perirectal • Optimal number of sites to swab • Optimal anatomical sites • Separate swabs for each site vs. one swab for all sites	• Non-screening test based strategy (e.g., gowning and gloving, hand hygiene, or standard care precautions)	• MRSA surgical site infection rate • Staff compliance with infection control procedures • Patient flow (e.g., median time interval between ED arrival and hospital admission) • Morbidity (e.g., complications of MRSA infection) • MRSA-attributable mortality • Harms (e.g., allergic reaction to treatment, satisfaction of patients in isolation) • Resource use (e.g., length of stay) • Turn-around times for test results • Cost-benefit analysis	• Time point at which screening is done (e.g., admission in ambulatory care or surgical unit) • Time point at which intervention is initiated based on screening results • Time point at ED arrival • Time point at hospital admission	• Inpatient (e.g., ambulatory care/ED, surgical unit) • Outpatient • Non-outbreak setting

Table D. Prioritized list of effectiveness research questions with PICOTS information (continued)

Research Question	Population(s)	Interventions	Comparators	Outcomes	Timing	Settings
3. For intensive care populations, what is the most effective strategy for reducing MRSA acquisition and infection rates and improving morbidity, mortality, patient flow and resource use? 4. For the neonatal intensive care setting, what is the most effective strategy for reducing MRSA acquisition and infection rates and improving morbidity, mortality, patient flow and resource use?	• Broad range of risk categories (low, medium, high) for universal screening strategies or • High risk populations for targeted screening strategies	• Screening-based strategy (e.g., screening and decolonization) + standard care precautions Types of MRSA screening tests to be considered: • Multiplex PCR • Culture Site(s) of MRSA screening: • Nares, throat, axilla, groin • Optimal number of sites to swab • Optimal anatomical sites • Separate swabs for each site vs. one swab for all sites	• Non-screening based strategy (e.g., gowning and gloving, hand hygiene, or standard care precautions only)	• MRSA acquisition rate • MRSA infection rate • Staff compliance with infection control procedures • Patient flow (e.g., median time interval between ED arrival and hospital admission) • Morbidity (e.g., complications of MRSA infection) • MRSA-attributable mortality • Harms (e.g., allergic reaction to treatment, satisfaction of patients in isolation) • Resource use (e.g., length of stay) • Turn-around times for test results • Mother-to-child transmission rate (for neonates only) • Cost-benefit analysis	• Time point at which screening is done (e.g., admission in ambulatory care or on ward) • Time point at which intervention is initiated based on screening results • Time point at ED arrival • Time point at hospital admission	• Inpatient (e.g., ambulatory care/ED, ICU, labor and delivery) • Non-outbreak setting

Table D. Prioritized list of effectiveness research questions with PICOTS information (continued)

Research Question	Population(s)	Interventions	Comparators	Outcomes	Timing	Settings
6. For general medical inpatients, what is the most effective strategy for reducing MRSA acquisition and infection rates and associated morbidity, mortality, patient flow and resource use?	• Broad range of risk categories (low, medium, high) for universal screening strategies or • High risk populations for targeted screening strategies	• Screening-based strategy (e.g., screening and decolonization) + standard care precautions Types of MRSA screening tests to be considered: • Multiplex PCR • Culture Site(s) of MRSA screening: • Nares, throat, axilla, groin • Optimal number of sites to swab • Optimal anatomical sites • Separate swabs for each site vs. one swab for all sites	• Non-screening based strategy (e.g., gowning and gloving, hand hygiene, or standard care precautions only)	• MRSA acquisition rate • MRSA infection rate • Staff compliance with infection control procedures • Patient flow (e.g., median time interval between ED arrival and hospital admission) • Morbidity (e.g., complications of MRSA infection) • MRSA-attributable mortality • Harms (e.g., allergic reaction to treatment, satisfaction of patients in isolation) • Resource use (e.g., length of stay) • Turn-around times for test results • Cost-benefit analysis	• Time point at which screening is done (e.g., admission in ambulatory care or on ward) • Time point at which intervention is initiated based on screening results • Time point at ED arrival • Time point at hospital admission	• Inpatient (e.g., ambulatory care/ED, ward) • Outpatient for elective admissions • Non-outbreak setting

ED = emergency room; ICU = intensive care unit; MRSA = methicillin-resistant Staphylococcus aureus; PCR = polymerase chain reaction; PICOTS = population(s), interventions, comparators, outcomes, timing, settings

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1. Glick SB, Webber S, Huang E, et al. Screening for Methicillin-Resistant *Staphylococcus aureus* (MRSA). Comparative Effectiveness Review No. 102. (Prepared by the Blue Cross and Blue Shield Technology Evaluation Center Evidence-based Practice Center under Contract No. 290-2007-10058-I.) AHRQ Publication No. 13-EHC043-EF. Rockville, MD: Agency for Healthcare Research and Quality. Forthcoming 2013. www.effectivehealthcare.ahrq.gov/reports/final.cfm.
2. Carey T, Sanders GD, Viswanathan M, et al. Framework for Considering Study Designs for Future Research Needs. Methods Future Research Needs Paper No. 8. (Prepared by the RTI–UNC Evidence-based Practice Center under Contract No. 290-2007-10056-I.) AHRQ Publication No. 12-EHC048-EF. Rockville, MD: Agency for Healthcare Research and Quality. March 2012. www.effectivehealthcare.ahrq.gov/reports/final.cfm.

Introduction

Background

MRSA Incidence

Methicillin-resistant *Staphylococcus aureus* (MRSA) emerged as a clinically relevant human pathogen more than five decades ago.[1] The virulent bacterium was first detected in hospitals and other health care facilities where vulnerable hosts, frequent exposure to the selective pressure of intensive antimicrobial therapy, and the necessity for invasive procedures created a favorable environment for dissemination. MRSA emerged as an important cause of health care–acquired infections, particularly central line-associated bloodstream infection, ventilator-associated pneumonia, and surgical site infection. Despite the adoption of infection control measures, the incidence of MRSA infection at most hospitals in the United States (U.S.) steadily increased for many years, but is now decreasing.[2-5]

In 2005, population-based surveillance in the U.S. found the standardized incidence rate of invasive MRSA was 31.8 per 100,000 (interval estimate 24.4–35.2); the standardized mortality rate was 6.3 per 100,000 (interval estimate, 3.3–7.5).[6] Eighty-five percent of the invasive MRSA infections were health-care acquired and 13.7 percent community acquired; the etiology of 1.3 percent of the infections could not be determined.[6] Estimates based on these data suggest that 94,360 invasive MRSA infections occurred in the U.S. in 2005 and that 18,650 of these infections were fatal.[6]

Screening Strategies

Conventional strategies for the control of MRSA (whether hospital- or community-acquired) have focused on the prevention of spread from patient to patient (horizontal transmission). While hand hygiene remains the cornerstone of MRSA transmission-control efforts and use of contact isolation has been widely promoted and adopted, these strategies have failed to adequately control MRSA. Routine clinical cultures may miss a large portion of patients who are silent carriers of these organisms and serve as reservoirs for further transmission. MRSA screening is receiving greater attention for its potential value in identifying carriers of MRSA to prevent further transmission.

To identify the population of colonized individuals, microbiological samples are obtained from at-risk patients even in the absence of signs or symptoms of infection. The screening strategy may use a testing modality with a rapid turnaround time (results available on the same day as the testing is performed, typically using polymerase chain reaction [PCR]), intermediate turnaround time (results available next day to 2 days after testing performed) or longer turnaround time (results available greater than 2 days after testing performed, typically culture). Because screening alone is not expected to affect health outcomes, screening strategies may include screening with or without isolation and with or without attempted decolonization or eradication.

By detecting the larger population of colonized individuals, at the very least conventional precautions (i.e., hand hygiene and contact isolation) can be implemented in a broader and timelier manner to interrupt horizontal transmission of MRSA. Detection of colonized patients also permits consideration of more aggressive interventions, including attempts at microbiological eradication or decolonization.

Objectives and Rationale of Comparative Effectiveness Review

The objective of the Comparative Effectiveness Review (CER), Screening for Methicillin-Resistant *Staphylococcus aureus* (MRSA), prepared by the Blue Cross and Blue Shield Association Technology Evaluation Center Evidence-based Practice Center (BCBSA TEC EPC) was to synthesize comparative studies that examined the benefits or harms of screening for MRSA carriage in the inpatient or outpatient settings.[1] The review examined MRSA-screening strategies applied to all hospitalized or ambulatory patients (universal screening), as well as screening strategies applied to selected inpatient or outpatient populations (e.g., patients admitted to the intensive care unit (ICU), patients admitted for a surgical procedure, or patients at high-risk of MRSA colonization or infection such as those on prolonged antibiotic therapy) and compared them to no screening or to screening of selected patient populations (targeted screening). The review evaluated MRSA-screening strategies that included screening with or without isolation and with or without attempted eradication/decolonization. The review included all ambulatory patients (outpatients) and hospitalized patients (inpatients).

Because conventional strategies have failed to adequately control MRSA, more aggressive measures have been promoted in an effort to check the spread of this particularly virulent pathogen. In some European countries, an aggressive containment program called "search and destroy" identifies contacts of colonized and infected patients in an effort to intercede to prevent dissemination. While such aggressive measures have not been widely adopted in most settings, some clinicians, scientists, and increasing numbers of public advocates and legislators have raised the call for more intensive efforts at MRSA control in the United States (U.S.) Particular attention has been given to the potential value of active surveillance screening for MRSA. Routine clinical cultures may identify as few as 18 percent of patients with asymptomatic carriage of antibiotic- resistant organisms such as MRSA leaving a large reservoir of patients who are silent carriers of these organisms. These individuals may serve as a reservoir for further transmission.

However, a limitation of these approaches—and specifically the use of isolation precautions— are their potential negative consequences. A series of studies have associated isolation precautions with worsened outcomes in terms of safety and patient satisfaction. Isolation precautions may be associated with worsened patient safety and satisfaction. In addition, questions have been raised about the effect of isolation precautions on specific performance measures such as the frequency with which patients on isolation precautions are visited by treating physicians and the timely recording of vital signs, but no rigorous definitive analysis has been completed to exonerate isolation precautions.

Therefore, while the specific evidence in support of active surveillance for MRSA has been promising, a number of questions remain about its effectiveness and whether screening should be applied to all patient populations (universal screening) or to selected populations (targeted screening). Thus, a systematic review of the evidence is both justified and timely. The importance of gaining a better understanding of the evidence is also highlighted by the increasing demand for better control of MRSA and a higher standard for prevention of hospital-acquired (HA) infections in general.

The following four Key Questions formed the basis for the CER:

Key Question 1. Among ambulatory or hospitalized patients, what are the effects of a universal screening strategy for MRSA-carriage (screen, isolate, eradicate/decolonize) – when compared with no screening?

Key Question 2. Among ambulatory or hospitalized patients, what are the effects of a universal screening strategy for MRSA-carriage (screen, isolate, eradicate/decolonize) – when compared with targeted screening?

Key Question 3.

a. Among ambulatory or hospitalized patients, what are the effects of screening ICU patients for MRSA-carriage (screen, isolate, eradicate/decolonize) – when compared with no screening?
b. Among ambulatory or hospitalized patients, what are the effects of screening surgical patients for MRSA-carriage (screen, isolate, eradicate/decolonize) – when compared with no screening?
c. Among ambulatory or hospitalized patients, what are the effects of screening high-risk patients for MRSA-carriage (screen, isolate, eradicate/decolonize) – when compared with no screening?

