

Draft Comparative Effectiveness Review

Number XX

Screening for Methicillin-Resistant *Staphylococcus Aureus* (MRSA)

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Preface

The Agency for Healthcare Research and Quality (AHRQ) conducts the Effective Health Care Program as part of its mission to organize knowledge and make it available to inform decisions about health care. As part of the Medicare Prescription Drug, Improvement, and Modernization Act of 2003, Congress directed AHRQ to conduct and support research on the comparative outcomes, clinical effectiveness, and appropriateness of pharmaceuticals, devices, and health care services to meet the needs of Medicare, Medicaid, and the Children's Health Insurance Program (CHIP).

AHRQ has an established network of Evidence-based Practice Centers (EPCs) that produce Evidence Reports/Technology Assessments to assist public- and private-sector organizations in their efforts to improve the quality of health care. The EPCs now lend their expertise to the Effective Health Care Program by conducting comparative effectiveness reviews (CERs) of medications, devices, and other relevant interventions, including strategies for how these items and services can best be organized, managed, and delivered.

Systematic reviews are the building blocks underlying evidence-based practice; they focus attention on the strength and limits of evidence from research studies about the effectiveness and safety of a clinical intervention. In the context of developing recommendations for practice, systematic reviews are useful because they define the strengths and limits of the evidence, clarifying whether assertions about the value of the intervention are based on strong evidence from clinical studies. For more information about systematic reviews, see

<http://www.effectivehealthcare.ahrq.gov/reference/purpose.cfm>

AHRQ expects that CERs will be helpful to health plans, providers, purchasers, government programs, and the health care system as a whole. In addition, AHRQ is committed to presenting information in different formats so that consumers who make decisions about their own and their family's health can benefit from the evidence.

Transparency and stakeholder input from are essential to the Effective Health Care Program. Please visit the Web site (<http://www.effectivehealthcare.ahrq.gov>) to see draft research questions and reports or to join an e-mail list to learn about new program products and opportunities for input. Comparative Effectiveness Reviews will be updated regularly.

We welcome comments on this CER. 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 e-mail to epc@ahrq.hhs.gov.

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Screening for Methicillin-Resistant *Staphylococcus Aureus* (MRSA)

Structured Abstract

Objectives: To synthesize comparative studies that examined the benefits and harms of screening for methicillin-resistant *Staphylococcus aureus* (MRSA) carriage in the inpatient or outpatient settings.

Data Sources: MEDLINE®, EMBASE®, the Cochrane Database of Systematic Reviews, National Institute for Clinical Excellence, the National Guideline Clearinghouse, and the Health Technology Assessment Programme were searched from January 1990, to September 2011. A search of the gray literature included databases with regulatory information, clinical trial registries, abstracts and conference papers, grants and federally funded research, and information from manufacturers.

Review Methods: We sought studies that compared MRSA screening strategies including universal screening, screening of selected patient populations (surgery, ICU, high-risk), and no screening. Outcomes were MRSA acquisition, MRSA infection, morbidity (including complications of MRSA infection), mortality, adverse events (including allergic and nonallergic toxicity (e.g., hypotension), antimicrobial resistance, reduced quality of care, and medical errors), and hospital resource utilization such as length of stay. Data were abstracted by a team of reviewers, and fact checked by another team of reviewers. Study quality was assessed using the U.S. Preventive Services Task Force framework. Strength of the body of evidence was assessed according to the *AHRQ Methods Guide*.

Results: Overall, 44 studies were abstracted for this review. Two studies reported outcomes that addressed Key Question (KQ) 1 (universal vs. no screening), two that addressed KQ2 (universal vs. screening of selected populations), 13 that addressed KQ3A (screening of ICU patients vs. no screening), 13 that addressed KQ3B (screening of surgery patients vs. no screening), nine that addressed KQ3C (screening of high-risk patients vs. no screening) and eight that addressed KQ4 (expanded vs. limited screening). Of these, only the 15 studies that attempted to control for confounding and/or secular trends (CCS studies) had the potential to support causal inferences about the impact of MRSA screening on health outcomes, and therefore, contributed to the strength of evidence syntheses across all key questions. For the four different screening strategies evaluated, this review found insufficient evidence to determine the comparative effectiveness on MRSA acquisition, infection, morbidity, mortality, harms or resource utilization.

Conclusions: There is insufficient evidence to support the benefits of routine implementation of screening for MRSA-carriage as part of organizational infection control in all settings. Future research of MRSA screening should evaluate strategies that employ a uniform approach to screening and infection control, should adopt the cluster-randomized trial design to reduce concerns regarding confounding, and should evaluate the effects of screening on morbidity, mortality, and resource utilization.

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Executive Summary

Background

Methicillin-resistant *Staphylococcus aureus* (MRSA) emerged as a clinically relevant human pathogen more than 3 decades ago.¹ The aggressive 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–associated 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 U.S. hospitals has steadily increased over the past 20 years.² A number of analyses suggest that MRSA infections are associated with increased mortality and cost of care when compared with those due to strains that are susceptible to methicillin. Even the availability of newer pharmaceutical agents with specific activity against MRSA, including linezolid and daptomycin, has not lessened the burden of MRSA for patients and clinicians. The widespread use of these agents has been limited in part due to toxicity, expense, and uncertainty as to optimal indications.³