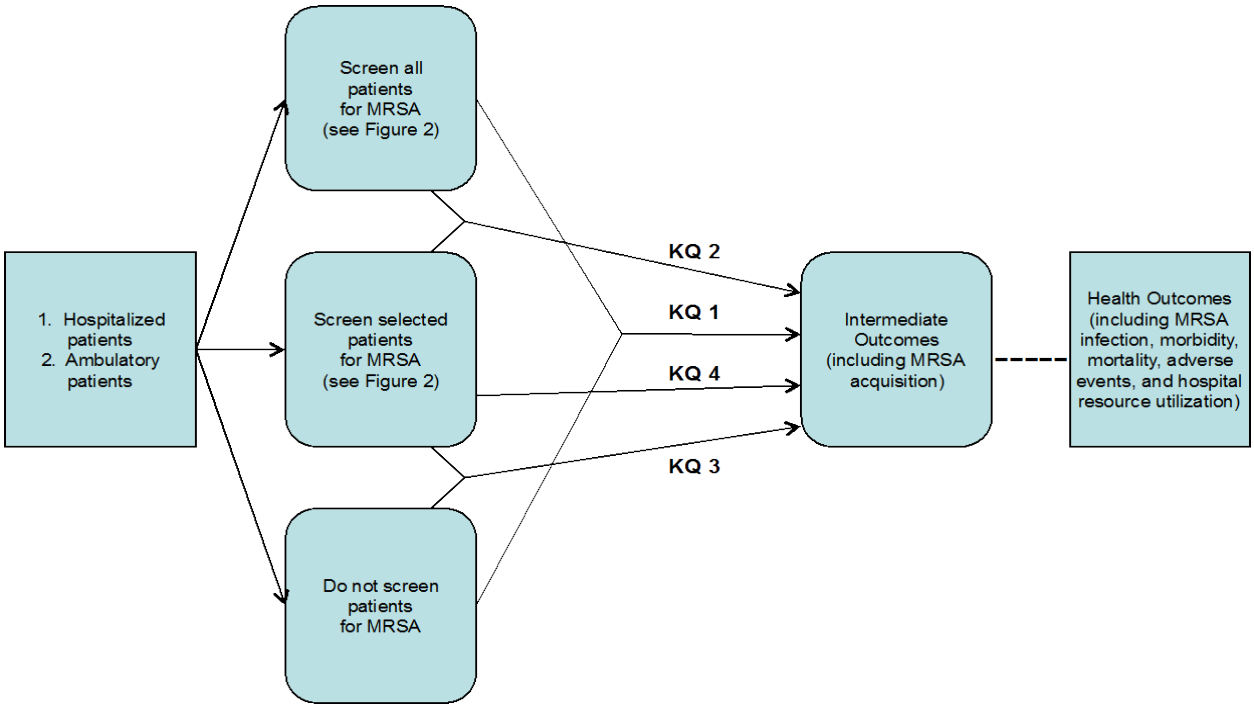
Key Question 4. Among ambulatory or hospitalized patients, what are the effects of an expanded screening strategy for MRSA-carriage (screen, isolate, eradicate/decolonize) – when compared with a limited screening strategy.[1]

The outcomes of interest for each of above questions were:

- Intermediate outcomes such as health care-acquired (HA)-MRSA transmission (as measured by new acquisition events).
- Health outcomes such as the incidence of HA-MRSA infection, morbidity (including complications of MRSA infection), mortality, adverse events (including allergic and non-allergic toxicity (e.g., hypotension), antimicrobial resistance, reduced quality of care, and medical errors), and hospital resource utilization such as length of stay.[1]

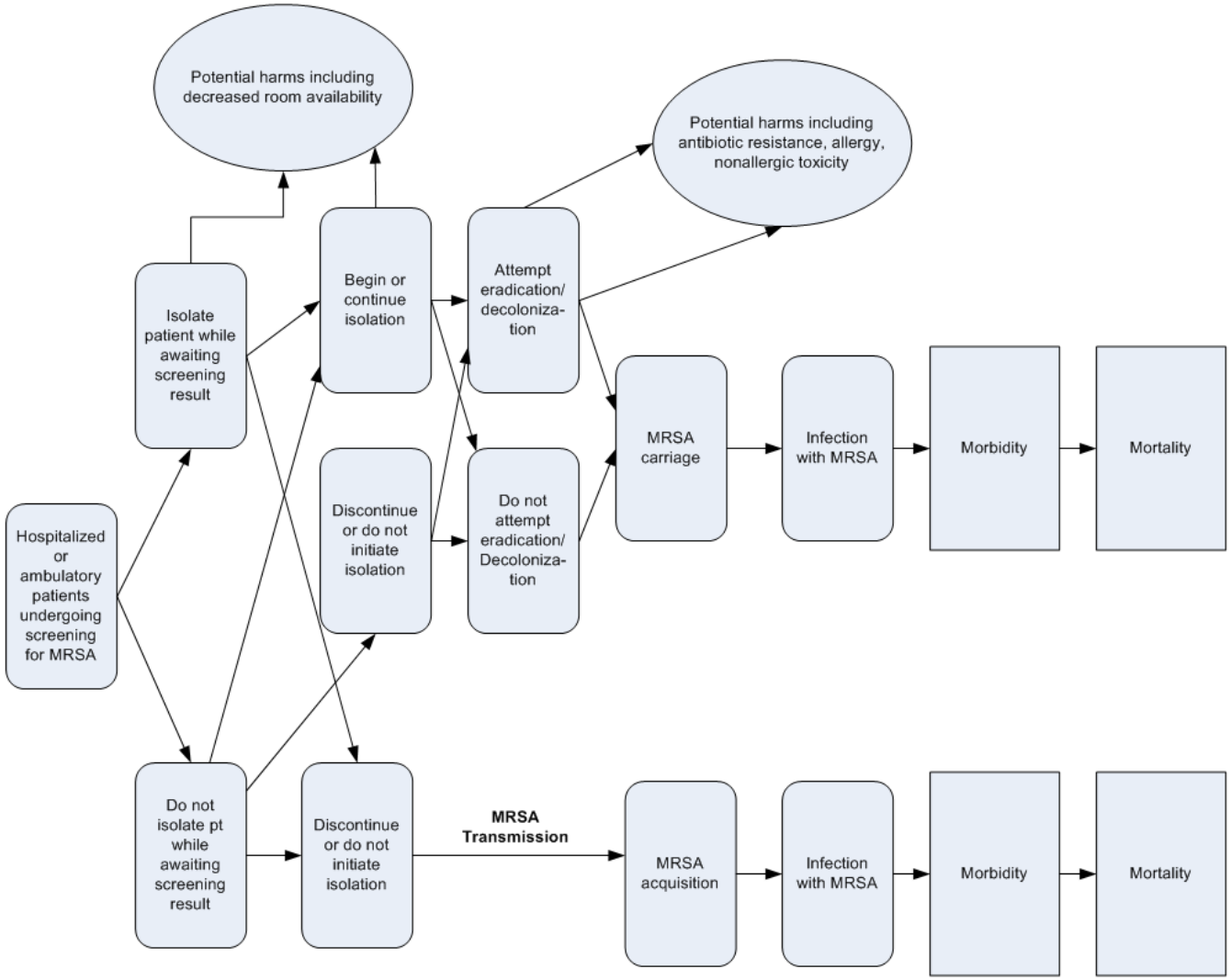
For the four different screening strategies evaluated: (1) universal screening compared with no screening; (2) universal screening compared with targeted screening of selected patient populations; (3) targeted screening of selected patient populations compared with no screening; and (4) expanded screening compared with limited screening, the CER found insufficient evidence to determine the comparative effectiveness of MRSA screening on MRSA acquisition, infection, morbidity, mortality, harms and resource utilization.[1] Two analytical frameworks that guided the CER are provided in Figure 1 and Figure 2. Figure 1 depicts the effects of screening for MRSA-carriage on intermediate outcomes (including MRSA acquisition) and health outcomes (including MRSA infection, morbidity and mortality); and Figure 2 depicts the effects of screening for MRSA carriage in detail. Appendix A provides the summary of outcomes measures and strength of evidence of the included studies in the draft CER.[1]

Figure 1. Analytic framework for MRSA screening



KQ = Key Question; MRSA = methicillin-resistant *Staphylococcus aureus*

Figure 2. Detailed analytic framework for MRSA screening



KQ = Key Question; MRSA = methicillin-resistant *Staphylococcus aureus*

Evidence Gaps

The CER identified a number of limitations in the evidence that prevents precise estimates of the comparative effectiveness of screening for MRSA-carriage on infection rates, morbidity and mortality.[1] Insufficient numbers of patients were enrolled in studies to be adequately powered to detect the effect of screening for MRSA-carriage compared with no screening or to screening of selected patient populations on morbidity and mortality. There is a paucity of rigorous, well-controlled studies employing uniform or even standardized microbiological and infection control techniques.[1] Inconsistency in the definition, application and measurement of the interventions commonly bundled together with MRSA screening limits the conclusions that can be drawn about the attributable benefit of screening compared with any other component of the infection control strategy such as more rigorous hand hygiene, barrier precautions, environmental cleaning, and antimicrobial decolonization.[1]

Studies failed to take a more uniform approach to the testing strategy used (e.g., PCR vs. culture), address test turn-around time, or account for the management of patients before screening test results are known.[1] The existing evidence failed to quantify and account for the potential bias introduced by secular trends that may contribute to variation in the incidence of infectious diseases over time.[1] Secular trends may include infection outbreaks, deviations and departures from best practice, dissemination of new prevention practices, changes in antibiotic prescribing, seasonal influences, or even the application of other interventions that may influence transmission or infection.

The evidence failed to account for the influence of concomitant infection prevention strategies and treatment interventions or staff compliance with them.[1] Omission of interventions such as institutional initiatives to improve hand hygiene and promote an institutional culture of safety, which have been shown to influence the frequency of many health care-associated infections, may be important. However, it is unrealistic to believe that a standardized and uniform approach can be recommended and applied to all future studies of screening for MRSA-carriage. Lacking such a standard, a maximally transparent approach to reporting interventions and potential confounders would be absolutely critical.[1]

There is a near complete absence of systematic evidence regarding the potential harms of screening for MRSA-carriage. Patients identified as MRSA-positive through screening programs may require isolation, potentially limiting the number of available beds at any given hospital, which, in turn, may decrease the number of patients who can be served locally, regionally and nationally. Because community-dwelling residents may develop health-care associated MRSA infection and because hospitalized patients may develop community-associated MRSA infection, understanding the benefits and harms of screening for MRSA in the outpatient setting is of increasing importance.[6,7] Perhaps most importantly, the harms of screening compared with no screening must be clearly delineated to determine the comparative effectiveness of screening for MRSA-carriage. To attempt to measure the favorable impact of screening for MRSA-carriage while ignoring its potential risks is to present incomplete and potentially misleading data.

Methods

Identification of Research Needs

Figure 3 outlines the process steps of this Future Research Needs project. The details are described in the text. First, the evidence gaps (i.e., research needs) identified in the BCBCS TEC EPC CER found insufficient evidence to recommend or refute the need for universal, targeted or expanded screening. The CER identified several evidence gaps (i.e., research needs) that needed to be addressed in future comparative effectiveness research. A Stakeholder Panel was convened to help prioritize these gaps and associated questions. The Evidence-based Practice Center (EPC) updated the literature search from the CER and searched clinicaltrials.gov to identify any recently completed or ongoing research studies that might address the research needs. Through an iterative process the Stakeholder Panel refined and prioritized the research needs and then generated and prioritized a list of research questions to address in future research (see section on engagement of stakeholders, researchers and funders). Research needs were prioritized using the SurveyMonkey® Web site. Finally, the EPC explored various research designs to address the research needs.

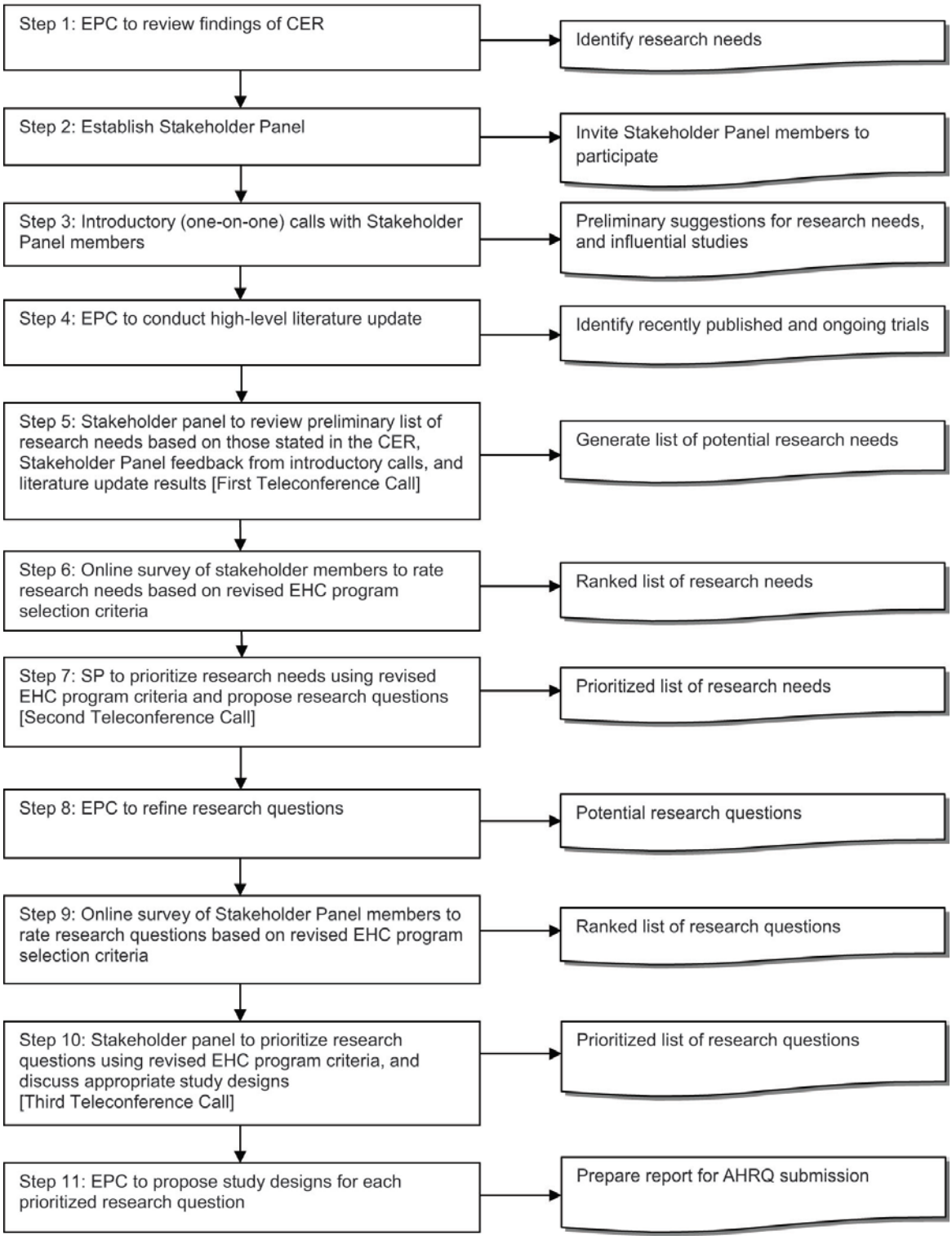
Literature Search Update

Rather than carry out a full update of the CER, we sought to identify recent, ongoing studies potentially addressing research needs and research question identification. We conducted searches on PubMed®, Embase ®, The Cochrane Library®, and the Clinicaltrials.gov database. The update captured 57 citations containing studies published since March 1, 2012, including 19 studies from Embase, 26 NCT clinical trials underway, recruiting, or with results, and 11 PubMed® studies. The Cochrane Library® yielded one new controlled trial report. Given the short time parameter (3 months), subject searches for MRSA and variations for MRSA were done using a MeSH® and free text studies filter (see Appendix B).

Criteria for Prioritization

To establish criteria for prioritization, we modified the Effective Health Care (EHC) Program Selection Criteria to be applicable to primary research rather than to systematic reviews of original research.[8] The Panel used the modified selection criteria to prioritize both research needs and corresponding research questions. The EPC staff compiled a final list, taking the Panel members' comments into consideration and paying particular attention to areas where ongoing efforts might overlap with prioritized research questions. Prioritization of study designs was handled by the EPC in accordance with the recent Future Research Needs methods report by the EPCs on behalf of the Agency for Healthcare Research and Quality (AHRQ).[9] The Stakeholder Panel provided insight into how future research agendas and proposed studies to address research needs fit within these prespecified criteria (see Table 1).

Figure 3. Process flow diagram



AHRQ = Agency for Healthcare Research and Quality; CER = Comparative Effectiveness Review; EHC = Effective Health Care; EPC = Evidence-based Practice Center

Table 1. Prioritization criteria for research needs and proposed research studies

Category	Criterion
Current importance	• Incorporates both clinical benefits and harms • Represents important variation in clinical care due to controversy/uncertainty regarding appropriate care • Addresses high costs to consumers, patients, health-care systems, or payers • Utility of available evidence limited by changes in practice, for example disease detection
Potential for significant health impact	• Potential for significant health impact: o To improve health outcomes o To reduce significant variation related to quality of care o To reduce unnecessary burden on those with health-care problems • Potential for significant economic impact, reducing unnecessary or excessive costs. • Potential for evidence-based change. • Potential risk from inaction, for example lack of evidence for decision-making produces unintended harms • Addresses inequities, vulnerable populations, patient subgroups with differential impact (e.g., by age)
Incremental value	• Adds useful new information to existing portfolio of research on topic OR • Validates existing research when body of evidence is scant.
Feasibility	*Factors to be considered:* • Interest among researchers • Duration • Cost • Methodological complexity (e.g., do existing methods need to be refined?) • Implementation difficulty • Facilitating factors • Potential funders

Methods for Ranking Research Needs

Research needs were ranked via the SurveyMonkey® Web site. The Stakeholder Panel was sent a link to the Web site where they ranked the research needs from 1 to 5 and generated research questions for each research need. The survey allowed each rank to be used only once. Points were assigned to each research need: 1 point for a ranking of fifth, up to 5 points for a ranking of first. The research need with the largest number of points was assigned the highest priority. The research needs were presented in a random order for the survey.

The comments received from the Stakeholder Panel were reviewed by EPC staff and incorporated where necessary. In addition to the modified EHC Program Selection Criteria, special attention was paid to where research needs overlapped with existing research. The reasons for each research need were categorized based on a classification scheme created by the Johns Hopkins University EPC on behalf of AHRQ.[10]

Engagement of Stakeholders, Researchers, Funders

Central to the methodology of this report was the use of the Stakeholder Panel to identify and prioritize research needs. A single multidisciplinary Stakeholder Panel was convened to provide input on this project. The Panel consisted of 10 participants representing diverse clinical perspectives (from infectious diseases, critical care, pediatrics, emergency medicine), methodological expertise (e.g., guidelines development, clinical trials, epidemiology), and consumer and payer representation. Panel members brought forth specific clinical and research

experience on MRSA screening, infection control, antimicrobial resistance, and new diagnostic/treatment strategies.

The Stakeholder Panel was asked to recommend important studies published since the BCBSA TEC EPC completed the CER,[1] revise and prioritize the research needs listed in the CER and gathered throughout this project, and develop and prioritize a list of potential research questions to address those research needs. As required by AHRQ, conflict of interest forms were completed by all panel members and staff on this project. The multidisciplinary character of the Stakeholder Panel and their varied affiliations enriched the process.

The Stakeholder Panel was asked to participate in three conference calls (1 hour each) over the project duration, and some interim communications by email. In addition, a brief introductory call (30 minutes) was scheduled separately with each individual member, to provide an overview of the project, to discuss the role of the Stakeholder Panel, and to solicit preliminary suggestions on further research needs. The first call was held on May 25, 2012. During this call, the members were asked to review the preliminary list of research needs. This list was a synthesis of research needs from the CER, those proposed by panel members during the individual introductory calls, and results of the literature search update. Members reviewed a list of revised research needs following this call. The Stakeholder Panel was then asked to rank, via an online survey, their top five research needs from 1 to 5 with 1 having the highest priority and 5 the lowest. Panel members rated these research needs based on revised EHC program selection criteria (Appendix C).

The second call was scheduled on June 6, 2012. During the second call, Stakeholder Panel members were invited to review the prioritized list of research needs and "brainstorm" research questions to address each research need. Members reviewed a list of potential research questions following this call. The Stakeholder Panel was then asked to prioritize the research questions via an online survey instrument (using SurveyMonkey™) similar to that used for selection of research needs. As with the online survey for research needs, members were asked to rank their top five research questions from 1 to 5 with 1 having the highest priority and 5 the lowest (Appendix D). The project team collated the "votes" and reported the results at the third call, convened on June 22, 2012, for prioritization of research questions. The meeting participants reviewed the results and discussed the importance of the research questions to patient and clinical decision making. These discussions formed the basis for the final prioritized list of research questions submitted to AHRQ. All teleconference call materials were distributed a few days prior to scheduled calls. To enhance public engagement, AHRQ will solicit broader input on this document from the public, which will be incorporated and reflected in the final report.

Research Question Development and Study Design Considerations

Key Questions for each research need were generated through an online survey instrument and discussions with the Stakeholder Panel (discussed previously). The project team compiled a final list of research questions taking the feedback of the Panel into consideration. The research needs and research questions were characterized using the PICOTS framework consisting of the population(s) (P), interventions (I), comparators (C), outcomes (O), timing (T), and settings (S).[11] The project team evaluated potential study designs to address each of the key research questions consistent with the guidance published by RTI-UNC EPC commission by AHRQ.[10] The appropriateness of a study design to address a research need was further evaluated using the following criteria:

- Advantages of the study design for producing a valid result
- Resource use, size, and duration
- Ethical, legal, and social issues
- Availability of data or ability to recruit

The project team relied on this framework[10] as a guide during discussions of the least biased study design that was most feasible to undertake. Public comments received after the document is posted will be incorporated into the final report.

Results

Research Needs

Appendix E provides a synthesis of research needs from the CER, those proposed by panel members during the individual introductory calls, and results of the literature search update. The Stakeholder Panel was asked to review this preliminary list of research needs during the first teleconference call. These needs were grouped based on the PICOTS framework used in the CER. The panel members discussed the implications of the published studies and ongoing trials identified through the literature search update during the first call. Issues brought forth for discussion at this call included:

- Who may benefit from MRSA screening? One key issue is to identify the appropriate populations for screening as this has implications for decision making about universal screening or 'one size fits all' legislative approaches.
- What are the most effective tests for MRSA screening? MRSA screening cannot be considered as a sole intervention; this needs to be coupled with other interventions to determine the impact of a MRSA screening strategy. The efficacy of interventions such as decolonization and contact isolation has not been assessed adequately in current research initiatives (e.g., How do those interventions compare to other infection control strategies with respect to reducing MRSA infection?).
- What outcomes should be considered in evaluation of MRSA screening?
    - From an emergency department (ED) perspective, we should expand our concept of adverse events to consider the broader impact on patient flow system-wide, recognizing that some of the adverse outcomes may occur in patients who are not part of the screening program.
    - Since payers are now partnering with hospitals regarding patient quality and safety issues, areas of key concern are whom to screen, how to screen, and which outcomes to measure (e.g., the downstream effects of treatment, including antimicrobial resistance and complications). There are actuarial implications for high-quality health care based on these outcomes, and it would be desirable to be partners and support these efforts.
- From a microbiological perspective, a 'one size fits all' approach may not work because of the wide variation in types of blood isolates and disparity between nasal and blood isolates across the U.S..[11] Without knowing the origin of the various organisms, prevention of MRSA transmission through nasal colonization eradication will be difficult to achieve.

A total of seven research needs were identified through a combination of the CER findings and conversations with the Stakeholder Panel. The results of the first survey ranking the importance of these research needs are found in Appendix F. The response rate was 100 percent (n=10); all seven research needs received votes. The final seven research needs are stated in Table 2 (in order of priority).

Table 2. Prioritized list of research needs

1.	What are the central components of a MRSA screening strategy?
2.	Who may benefit from MRSA screening?*
3.	What outcomes should be considered for evaluations of MRSA screening?*
4.	What are the most effective tests for MRSA screening?
5.	What factors could influence MRSA test results (e.g., when to screen, which sites to swab)?
6.	What are the appropriate comparators for MRSA screening?
7.	From which perspective(s) should evaluations of MRSA screening be conducted (e.g., societal, hospital, emergency room, patient, payer)?

MRSA = methicillin-resistant *Staphylococcus aureus*
*Both questions received equal votes.

The Stakeholder Panel provided feedback during the second teleconference call on the survey results in terms of their importance to clinical and patient decision making. The panel members concurred that the overall rankings highlight the major issues. Panel members highlighted the difficultly in prioritizing these research needs given their inter-relatedness; for example, the top-ranked research need on the central components of an MRSA screening strategy encompasses many of the other research needs on this list (e.g., research needs 2, 3, and 4). Panel members discussed the need to address the fundamentals of screening (e.g., who is at high risk, who may benefit, what are the key components of a screening strategy, and how this might differ depending on which risk groups are under study, etc.). Further issues brought forth for discussion at the second call included:

- From a consumer perspective, the most negative impact is acquiring MRSA infection in the health-care setting. Every new patient infected with MRSA represents a need for prevention in the U.S. health care system and for patient-outcomes research (i.e., this produces a gap in consumer confidence and trust in our health care system). Screening needs to be best viewed as a tool for prevention of spread and active infections within a health care setting.
    - Methodologic transparency is important to consumers. Choice of outcomes will depend on what is most valid and important to report and generalizable across all health care settings with clear description of how they are measured. There is a need to ensure that these outcomes are fair measures for hospitals so that consumers can make informed decisions about their care.
- From a public health perspective, early detection and intervention are secondary prevention strategies which may only work in certain patient populations or certain high risk situations. It is important that future studies not lose sight of primary prevention of disease and the injury associated with it.
- Evaluation of MRSA screening.
    - The effectiveness of a particular strategy will depend on the followup action of a positive screen, and the goals of the strategy (e.g., whether to prevent transmission or undergo treatment). There are many potential followup actions and variables to consider that will require multiple study questions.
    - When evaluating various strategies, there is a need to consider the benefits and harms to the individuals exposed to the strategy (e.g., screened), as well as to other patients who were not directly exposed to the strategy.
    - Screening should be assessed in an environment that employs best practices routinely for prevention of MRSA infections, e.g., evaluating an ICU population in an environment where all ventilator-associated pneumonia preventive practices

are already in place. The challenge in studying this issue in terms of health outcomes such as newly documented MRSA infections or attributable mortality is the low rate of MRSA infection in specific health-care settings.

- While there are several ongoing clinical trials, additional research is needed to determine the role of screening-guided decolonization therapy versus universally applied decolonization therapy in applied more universally in certain high risk patient populations (e.g., role of the universal application of contact precaution gown and gloving in ICU or surgical patients).

Research Questions

Following the second Stakeholder Panel call, the EPC drafted a preliminary list of research questions to address the prioritized research needs and solicited feedback from panel members via email. This feedback was incorporated into a second survey of research questions that was submitted to Panel members for ranking prior to the third Stakeholder Panel call. As with the research needs, the research questions were presented in a random order for the survey. The results of the second survey ranking the importance of the research questions are found in Appendix G. The response rate was 100 percent (n=10); 16 (of 19) questions received votes.

The panel members discussed consolidating some of the research questions into a short list to take forward. The panel members concurred that the two top-ranked questions relating to surgical admissions and for the intensive care setting highlighted the major issues. As with the research needs, panel members discussed the difficulty in prioritizing the research questions given their inter-relatedness. The Stakeholder Panel also discussed the importance and usefulness of future studies on the top-ranked questions based on the voting results at the third panel call.

Future research issues brought forth for discussion on the third call were:

- General issues:
    - It was proposed that the research questions address both adult and pediatric populations (rather than treating the latter as a separate study group). Rather than formulating specific research questions for pediatrics, it would be beneficial to integrate this segment of the population within the two patient groups prioritized in the research needs (i.e., surgical patients, ICU patients), recognizing that future studies in children will need a separate analysis. An important subgroup to address within the pediatric population would be the neonates within the intensive care setting.
    - The fundamental question of whether screening works will depend on the patient population of interest as MRSA rates may differ by patient group. A study could look at MRSA screening versus non-screening strategies for identifying high risk patient populations targeted for interventions.
    - Many patients come into the hospital not colonized with MRSA and leave colonized. The number of patients who become colonized likely exceeds the number of patients who become infected. Since more than 80 percent of infected patients are infected with their own colonizing strain, a strategy that prevents colonization would be desirable. Therefore, colonization acquisition should be assessed as a part of any study. This would mean measuring colonization upon hospital admission, during hospitalization and at discharge in the study population.

- Specific issues:
    - **Question rank 1: For surgical admissions, what is the most effective strategy for reducing HA-MRSA infection, morbidity, mortality and resource use?** It would be important to determine whether to address all surgical patients or the listed subgroups of patients who are most likely to benefit? For example, there is a need to identify a priori who is actually considered "high risk" (e.g., general surgery patients vs. orthopedic or cardiac surgery patients) as these patient groups may have different risk profiles for MRSA.
    - **Question rank 2: In the intensive care setting, what is the most effective strategy for reducing MRSA infection rates, morbidity, mortality and resource use for patients with a positive MRSA culture?** The phrase "patients with a positive MRSA culture" (which is interpreted as a positive MRSA screening culture implying that screening is an implicit part of the strategy) should be deleted to allow comparison of screening versus non-screening based strategies. For example, one could compare a screening based strategy that identifies, isolates, and decolonizes carriers + standard measures with a non-screening based strategy that applies only standard measures to all patients (which needs to be defined but may include a hand hygiene program, chlorhexidine bathing, adherence to central line-associated bloodstream infection and ventilator-associated pneumonia bundle measures, etc.). This comment also applies to question rank 7 related to general medical adult inpatients.
    - **Question rank 5: What factors are associated with increased risk of HA-MRSA infection among general medical adult inpatients?** This choice focuses on what could be considered basic research needs – i.e., who are the high-risk groups (within selected categories of patients) who may actually benefit from screening if it were performed (or other targeted infection prevention strategies) and does screening work (in comparison to non-screening/broader-based infection prevention strategies) to prevent infections. Preventing transmission is important, but as an endpoint it may not be useful if we cannot show that preventing transmission equates preventing actual infection.
    - **Question rank 10: What factors are associated with increased risk of MRSA infection in surgical inpatients?** This question should not be limited to surgical inpatients, as many surgeries involving implants (prosthetic joints) in patients who may be at increased risk for HA-MRSA infection are performed electively, and surgical patients often come from the outpatient setting. One of the logistical issues is how best to screen surgical outpatients prior to surgery (if a screening-based strategy is used).
    - **Question rank 15: What is the most effective strategy for preventing MRSA infection among carriers after discharge from the hospital?** This question is important from a public health perspective based on population-based surveillance data of invasive MRSA disease that includes both community-onset and health care-acquired infections. Most cases of community-onset invasive disease occur outside of the hospital setting but involve patients who have been exposed to MRSA in hospitals. At present, there are lack of data about how to prevent infections in this population; there are few studies to date looking at decolonizing patients when they leave the hospital.

These discussions formed the basis for the final prioritized list of seven research questions (Table 3; in order of the key prioritized populations).

Table 3. Prioritized list of research questions

1.	For surgical admissions, what is the most effective strategy for reducing MRSA acquisition and infection rates and improving morbidity, mortality, patient flow and resource use?
2.	For surgical admissions what factors are associated with increased risk of MRSA acquisition and infection?
3.	For intensive care populations, what is the most effective strategy for reducing MRSA acquisition and infection rates and improving morbidity, mortality, patient flow and resource use?
4.	For the neonatal intensive care setting, what is the most effective strategy for reducing MRSA acquisition and infection rates and improving morbidity, mortality, patient flow and resource use?
5.	For intensive care populations, what factors are associated with increased risk of HA-MRSA acquisition and infection?
6.	For general medical inpatients, what is the most effective strategy for reducing MRSA acquisition and infection rates and associated morbidity, mortality, patient flow and resource use?
7.	For general medical inpatients, what factors are associated with increased risk of HA-MRSA acquisition and infection?

HA = hospital acquired; MRSA = methicillin-resistant *Staphylococcus aureus*

Study Design Considerations

The Stakeholder Panel discussed specific aspects of study designs and potential designs for the prioritized list of research questions at the third panel call. Issues brought forth for discussion at this call included:

- Comparators: It is important to design a trial that includes non-screening test based strategies. For example, hand hygiene would be a highly relevant comparator. If there was 100 percent compliance among health care workers for hand hygiene, some of the need for contact precautions to prevent transmission may not be required. This is a fundamental element of infection prevention, and it has not really been studied in any well-designed manner. One challenge in comparing culture decolonization with a nonculture-based strategy like gowning and gloving would be how to conduct a randomized study in one institution; a multicenter study may be the best option.
- Outcomes: It is important to clarify the study objectives as they will determine the appropriate outcomes for the study. For example, in the surgical population, the more appropriate outcome may be preventing surgical site infection whereas for the ICU population, MRSA acquisition would be of more concern.
- Timing: It is important to consider the time point at which the screening is being done and the time point at which the interventions are undertaken based on the screening results. Likewise, the effect of screening results on the time interval from ED admission to hospital admission, would have implications for the effectiveness of screening as well as for some of the associated effects of screening such as patient flow (e.g., from ambulatory care/ED into the high-risk setting) and negative secondary outcomes on patient populations who were not screened. For example, one study design might introduce screening on alternate days at a hospital ED that currently does not do screening; those who screen positive for MRSA would be admitted into contact isolation. A comparison of the median time interval between ED admission and hospital admission on screening versus non-screening days would assess the potential negative impact of screening on downstream patient flow.

When should you screen elective surgical admissions? Should you screen patients when they have their pre-surgical evaluation at the time of admission? Logistical issues would need to be addressed such as communication of test results that may require, for example, a team approach to coordinate results and follow up with appropriate interventions (e.g., decolonization prior to surgery). If screening is performed in the inpatient setting, is there enough time to receive a timely result and act upon this before the patient goes to the operating room?

- Study designs: In terms of robust designs, the cluster randomized clinical trial (RCT) offers the opportunity to compare different MRSA strategies. From an epidemiological perspective, there is a need to discuss the pros and cons of cluster trials, e.g., challenges of doing them and the desired outcomes, because different studies will have different objectives and outcomes.[12] Although more cluster RCTs will emerge within the next year and a half, realistically the cost of these trials will prevent many from being done. It may be harder to address rare outcomes such as infection rates using cluster RCTs because very large studies would be needed, so other study designs need to be considered.

For the assessment of study designs, EPC staff evaluated the appropriateness of various designs for each prioritized research question. For the three questions that identify factors associated with an increased risk of MRSA acquisition and infection in these priority populations, epidemiological studies offer the most valid and practical approaches to quantify the relationship between risk factors and disease. They are: cohort studies; nested case-control or case-control studies; and cross-sectional studies. On the other hand, for the four remaining questions that address the effectiveness of MRSA screening, experimental designs are needed to determine the causal effect of MRSA screening strategies on patient outcomes. The optimal design would allow the researcher to address multiple research needs by manipulating one or more variables and controlling and measuring their effects on other variables, while balancing the feasibility and practicality of carrying out the design. The EPC staff proposed the following study designs: cluster randomized controlled trials; quasi-experimental (before-after) studies; and modeling.

Higher quality before-and-after or quasi experimental studies at multiple sites that account for secular trends may be able to address Key Questions. These include identifying patients at high-risk for MRSA acquisition or infection, determining the actual turn-around times for various screening tests such as multiplex PCR analysis and blood tests, and determining which anatomical sites to screen. If the design of these types of studies is improved, they may be a less-costly option compared with the cluster randomized trial.

The project team identified additional study-design considerations:

- Who would benefit from screening? There are unanswered questions regarding the value of universal screening versus targeted screening strategies. From a practical standpoint, targeted screening may be more feasible to undertake at this time. Knowledge about risk factors can be used to identify high risk populations suitable as target groups for MRSA prevention strategies. Risk factors for HA-MRSA acquisition include recent hospitalization, having an invasive device or residing in a long term care facility. Risk factors for community-acquired MRSA identified in outbreak reports include participation in contact sports and living in crowded or unsanitary conditions. However, some populations (e.g., pediatrics) in which MRSA colonization is quite prevalent may present with none of the known risk factors making targeted screening difficult to undertake and universal screening impractical to implement.

- Alternate study designs for consideration
    - Cross-sectional studies may identify the prevalence of other factors that place these populations at risk. Patients with these risk factors, especially mutable risk factors, may then be targeted for prevention/intervention strategies. Definitions of a number of patient characteristics and outcomes would need to be formulated a priori. This design would not be suitable for rare outcomes such as MRSA infection rates.
    - Cohort studies and case-control studies may be used to compare the incidence of MRSA acquisition or infection between the intervention (screening) and control groups. Case-control studies may be more feasible or practical when the occurrence of new cases is relatively rare (e.g., HA-MRSA infection). Interventional studies could possibly combine questions of treatment effectiveness with evaluation of less-studied hypothesized risk factors (e.g., livestock exposure or living in urban underserved populations in community-acquired MRSA) as well as known risk factors (e.g., exposure to a health care setting).
    - In these studies it is essential to choose a representative sampling of the source population with justification for sample size to minimize selection bias. The internal validity should be ensured through methodologic transparency that accounts for such design elements as data completeness (e.g., loss to followup, missing data) and variables that may bias the results. The external validity of results may allow for generalization of the results to other settings and for comparison of health care institutions that would permit providers and other stakeholders (e.g., patients, payers) to make informed decisions regarding the quality of care.

Tables 4 and 5 present the final prioritized lists of research questions along with feedback from the Stakeholder Panelists that were incorporated into the PICOTS information. Similar PICOTS elements (e.g., interventions and outcomes) can be applied to questions 2, 5 and 7 that identify factors that increase the risk of MRSA acquisition and infection across the three priority patient groups (i.e., surgery, intensive care, general medical inpatients) in Table 4. Likewise, similar PICOTS elements (e.g. interventions, comparators and primary outcomes) can be applied to questions 1, 3, 4 and 6 that address the effectiveness of MRSA screening in these priority patient groups, as shown in Table 5.

Table 4. Prioritized list of risk factor research questions with PICOTS information

Research Question	Population(s)	Interventions	Comparators	Outcomes	Timing	Settings
For surgical admissions what factors are associated with increased risk of MRSA acquisition and infection?	Full or representative sample of surgical admissions: • Ambulatory care/ED admissions • Surgical unit admissions • Elective admissions	• MRSA screening/culture • Surveillance of potential risk factors for MRSA acquisition or infection (e.g., interview, questionnaire, database)	• No screening • Surveillance of potential risk factors for MRSA acquisition or infection (e.g., interview, questionnaire, database)	• MRSA surgical site infection rate • MRSA acquisition rates • Risk factors for MRSA acquisition • Risk factors for MRSA infection	• On admission e.g., in the ED or surgical unit • Pre-admission • At discharge • At followup visit	• Inpatient • Outpatient • Non-outbreak setting
For intensive care populations, what factors are associated with increased risk of HA-MRSA acquisition and infection?	Full or representative sample of intensive care admissions with the potential to acquire MRSA. May come from: • Ambulatory care/ED • General inpatient population	• MRSA screening/culture • Surveillance of potential risk factors for MRSA acquisition or infection (e.g., interview, questionnaire, database)	• No screening • Surveillance of potential risk factors for MRSA acquisition or infection (e.g., interview, questionnaire, database)	• MRSA acquisition • Risk factors for MRSA acquisition • MRSA infection • Risk factors for MRSA infection	• On admission e.g., in the ED or ICU	• Inpatient • Non-outbreak setting
For general medical inpatients, what factors are associated with increased risk of HA-MRSA acquisition and infection?	Full or representative sample of general medical admissions with the potential to acquire MRSA. May come from: • Ambulatory care/ED • Elective admissions	• MRSA screening/culture • Surveillance of potential risk factors for MRSA acquisition or infection (e.g., interview, questionnaire, database)	• No screening • Surveillance of potential risk factors for MRSA acquisition or infection (e.g., interview, questionnaire, database)	• MRSA acquisition • Risk factors for MRSA acquisition • MRSA infection • Risk factors for MRSA infection	• On admission e.g., in the ED or to the ward	• Outpatient (for elective admissions) • Inpatient • Non-outbreak setting

ED = emergency department; HA = hospital acquired; ICU = intensive care unit; MRSA = methicillin-resistant Staphylococcus aureus; PICOTS = population(s), interventions, comparators, outcomes, timing, settings

Table 5. Prioritized list of effectiveness research questions with PICOTS information

Research Question	Population(s)	Interventions	Comparators	Outcomes	Timing	Settings
1. For surgical admissions, what is the most effective strategy for reducing MRSA acquisition and infection rates and improving morbidity, mortality, patient flow and resource use?	• Broad range of risk categories (low, medium, high) for universal screening strategies or • High risk populations for targeted screening strategies	• Screening-based strategy (e.g., screening and decolonization) + standard care precautions Types of MRSA screening tests to be considered: • Multiplex PCR • Culture Site(s) of MRSA screening: • Nares, throat, axilla, groin, perirectal • Optimal number of sites to swab • Optimal anatomical sites • Separate swabs for each site vs. one swab for all sites	• Non-screening test based strategy (e.g., gowning and gloving, hand hygiene, or standard care precautions)	• MRSA surgical site infection rate • Staff compliance with infection control procedures • Patient flow (e.g., median time interval between ED arrival and hospital admission) • Morbidity (e.g., complications of MRSA infection) • MRSA-attributable mortality • Harms (e.g., allergic reaction to treatment, satisfaction of patients in isolation) • Resource use (e.g., length of stay) • Turn-around times for test results • Cost-benefit analysis	• Time point at which screening is done e.g., admission in ambulatory care or surgical unit • Time point at which intervention is initiated based on screening results • Time point at ED arrival • Time point at hospital admission	• Inpatient (e.g., ambulatory care/ED, surgical unit) • Outpatient • Non-outbreak setting

Table 5. Prioritized list of effectiveness research questions with PICOTS information (continued)

Research Question	Population(s)	Interventions	Comparators	Outcomes	Timing	Settings
3. For intensive care populations, what is the most effective strategy for reducing MRSA acquisition and infection rates and improving morbidity, mortality, patient flow and resource use? 4. For the neonatal intensive care setting, what is the most effective strategy for reducing MRSA acquisition and infection rates and improving morbidity, mortality, patient flow and resource use?	• Broad range of risk categories (low, medium, high) for universal screening strategies or • High risk populations for targeted screening strategies	• Screening-based strategy (e.g., screening and decolonization) + standard care precautions Types of MRSA screening tests to be considered: • Multiplex PCR • Culture Site(s) of MRSA screening: • Nares, throat, axilla, groin • Optimal number of sites to swab • Optimal anatomical sites • Separate swabs for each site vs. one swab for all sites	• Non-screening test based strategy (e.g., gowning and gloving, hand hygiene, or standard care precautions only)	• MRSA acquisition rate • MRSA infection rate • Staff compliance with infection control procedures • Patient flow (e.g., median time interval between ED arrival and hospital admission) • Morbidity (e.g., complications of MRSA infection) • MRSA-attributable mortality • Harms (e.g., allergic reaction to treatment, satisfaction of patients in isolation) • Resource use (e.g., length of stay) • Turn-around times for test results • Mother-to-child transmission rate (for neonates only) • Cost-benefit analysis	• Time point at which screening is done e.g., admission in ambulatory care or surgical unit • Time point at which intervention is initiated based on screening results • Time point at ED arrival • Time point at hospital admission	• Inpatient (e.g., ambulatory care/ED, ICU, labor and delivery) • Non-outbreak setting

Table 5. Prioritized list of effectiveness research questions with PICOTS information (continued)

Research Question	Population(s)	Interventions	Comparators	Outcomes	Timing	Settings
6. For general medical inpatients, what is the most effective strategy for reducing MRSA acquisition and infection rates and associated morbidity, mortality, patient flow and resource use?	• Broad range of risk categories (low, medium, high) for universal screening strategies or • High risk populations for targeted screening strategies	• Screening-based strategy (e.g., screening and decolonization) + standard care precautions Types of MRSA screening tests to be considered: • Multiplex PCR • Culture Site(s) of MRSA screening: • Nares, throat, axilla, groin • Optimal number of sites to swab • Optimal anatomical sites • Separate swabs for each site vs. one swab for all sites	• Non-screening based strategy (e.g., gowning and gloving, hand hygiene, or standard care precautions only)	• MRSA acquisition rate • MRSA infection rate • Staff compliance with infection control procedures • Patient flow (e.g., median time interval between ED arrival and hospital admission) • Morbidity (e.g., complications of MRSA infection) • MRSA-attributable mortality • Harms (e.g., allergic reaction to treatment, satisfaction of patients in isolation) • Resource use (e.g., length of stay) • Turn-around times for test results • Cost-benefit analysis	• Time point at which screening is done (e.g., admission in ambulatory care or on ward) • Time point at which intervention is initiated based on screening results • Time point at ED arrival • Time point at hospital admission	• Inpatient (e.g., ambulatory care/ED, ward) • Outpatient for elective admissions • Non-outbreak setting

ED = emergency room; ICU = intensive care unit; MRSA = methicillin-resistant Staphylococcus aureus; PCR = polymerase chain reaction; PICOTS = population(s), interventions, comparators, outcomes, timing, settings

The EPC considered the Stakeholder Panelists' feedback when recommending the most valid and feasible study designs for future research of MRSA screening that may be considered for each of the prioritized research questions. Table 6 presents study designs for identifying factors associated with an increased risk of MRSA acquisition and infection in three priority populations (surgical, intensive care and general medical), which, in turn, may help target strategies toward those who are most likely to benefit from MRSA prevention strategies. Table 7 displays the most feasible and valid experimental study designs for determining the effectiveness of interventions for preventing and treating MRSA acquisition and infection in four priority populations (surgical, intensive care, neonatal intensive care, general medical).

Table 6. Study design considerations for determining associations between risk factors and outcomes

Research Question 2. For surgical admissions what factors are associated with increased risk of MRSA acquisition and infection?
Research Question 5. For intensive care populations, what factors are associated with increased risk of HA-MRSA acquisition and infection?
Research Question 7. For general medical inpatients, what factors are associated with increased risk of HA-MRSA acquisition and infection?

Study Design Considerations	Cohort Study	Nested Case-Control Study	Case-Control Study	Cross-Sectional Study
Description of design	Individuals nonrandomly assigned MRSA prevention strategy or other strategy by physician and followed for a defined period. Data gathered on effectiveness and risk factors of interest. May be done prospectively or retrospectively.	A sampling of patients who have been exposed to MRSA prevention strategy and developed infection (cases) or did not develop infection (controls) are included from a prospective cohort and followed for a defined period. Data on risk factors are collected retrospectively. May be nested within prospective studies of treatment effectiveness.	Patients with MRSA acquisition or infection are compared with patients without MRSA, with a retrospective review of how many patients in each group were exposed to the MRSA prevention strategy and other risk factors.	Both the exposure and outcome status of a target population are assessed concurrently to estimate prevalence of possible risk factors in need of further study.
Advantages of study design for producing a valid result	Prospective cohort studies permit calculation of relative risk and measure events in temporal sequence thereby distinguishing causes from effects. Baseline characteristics may not be balanced and susceptible to confounders, but results may be more generalizable. Susceptible to bias such as selection bias and loss to follow up. Disadvantages include reliance on existing data that may have been collected for another purpose or may have key data missing.	Usually more valid than case-control study but balance of baseline characteristics is largely dependent on the original cohort. Disadvantages of this design include reliance on existing data which may be incomplete, confounders and bias such as sampling bias.	Relatively quick to collect data, but has multiple threats to validity. Sample should accurately reflect population of interest and sampling method should be clearly described. Useful for generating hypotheses that can be tested in experimental designs. Large numbers of exposure variables can be studied, but only one outcome variable can be studied at a time. May be the only option for collecting information on rare outcomes such as HA-MRSA infection. Permits estimation of relative risk through an odds ratio.	Fairly quick and inexpensive to conduct. Can study multiple outcomes. Design is not suitable for the study of rare outcomes. Susceptible to recall bias. Does not differentiate between cause and effect or the sequence of events. Study can generate a hypothesis regarding causation which can be tested in prospective cohort or randomized clinical trial designs.

Table 6. Study design considerations for determining associations between risk factors and outcomes (continued)

Research Question 2. For surgical admissions what factors are associated with increased risk of MRSA acquisition and infection?
Research Question 5. For intensive care populations, what factors are associated with increased risk of HA-MRSA acquisition and infection?
Research Question 7. For general medical inpatients, what factors are associated with increased risk of HA-MRSA acquisition and infection?

Study Design Considerations	Cohort Study	Nested Case-Control Study	Case-Control Study	Cross-Sectional Study
Resource use, size and duration	Likely to require substantial resources to collect epidemiological data of interest and to recruit adequate sample sizes, and multiple sites may be needed. Duration of followup will depend on desired outcome. Retrospective cohorts where available are cheaper and quicker but are susceptible to incomplete data collection that was collected for a different purpose, as well as to multiple threats to validity such as sampling bias and confounders such as staff compliance with infection control procedures.	Resources are low as it uses existing data and fewer subjects. Duration may be shorter than prospective studies.	Comparatively few subjects are required so more resources may be available for studying each subject. Requires collecting data on exposure to MRSA prevention strategy, which may or may not be easy to collect (e.g., if transferred from another hospital). Duration of study is relatively brief.	Only one group is used, data are collected only once and multiple outcomes can be studied; thus this type of study is relatively inexpensive. Resources may be higher than a nested case-control study as more subjects may be needed depending on the study question and outcome of interest.
Ethical, legal, and social issues	Fewer ethical issues than with RCT because of non-randomized assignment. Enrollment and consent of critically ill or urgent care patients could be an issue.	Minimal since data are already collected and no intervention is involved.	Generally low since events (exposures and outcomes) have already occurred.	Generally low since no intervention is involved, but could be moderate if additional data collection is needed.
Availability of data or ability to recruit	This design is generally more acceptable to participants. Recruitment may be slow at any one site, and multiple centers may be needed.	Availability of data should be high, since study sample data already collected.	Generally high since events have already occurred but collecting data on exposures can be difficult if multiple sites are involved.	This design is generally acceptable to participants. Some data may be already available.

HA = hospital acquired; MRSA = methicillin-resistant *Staphylococcus aureus*; RCT = randomized controlled trial

Table 7. Study design considerations for determining the effectiveness of strategies for prevention and treatment of MRSA acquisition and infection in target populations

Research Question 1. For surgical admissions, what is the most effective strategy for reducing MRSA acquisition and infection rates and improving morbidity, mortality, patient flow and resource use?
Research Question 3. For intensive care populations, what is the most effective strategy for reducing MRSA acquisition and infection rates and improving morbidity, mortality, patient flow and resource use?
Research Question 4. For the neonatal intensive care setting, what is the most effective strategy for reducing MRSA acquisition and infection rates and improving morbidity, mortality, patient flow and resource use?
Research Question 6. For general medical inpatients, what is the most effective strategy for reducing MRSA acquisition and infection rates and associated morbidity, mortality, patient flow and resource use?

Study Design Considerations	Randomized Controlled Trial	Quasi-Experimental: Before-After study (Variations)	Modeling
Description of design	Individuals or groups randomly assigned to receive one of two or more strategies for prevention or treatment, depending on the goal of the study. Outcomes include incidence of MRSA infection, MRSA acquisition and other outcomes such as MRSA carriage. Other associated cases (e.g., staff, roommates of study subjects) may be followed similarly. Longer followup post implementation may be required if sustainability of outcome is desired. Cluster RCTs that randomize at a hospital or ward level are more suitable for population-level strategies when outcomes for individuals from a given unit are not independent. If pooling data across institutions is required, consensus on outcome measures, minimum datasets and followup periods would be needed.	Incidence of MRSA compared in a group of individuals before and after exposure to the preventive strategy or treatment strategy. Investigator controls timing of measurement(s) and variables (e.g., baseline disease severity) measured, but not all intervention variables are in the control of the investigator. Data on potential confounding factors and temporal trends would be needed. If pooling data across institutions is required, consensus on outcome measures, minimum datasets and followup periods would be needed.	Simulation model developed and validated to assess the value of individual strategies or individual components of bundled strategies across a range of populations, settings and conditions. Use of agent based modeling for tracking MRSA transmission and infection would allow for assessing the impact of different interventions.
Advantages of study design for producing a valid result	Although individual RCTs are generally the preferred research design, in this context cluster RCTs are preferred because of the likelihood of interdependence of care patterns, background infection rates, and outcomes within a given hospital or unit. It should produce the most valid results, but the use of clusters often limits the available sample size. Requires planning to balance baseline characteristics and sample size considerations to achieve adequate power.	Simple design with generalizable results. May be best option if randomization is not possible. Highly susceptible to confounding variables, regression to the mean and maturation effects. Internal validity may be strengthened by use of a concurrent non-randomized comparison group that is not exposed to the preventive strategy or exposed to a different strategy, by multiple pre-intervention observations and by replication in different groups at multiple times. These studies must have adequate statistical methods to control for confounding and secular trends, otherwise no causal inference can be made.	May be the best option to use when questions cannot be addressed using conventional clinical trial methods or existing data analysis. May inform and help focus future clinical trials and data collection. Models can be tailored to multiple end users/perspectives, conditions and settings to enhance generalizability of findings and to help target interventions (different situations may call for different interventions). Other forms of modeling (e.g., compartment based, decision tree, etc.) can be informative but will require more assumptions and thus greater variability with less confidence in the results.

Table 7. Study design considerations for determining the effectiveness of strategies for prevention and treatment of MRSA acquisition and infection in target populations (continued)

Research Question 1. For surgical admissions, what is the most effective strategy for reducing MRSA acquisition and infection rates and improving morbidity, mortality, patient flow and resource use?
Research Question 3. For intensive care populations, what is the most effective strategy for reducing MRSA acquisition and infection rates and improving morbidity, mortality, patient flow and resource use?
Research Question 4. For the neonatal intensive care setting, what is the most effective strategy for reducing MRSA acquisition and infection rates and improving morbidity, mortality, patient flow and resource use?
Research Question 6. For general medical inpatients, what is the most effective strategy for reducing MRSA acquisition and infection rates and associated morbidity, mortality, patient flow and resource use?

Study Design Considerations	Randomized Controlled Trial	Quasi-Experimental: Before-After study (Variations)	Modeling
Resource use, size and duration	Depending on the strategy and desired effect size, costs, sample size and staff time needed for recruitment and implementation could be high. Recruitment of individuals or unit "clusters" willing to be randomized may be a constraint on sample size. Duration of hospitalization is likely to be brief which may keep costs down, but if sustainability of outcome or delayed outcomes such as MRSA acquisition or infection rates is desired, then longer followup may be required.	Generally less resource intensive than an experimental design. Otherwise, size and duration issues would be similar to RCT.	May require substantial personnel time but is generally less resource intensive than primary studies. Once agent based modeling identifies the transmission chains of MRSA, other modeling studies (e.g., decision tree) can be performed, but may require primary data collection to inform components if reliable estimates cannot be obtained from the literature, empiric studies or experts.
Ethical, legal, and social issues	For cluster RCTs, a waiver of informed consent may be required. Legal mandates or clinical culture may impede randomization to novel interventions or supersede trial objectives.	Need for informed consent, unless the comparison is done retrospectively. Legal mandates or clinical culture may supersede trial objectives.	Additional data collection may require institutional approvals or informed consent.
Availability of data or ability to recruit	Cluster RCTs require collaborative network of sites willing to participate. Strategies implemented at the unit level require participation of all individuals within that unit, which could affect recruitment.	Recruitment is generally feasible, particularly where randomization is unacceptable. Strategies implemented at the unit level require participation of all individuals within that unit, which could affect recruitment.	Data would be obtained primarily from published sources, proprietary institutional databases, and expert opinion.

MRSA = methicillin-resistant Staphylococcus aureus; RCT = randomized controlled trial

Discussion and Conclusions

Using the 2013 BCBSA TEC EPC evidence review, Screening for Methicillin-Resistant *Staphylococcus aureus* (MRSA),[1] we developed an 11-step process for identifying and prioritizing clinically important research needs and research questions, with key input from a diverse group of stakeholders. The final research questions reflect the research needs in the evidence related to the key populations identified in the CER. Through this process, we propose a final list of seven research questions across three prioritized populations.

It should be noted that the Stakeholder Panel highlighted research needs that were outside the scope of the original review, such as the need to address methicillin-susceptible *Staphylococcus aureus* (MSSA). For example, in evaluating a screening strategy in surgical patients, it would be important to consider including MSSA, as certain interventions (i.e. decolonization with mupirocin/chlorhexidine) would target both infections. Strategies found to be effective in reducing HA MRSA infection would likely reduce HA MSSA, as well. By excluding MSSA, there will be a missed opportunity to target another major cause of surgical-site infections. This would also be relevant to pediatrics, as most hospitals see more nosocomial MSSA then MRSA in pediatric populations. Future study designs could prespecify MRSA and MSSA as different subgroups. Panel members brought forth the need for further basic epidemiological investigation to determine which groups are at high-risk for MRSA infection to help target and design appropriate interventions.

The Stakeholder Panel noted that at least two of the questions ranked of lower priority should be considered priority research needs. First, additional research is needed to address the most effective strategy for preventing MRSA infection among carriers after hospital discharge. This question has a high public health impact, and it may actually be one of the easier questions to assess in terms of developing an effective strategy for prevention. Similarly, the question addressing the most effective anatomical-site screening protocol for detecting MRSA and MSSA carriage especially in high-risk surgical patients is presently an “under-studied” area in need of further research.

There are several strengths to our process. First, it is important that panel members represented a wide range of relevant disciplines to ensure balanced and broad perspectives on research needs from the CER on this topic. Each stakeholder was highly interested and committed with high levels of participation at each step. The consumer/patient perspective was especially useful in drawing attention to the importance of screening as part of an effective MRSA control program. Specific issues brought forth by the consumer representative addressed who is at increased risk for MRSA infection, the focus of screening, and the economic impact of MRSA infections for patients and their caregivers as well as health care providers.

Second, given the breadth of potential topics, the introductory one-on-one calls with panelists helped establish the preliminary list of research needs. This made the first conference call with the Stakeholder Panel more productive. Third, the literature search update allowed for more informed decisions in selecting topics that were not duplicative with current ongoing trials and to which further research would add the greatest value. Given the multiple populations under study, it was helpful to the project team to organize the literature search update and stakeholder information according to the research needs identified in the CER that evolved into specific research questions. These themes allowed the team to cover more comprehensively aspects of disease management along the continuum of care, care settings, and populations. The project team also sought feedback from the stakeholders to identify key published studies and ongoing trials across the list of research needs.

Finally, the online survey instrument was very successful in prioritizing issues across a broad range of categories. When provided with information on available research, rankings by the Stakeholder Panel appeared to be based on the amenability to comparative effectiveness research. A number of stakeholders complimented our process. The panel members agreed that the final list of research needs and research questions covered key topics for future study on MRSA screening.

We encountered several challenges to our process. First, it was difficult to prioritize the research needs and associated research questions given their inter-relatedness. There were several ways to combine/categorize many of the proposed topics. There was overlap among various research needs and the key underlying research questions across the top-ranked research needs. The categorization depended on how the Stakeholder Panel wanted to approach different topic areas. For example, the proposed topics could be categorized either by different segments of the population (adult, pediatrics) or specific settings (e.g., surgical, ICU, ambulatory care/ED).

Second, it was difficult to propose appropriate types of study designs for the prioritized research questions given that these are broad-based questions with multiple components and outcomes. The Stakeholder Panel discussed the limitations of using cluster randomized controlled trials to study these questions especially with rare outcomes such as MRSA infection rates; a very large trial would be needed (in terms of the number of sites and clusters) to address such questions. Better quality before-and-after or quasi experimental studies at multiple sites may be able to address some of these KQs.

Third, it was important to maintain the focus on the research needs and scope addressed in the CER. The research questions were grouped by categories that could be linked to the CER scope, as the team had the evidence reviews and the updated literature search to back the findings. This always presents a challenge as evidenced by some of the topics brought up by the Stakeholder Panel listed in the previous paragraphs. Finally, one additional challenge or a limitation of this process was that the Stakeholder Panel was presented with the draft results of the CER during the prioritization process; the conclusions did change between the draft and the final report and thus the impact of these results on the rankings of the research needs is unknown.

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Abbreviations

AHRQ	Agency for Healthcare Research and Quality
BCBSA TEC EPC	Blue Cross and Blue Shield Association Technology Evaluation Center Evidence-based Practice Center (BCBSA TEC EPC)
CER	Comparative Effectiveness Review
ED	Emergency department
EHC	Effective Health Care
EPC	Evidence-based Practice Center
HA	Hospital-acquired
ICU	Intensive care unit
MRSA	Methicillin-Resistant *Staphylococcus aureus*
MSSA	Methicillin-Susceptible *Staphylococcus aureus*
PCR	Polymerase chain reaction
PICOTS	Population(s), interventions, comparators, outcomes, timing, settings
RCT	Randomized controlled trial
U.S.	United States

Appendix A. Summary of Evidence from Draft Comparative Effectiveness Review

Key Questions	Outcome	# of Studies[§]	Reference	# of subjects	B	C	D	P	Overall Grade
KQ1 Universal screening vs. No screening	MRSA Transmission	1 QEX	Jain 2011[1]	1,934,598	H	U	N	N	Insufficient
	MRSA Infection	2 QEX	Robicsek 2008[2] Jain 2011[1]	112,985 1,934,598	M	Y	Y	N	Insufficient
	MRSA Bacteremia or Blood Stream Infection	2 QEX	Robicsek 2008[2] Jain 2011[1]	112,985 1,934,598	M	Y	Y	N	Insufficient
	MRSA Surgical Site Infection	1 QEX	Robicsek 2008[2]	112,985	L	U	Y	N	Insufficient
	Morbidity, Mortality, Harms, Resource Utilization	0	NA	No studies	NA	NA	NA	NA	Insufficient
KQ2 Universal screening vs. Targeted Screening	MRSA Transmission	0	NA	No studies	NA	NA	NA	NA	Insufficient
	MRSA Infection	2 QEX	Robicsek 2008[2] Leonhardt 2011[3]	128,334	M	N	Y	N	Insufficient
	Morbidity, Mortality, Harms, Resource Utilization	0	NA	No studies	NA	NA	NA	NA	Insufficient
KQ3A Screening of ICU Risk Pts Vs No Screening	MRSA Transmission	1 RCT	Huskins 2011[4]	4,056	M	N	N	N	Insufficient
		3 QEX	Holzmann-Pazgal 2011[5] Huang 2006[6] Raineri 2007[7]	3,097 Unclear 21,754; (166,877[‡])					
	MRSA Infection	1 QEX	Robicsek 2008[2]	Unclear	L	U	Y	N	Insufficient
	MRSA Bacteremia or Blood Stream Infection	2 QEX	Robicsek 2008[2] Huang 2006[6]	Unclear	M	N	Y	N	Insufficient
	MRSA Surgical Site Infection	1 QEX	Robicsek 2008[2]	Unclear	L	U	Y	N	Insufficient
	Morbidity, Mortality, Harms, Resource Utilization	0	No studies	NA	NA	NA	NA	NA	Insufficient

Key Questions	Outcome	# of Studies§	Reference	# of subjects	B	C	D	P	Overall Grade
KQ3B Screening of Surgical Pts Vs No Screening	MRSA Transmission	1 QEX-XR	Harbarth 2008[8]	21,754	L	U	N	N	Insufficient
	MRSA infection	1 QEX-XR	Harbarth 2008[8]	21,754	M	N	Y	N	Insufficient
		1 QEX	Muder 2008[9]	21,449‡					
	MRSA Surgical Site Infection	1 QEX-XR	Harbarth 2008[8]	21,754	M	N	Y	N	Insufficient
		1 QEX	Muder 2008[9]	21,449‡					
	Morbidity, Mortality, Harms, Resource Utilization	0	No Studies	NA	NA	NA	NA	NA	Insufficient
KQ3C Screening of High Risk Pts Vs No Screening	MRSA Transmission	2 QEX	Rodriguez-Bano 2010[10] Ellingson 2011[11]	Unclear	H	U	N	N	Insufficient
	MRSA Infection	1 QEX	Harbarth 2000[12]	506,012	H	U	Y	N	Insufficient
	MRSA Bacteremia/ Blood Stream Infection	3 QEX	Rodriguez-Bano 2010[10] Chowers 2009[13] Ellingson 2011[11]	Unclear 377,945; (1,535,806‡) Unclear	H	Y	Y	N	Insufficient
	MRSA Surgical Site Infection	1 QEX	Harbarth 2000[12]	506,012	H	U	Y	N	Insufficient
	Morbidity, Mortality, Harms, Resource Utilization	0	No Studies	NA	NA	NA	NA	NA	Insufficient
KQ4 Expanded screening vs. Limited Screening	MRSA Transmission	1 QEX	Rodriguez-Bano 2010[10]	Unclear	H	U	N	N	Insufficient
	MRSA Infection	1 QEX	Chaberny 2008[14]	219,124; (1,987,676‡)	H	U	N	N	Insufficient
	MRSA Bacteremia	1 QEX	Rodriguez-Bano 2010[10]	Unclear	H	N	Y	N	Insufficient
	Morbidity, Mortality, Harms, Resource Utilization	0	No Studies	NA	NA	NA	NA	NA	Insufficient

Note: This table lists the findings from the draft CER report; the conclusions have changed between the draft and the final report.
B: Risk of bias; C: Consistency; D: Directness; H: high; P: Precision, NA: not applicable; N: No; QEX: quasi experimental; RCT: randomized controlled trial; U: Unknown; Y: Yes; XR: cross over.
§CCS Studies
‡ Patient days

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Appendix B. Search Strategies for Updating of Evidence

PUBMED on 5/14/2012
"Methicillin-Resistant Staphylococcus aureus"[Mesh] AND (("2012/03/01"[PDat] : "2012/06/31"[PDat]))
Limits: Humans, English, published in the last year
OR
Methicillin-Resistant Staphylococcus aureus AND (("2012/03/01"[PDat] : "2012/06/31"[PDat]))
OR
("Methicillin Resistance" AND "Staphylococcus aureus") OR "methicillin-resistant staphylococcus aureus" OR MRSA AND (("2012/03/01"[PDat] : "2012/06/31"[PDat]))
AND
randomized controlled trial[pt] OR controlled clinical trial[pt] OR randomized controlled trials[mh] OR random allocation[mh] OR double-blind method[mh] OR single-blind method[mh] OR clinical trial[pt] OR clinical trials[mh] OR "clinical trial" OR ((singl* OR doubl* OR trebl* OR tripl*) AND (mask* OR blind*)) OR placebos[mh] OR placebo* OR random* OR research design[mh:noexp] OR follow-up studies[mh] OR prospective studies[mh] OR prospectiv* OR volunteer* OR "Comparative Study "[Publication Type] OR "Evaluation Studies "[Publication Type] OR control OR controlled OR controls OR comparative study[tiab] OR comparative[title]

Results: 11 Studies

EMBASE.COM on 5/14/2012
'mrsa'/exp OR mrsa OR 'methicillin resistance'/exp OR 'methicillin resistance'
OR
'methicillin'/exp
OR
methicillin AND resistan* AND staphylococcus*
AND
randomized AND controlled AND trial OR controlled AND clinical AND trial* OR randomized AND controlled AND trials OR random AND allocation OR 'double blind' AND 'method'/exp OR 'single blind' AND 'method'/exp OR clinical AND trial OR clinical AND trials OR 'clinical trial'/exp OR (singl* OR doubl* OR trebl* OR tripl* AND (mask* OR blind*)) OR 'placebos'/exp OR placebo* OR random* OR 'follow up'/exp AND studies OR prospective AND studies OR prospectiv* OR 'comparative study'/exp OR 'evaluation'/exp AND studies OR controlled OR comparative AND 'study'/exp OR comparative:ti

Results: 19 Studies

Cochrane Central on 4/28/2012
methicillin-resistant staphylococcus aureus OR 'methicillin resistance AND staphylococcus aureus OR MRSA

Results: 1 new trial in the CCTR

Clinical Trials.Gov
methicillin-resistant staphylococcus aureus
OR
methicillin resistance AND staphylococcus aureus
OR
MRSA

Results: 26 recently updated trial records

Appendix C. Survey Tool Used To Rate Research Needs

Instructions to fill the survey

The objective is to rate the research needs based on pre-specified criteria by using a voting mechanism. Please read the following instructions carefully before proceeding with your voting.

Instructions:

- There are in total 7 research needs
- Each panel member has been allotted a total of 5 votes.
- Choose and rank gaps in the order of your perceived importance with a score of 1 representing the highest importance and 5 representing lower importance.

Please cast your votes based on the following criteria:

• Current importance
• Potential for significant health impact
• Incremental value
• Feasibility

You can review these criteria in detail [below].

Prioritization Criteria for Research Needs

Current importance
• Incorporates both clinical benefits and harms
• Represents important variation in clinical care due to controversy/uncertainty regarding appropriate care
• Addresses high costs to consumers, patients, health-care systems, or payers
• Utility of available evidence limited by changes in practice, e.g., disease detection

Potential for significant health impact
• Potential for significant health impact:
o To improve health outcomes
o To reduce significant variation related to quality of care
o To reduce unnecessary burden on those with health-care problems
• Potential for significant economic impact, reducing unnecessary or excessive costs
• Potential for evidence-based change
• Potential risk from inaction, i.e., lack of evidence for decision-making produces unintended harms
• Addresses inequities, vulnerable populations, patient subgroups with differential impact (e.g., by age)

Incremental value
• Adds useful new information to existing portfolio of research on topic OR
• Validates existing research when body of evidence is scant

Feasibility

• Factors to be considered:
o Interest among researchers
o Duration
o Cost
o Methodological complexity (e.g., do existing methods need to be refined?)
o Implementation difficulty
o Facilitating factors
o Potential funders

(Criteria modified for primary research from: Whitlock EP et al. AHRQ Series Paper 3: Identifying, selecting, and refining topics for comparative effectiveness systematic reviews: AHRQ and the Effective Health-Care program. Journal of Clinical Epidemiology 2010; 63: 491-501)

*Please rank your top 5 research needs from 1 to 5 with 1 having the highest priority and 5 the lowest.

1. What factors could influence MRSA test results (e.g., when to screen, which sites to swab)?
2. Who may benefit from MRSA screening?
3. What are the most effective tests for MRSA screening?
4. What are the central components of a MRSA screening strategy
5. What are the appropriate comparators for MRSA screening?
6. What outcomes should be considered for evaluations of MRSA screening?
7. Which study perspectives should be considered for evaluations of MRSA screening (e.g., societal, hospital, patient, payer)?

If you have any further comments please give them below:

Appendix D. Survey Tool Used To Rate Research Questions

Instructions to fill the survey

The objective is to rate the research questions based on pre-specified criteria by using a voting mechanism. Please read the following instructions carefully before proceeding with your voting.

Instructions:

- There are in total 19 research questions
- Each panel member has been allotted a total of 5 votes.
- Choose and rank questions in the order of your perceived importance with a score of 1 representing the highest importance and 5 representing lower importance.

Please cast your votes based on the following criteria:

• Current importance
• Potential for significant health impact
• Incremental value
• Feasibility

You can review these criteria in detail [below].

Prioritization Criteria for Research Questions

Current importance

• Incorporates both clinical benefits and harms
• Represents important variation in clinical care due to controversy/uncertainty regarding appropriate care
• Addresses high costs to consumers, patients, health-care systems, or payers
• Utility of available evidence limited by changes in practice, e.g., disease detection

Potential for significant health impact

• Potential for significant health impact:
o To improve health outcomes
o To reduce significant variation related to quality of care
o To reduce unnecessary burden on those with health-care problems
• Potential for significant economic impact, reducing unnecessary or excessive costs
• Potential for evidence-based change
• Potential risk from inaction, i.e., lack of evidence for decision-making produces unintended harms
• Addresses inequities, vulnerable populations, patient subgroups with differential impact (e.g., by age)

Incremental value
• Adds useful new information to existing portfolio of research on topic OR
• Validates existing research when body of evidence is scant

Feasibility
• Factors to be considered:
o Interest among researchers
o Duration
o Cost
o Methodological complexity (e.g., do existing methods need to be refined?)
o Implementation difficulty
o Facilitating factors
o Potential funders

(Criteria modified for primary research from: Whitlock EP et al. AHRQ Series Paper 3: Identifying, selecting, and refining topics for comparative effectiveness systematic reviews: AHRQ and the Effective Health-Care program. Journal of Clinical Epidemiology 2010; 63: 491-501)

*Please rank your top 5 research questions from 1 to 5 with 1 having the highest priority and 5 the lowest.

1. What factors are associated with increased risk of MRSA infection in surgical inpatients?

2. What is the most effective strategy for preventing MRSA cross-transmission among adult patients in the intensive care setting?

3. What is the most effective strategy for preventing MRSA infection among critically and chronically ill carriers after discharge from the hospital?

4. What is the most effective anatomical-site screening protocol (e.g., site(s), number of swabs etc.) for detecting MRSA in adult patients in intensive care?

5. What factors are associated with increased risk of HA-MRSA infection among general medical adult inpatients?

6. What is the most effective strategy for reducing MRSA infection and associated morbidity, mortality and resource use in pediatric inpatients?

7. What is the most effective strategy for preventing MRSA cross-transmission among high-risk surgical inpatients?

8. Who should be screened for MRSA in the ambulatory care/ER setting?

9. What is the most effective strategy for preventing MRSA cross-transmission among general medical adult inpatients?

10. What is the most effective anatomical-site screening protocol (e.g., site(s), number of swabs etc.) for detecting MRSA among general medial adult inpatients?

11. What is the most effective strategy for reducing MRSA infection rates, morbidity, mortality and resource use among general medical adult inpatients with a positive MRSA culture?

12. What factors are associated with increased risk of HA-MRSA infection in the intensive care

setting?

13. What is the most effective anatomical-site screening protocol (e.g., site(s), number of swabs etc.) for detecting MRSA in high-risk surgical inpatients?

14. What is the most effective anatomical-site screening protocol (site(s), number of swabs etc.) for detecting MRSA in pediatric inpatients?

15. What is the most effective strategy for preventing MRSA cross-transmission among pediatric inpatients?

16. What is the most effective strategy for managing patients with a positive MRSA screening test in the ambulatory care/ER setting with respect to morbidity, mortality, resource use and patient flow?

17. What is the most effective strategy for reducing CA-MRSA infection rates in patients who are admitted through ambulatory care/ER setting?

18. For surgical admissions, what is the most effective strategy for reducing HA-MRSA infection, morbidity, mortality and resource use?

19. In the intensive care setting, what is the most effective strategy for reducing MRSA infection rates, morbidity, mortality and resource use for patients with a positive MRSA culture?

If you have any further comments please give them below:

Appendix E. List of Research Needs

Research Needs	Draft CER	Stakeholder Panel Comments	Primary Studies	Ongoing Clinical Trials*
Who may benefit from MRSA screening? (Population/Setting)	• Evidence is inconclusive due to the variation in the clinical context in which screening has been evaluated. • Higher risk populations e.g., ICU or inpatient surgical patients are likely to derive the most benefit. • Factors that may affect the applicability of results from either targeted or broad-based screening include: o Individual risk of acquisition or colonization of MRSA. o Variations in practice and in MRSA carriage and infection rates across geographic regions and individual institutions.	• Who is "high risk"? o No clear definitions. Prevalence studies may be helpful. o Many children with MRSA infection would not be considered high risk. • For pediatrics, screening on hospital admission is impractical because high prevalence of MRSA colonization in the community will yield very large numbers; targeting specific hospital populations may be more manageable e.g., ICU populations. It would be very difficult to perform multicenter studies. • Universal vs. targeted screening? Do we need universal screening of inpatients? 'Do you own the infections of your roommate'?	Provided by Stakeholder Panel: • Milstone AM. MRSA colonization and risk of subsequent infection in critically ill children: importance of preventing nosocomial MRSA transmission. Clin Infect Dis. 2011 Nov;53:853-9. • Fritz SA. The natural history of contemporary Staphylococcus aureus nasal colonization in community children. Pediatr Infect Dis J. 2011 Apr;30:349-51. • Walsh EE. Sustained reduction in MRSA wound infections after cardiothoracic surgery. Arch Intern Med. 2011;171:68-73.	NCT Number: NCT00980980 **Title:** Cluster Randomized Trial of Hospitals to Assess Impact of Targeted Versus Universal Strategies to Reduce MRSA in Intensive Care Units (ICUs) [REDUCE-MRSA] **Recruitment:** Completed (no results). **URL:** ClinicalTrials.gov/show/NCT00980980
What are the most effective tests for MRSA screening? (Interventions) What factors could influence MRSA test results? (Timing)	• Findings: o Variation in the screening methodology and reporting standards limit applicability of results. • Recommendations: o Examine each element of an intervention bundle to accurately determine the benefit or harm that can be attributed to it. o Transparent and thorough reporting of all transmission prevention strategies and decolonization therapy deployed with screening. o Uniformity in testing strategy used (e.g., PCR vs. culture), test turnaround time, and the	• Benefit of MRSA screening depends on the overall rationale of the screening strategy, as it is often coupled with other infection control strategies • Compliance will depend on what motivates practitioners, e.g., skepticism about its usefulness, need for quality data. • Logistics of screening: o Which site(s)? There are no data correlating screening to specific sites of infection. o Not all community infections colonize nasally; pediatrics commonly colonized in other areas, (e.g., perineal). o How many sites to swab? o How many swabs/site?	• Haith L. Evaluation of nasal MRSA polymerase chain reaction (PCR) as a screening tool in burn center patients. Surgical Infections 2012;13:S36. Provided by Stakeholder Panel: • Gurieva T. The successful Veterans Affairs initiative to prevent MRSA Infections revisited. Clin Infect Dis. 2012 Apr 4:1618-20.	None identified

Research Needs	Draft CER	Stakeholder Panel Comments	Primary Studies	Ongoing Clinical Trials*
	handling of patients while awaiting lab results. o Account for compliance with infection control strategies. o Accounting for the management of patients before screening test results are known.	o When to screen? e.g., should elective admissions be screened 7-10 days prior to admission to avoid delays?		
What are the appropriate comparators for MRSA screening? (Comparators)	• Systematic review included "no screening" or "targeted screening" as comparators.	• Other infection control practices should be considered viable comparators, because new data suggest non-screening strategies using chlorhexidine bathing or universal gown/glove may be effective at reducing transmission and decolonization rates (See *M*astering h*OS*pital *A*ntimicrobial *R*esistance (MOSAR) network studies).	• Derde LP. Chlorhexidine body washing to control antimicrobial-resistant bacteria in intensive care units: a systematic review. Intensive Care Med 2012 Apr 12. • Tatokoro M. Successful control of MRSA in a urology ward possibly due to avoidance of antimicrobial prophylaxis in minimally invasive surgery: Our 11 years trial. Journal of Urology 2012;187:e24. Provided by Stakeholder Panel: • Fritz SA. Household versus individual approaches to eradication of community-associated Staphylococcus aureus in children: a randomized trial. Clin Infect Dis. 2012 Mar;54:743-51.	NCT Number: NCT00976638 **Title:** Clinical Trial to Reduce Antibiotic Resistance in European Intensive Cares (MOSAR-ICU) **Status:** Completed (no results) **URL:** ClinicalTrials.gov/show/NCT00976638 NCT Number: NCT00685867 **Title:** Two Strategies for Methicillin-resistant Staphylococcus Aureus (MRSA) Infection Prevention in Surgical Patients (MOSAR-04) **Status:** Unknown **URL:** http://ClinicalTrials.gov/show/NCT00685867 NCT Number: NCT01127516 **Title:** The Causes and Interpretation of Low-level Resistance in Staphylococcus Aureus **Status:** Completion, May 2013 **URL:** http://ClinicalTrials.gov/show/NCT01127516

Research Needs	Draft CER	Stakeholder Panel Comments	Primary Studies	Ongoing Clinical Trials*
What outcomes should be considered in evaluation of MRSA screening? (Outcomes)	• Precise estimates of the impact of screening for MRSA-carriage on morbidity and mortality are needed. • Harms of screening must be clearly delineated.	• From an ER perspective what is the impact of rapid testing strategies on patient flow and bed flow? o A backlog can result in negative outcomes outside the ER e.g., delays in care, ambulance transfers or diversions to other facilities and patients dying 'en route'. o Extended boarding if hospital isolation beds are not available, etc. • What do you do with patients who screen positive, culture results are not available and isolation rooms may be in short supply or when it is difficult to get a specimen? o Patients on precautions checked on less often. o Adherence to infection control practices. o Patient satisfaction and emotional wellbeing. • Research should take into account the emotional, financial and health loss of the patient.		None identified

***** Literature search update covering March 1, 2012 through May 15, 2012

Broad-based Issues	Draft CER	Stakeholder Panel Comments
Improvement in the quality of evidence supporting MRSA screening.	Recommendations • Use of the cluster RCT rather than before-after designs adequately powered to detect effect on outcome. o Large multicenter trials needed. • RCTs must adequately control for bias and confounding owing to epidemiologic trends, concomitant infection prevention strategies and account for compliance with interventions. • Maximally transparent reporting of: o Interventions and potential confounders. o Transmission prevention strategy and the use of decolonization therapy.	• The impact of MRSA screening will depend on setting, rationale for screening and patient populations. • Need to focus on % total *staph aureus* infections, including MSSA, as the individual rates may differ substantially across institutions. • Need to standardize research approaches and use ecologically-controlled designs over the traditional before-after observational designs. • Need for a definition of MRSA "outbreak". • Need to account for the impact of multi-drug resistant pathogens and inter-hospital patient sharing as a mechanism of disease transmission. • Research should focus on who should get screened, how often, and how long to isolate and cohort patients when we are uncertain how long they may have been infected. • How do improved patient outcomes and associated costs link back to a screening program when multiple components may be involved? • The first priority is preventing MRSA infection. Failing that, early identification of potential MRSA infection is important. • Data are lacking on effective strategies that respond to a positive culture e.g., decolonization vs. prevention of transmission. • Meaningful pay for performance programs are needed that will reduce health care-associated infection rates, especially MRSA and surgical site infections, and associated mortality and morbidity. • Community-acquired infections should also be considered.

Other topics posed by Stakeholder Panel

- MRSA screening in prevention of MRSA lung infections.
- Use of MRSA screening results to predict who is at risk for MRSA lung infection.

Additional References Provided by Stakeholder Panel for Further Perspective/To Guide Future MRSA Studies

1. Bode LGM. Preventing surgical-site infections in nasal carriers of *Staphylococcus aureus*. N Engl J Med. 2010;362:9-17.
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Appendix F. Survey Results of Research Needs

Rank	Research Needs	Total Votes *	Weighted Score
1	What are the central components of a MRSA screening strategy?	10	30
2	Who may benefit from MRSA screening?	9	35
2	What outcomes should be considered for evaluations of MRSA screening?	9	35
4	What are the most effective tests for MRSA screening?	9	18
5	What factors could influence MRSA test results (e.g., when to screen, which sites to swab)?	7	19
6	What are the appropriate comparators for MRSA screening?	4	8
7	Which study perspectives should be considered for evaluations of MRSA screening (e.g., societal, hospital, patient, payer)?	2	5

*Responses from 10 (of 10) panel members

Appendix G. Survey Results of Research Questions

Rank	Research Questions	Total Votes*	Weighted Score
1	For surgical admissions, what is the most effective strategy for reducing HA-MRSA infection, morbidity, mortality and resource use?	8	30
2	In the intensive care setting, what is the most effective strategy for reducing MRSA infection rates, morbidity, mortality and resource use for patients with a positive MRSA culture?	7	23
3	What is the most effective strategy for preventing MRSA cross-transmission among high-risk surgical inpatients?	5	18
4	What is the most effective strategy for preventing MRSA cross-transmission among adult patients in the intensive care setting?	4	17
5	What factors are associated with increased risk of HA-MRSA infection among general medical adult inpatients?	4	5
6	What is the most effective strategy for preventing MRSA cross-transmission among general medical adult inpatients?	3	13
7	What is the most effective strategy for reducing MRSA infection rates, morbidity, mortality and resource use among general medical adult inpatients with a positive MRSA culture?	3	7
8	What is the most effective strategy for reducing CA-MRSA infection rates in patients who are admitted through ambulatory care/ER setting?	3	6
9	What is the most effective strategy for reducing MRSA infection and associated morbidity, mortality and resource use in pediatric inpatients?	3	5
10	What factors are associated with increased risk of MRSA infection in surgical inpatients?	2	5
11	What is the most effective strategy for preventing MRSA cross-transmission among pediatric inpatients?	2	4

Rank	Research Questions	Total Votes*	Weighted Score
11	What is the most effective strategy for managing patients with a positive MRSA screening test in the ambulatory care/ER setting with respect to morbidity, mortality, resource use and patient flow?	2	4
13	What is the most effective anatomical-site screening protocol (e.g., site(s), number of swabs etc.) for detecting MRSA among general medial adult inpatients?	1	4
13	What factors are associated with increased risk of HA-MRSA infection in the intensive care setting?	1	4
15	What is the most effective strategy for preventing MRSA infection among critically and chronically ill carriers after discharge from the hospital?	1	3
16	What is the most effective anatomical-site screening protocol (e.g., site(s), number of swabs etc.) for detecting MRSA in high-risk surgical inpatients?	1	2
17	What is the most effective anatomical-site screening protocol (e.g., site(s), number of swabs etc.) for detecting MRSA in adult patients in intensive care?	0	0
18	Who should be screened for MRSA in the ambulatory care/ER setting?	0	0
19	What is the most effective anatomical-site screening protocol (site(s), number of swabs etc.) for detecting MRSA in pediatric inpatients?	0	0

*Responses from 10 (of 10) panel members