The management and control of MRSA has been further complicated by dramatic changes in the epidemiology of transmission and infection observed over the past 2 decades. Specifically, *S. aureus* strains resistant to methicillin, once exclusively linked to hospital care, have increasingly been detected among patients in the community who lack conventional risk factors for MRSA infection.^{4, 5} Community-acquired MRSA has increasingly been linked to outbreaks of infection in hospitals and health care facilities.⁶

Conventional strategies for the control of MRSA (whether hospital- or community-associated) have focused on the prevention of spread from patient to patient (horizontal transmission). The effectiveness of hand hygiene in preventing the spread of MRSA has been most convincingly demonstrated in observational studies in which hand hygiene-promotion campaigns were associated with subsequent reductions in the incidence of MRSA among hospitalized patients.⁷ While hand hygiene remains the cornerstone of MRSA transmission-control efforts, the continued spread of the pathogen after initial introduction in most facilities has prompted efforts to identify additional strategies. The use of contact isolation—including the donning of gowns and gloves when interacting with patients colonized or infected with MRSA and the assignment of such patients to single rooms or to a room with a group of affected patients—has been widely promoted and adopted. Such isolation precautions now are the centerpiece of most authoritative guidelines for MRSA control.⁸ Despite the broad consensus associated on the use of contact isolation for MRSA prevention, the specific evidence in support of this practice remains limited and indirect.

Given the continued dissemination of MRSA at most U.S. hospitals, it is clear that these measures, as presently deployed, have been insufficient to check the spread of MRSA and other antibiotic-resistant pathogens.

A further limitation of these approaches—and specifically the use of isolation precautions—is the potential negative consequences of these measures. A series of studies have associated isolation precautions with worsened outcomes in terms of safety and patient satisfaction.⁹ In addition, questions have been raised about 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. While the methodology employed in some of these studies has been questioned, no rigorous definitive analysis has been completed to exonerate isolation precautions.¹⁰

Based on the failure of conventional strategies 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.¹¹ 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 U.S. Particular attention has been given to the potential value of active surveillance screening for MRSA. Because routine clinical cultures may identify as few as 18 percent of patients overtly infected with antibiotic-resistant organisms such as MRSA, there exists a large reservoir of patients who are silent carriers of these organisms. These individuals may serve as a reservoir for further transmission. With active surveillance, microbiological samples are obtained from at-risk patients even in the absence of signs or symptoms of infection in an effort to identify the underlying population of colonized individuals. By detecting the larger population of colonized individuals, at the very least conventional precautions can be implemented in a broader and more timely manner so as to interrupt horizontal transmission of MRSA. Detection of colonized patients also permits consideration of more aggressive interventions, including attempts at microbiological eradication or decolonization.

The specific evidence in support of active surveillance for MRSA has been promising, although a number of questions remain about the effectiveness of active surveillance for MRSA-carriage 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 infections in general.

Objective

The objective of this systematic review was to synthesize comparative studies that examined the benefits or harms of screening for Methicillin-resistant *Staphylococcus aureus* (MRSA) carriage in the inpatient or outpatient settings. 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 ICU, patients admitted for a surgical procedure, or patients at high-risk of MRSA colonization or infection) 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 patient population included all ambulatory patients (outpatients) and hospitalized patients (inpatients).

Key Questions

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 to no screening on:

- Intermediate outcomes such as MRSA transmission (as measured by new acquisition events)?
- Health outcomes such as the incidence of 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?

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 to screening of selected patient populations (targeted screening) on:

- Intermediate outcomes such as MRSA transmission (as measured by new acquisition events)?
- Health outcomes such as the incidence of 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?

Key Question 3A

Among ambulatory or hospitalized patients, what are the effects of screening ICU patients for MRSA-carriage (screen, isolate, eradicate/decolonize) – when compared to no screening on:

- Intermediate outcomes such as MRSA transmission (as measured by new acquisition events)?
- Health outcomes such as the incidence of 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?

Key Question 3B

Among ambulatory or hospitalized patients, what are the effects of screening surgical patients for MRSA-carriage (screen, isolate, eradicate/decolonize) – when compared to no screening on:

- Intermediate outcomes such as MRSA transmission (as measured by new acquisition events)?
- Health outcomes such as the incidence of 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?

Key Question 3C

Among ambulatory or hospitalized patients, what are the effects of screening high-risk patients for MRSA-carriage (screen, isolate, eradicate/decolonize) – when compared to no screening on:

- Intermediate outcomes such as MRSA transmission (as measured by new acquisition events)?
- Health outcomes such as the incidence of 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?

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 to a limited screening strategy on:

- Intermediate outcomes such as MRSA transmission (as measured by new acquisition events)?
- Health outcomes such as the incidence of 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?

PICOTS (Patient, Intervention, Comparator, Outcome, Timing, and Setting) for the Key Questions

Patients All ambulatory patients (outpatients) and all hospitalized patients (inpatients). In addition, the following subpopulations were evaluated: 1) patients admitted to an intensive care unit; 2) patients undergoing surgical procedures; and 3) patients at high-risk of MRSA colonization or infection.

Intervention A MRSA screening strategy applied to all patients in a setting (universal screening) or applied to particular wards, units or patients (targeted screening) that includes:

- 1) MRSA screening using a testing modality (typically PCR) with rapid turnaround (results available on the same day as the testing is performed) or
- 2) MRSA screening using a testing modality with intermediate turnaround (results available next day to 2 days after testing performed) or
- 3) MRSA screening using a testing modality (typically culture) with a longer turnaround time (results available greater than 2 days after testing performed)

And that may include:

- 1) Isolation and/or
- 2) Eradication/decolonization.

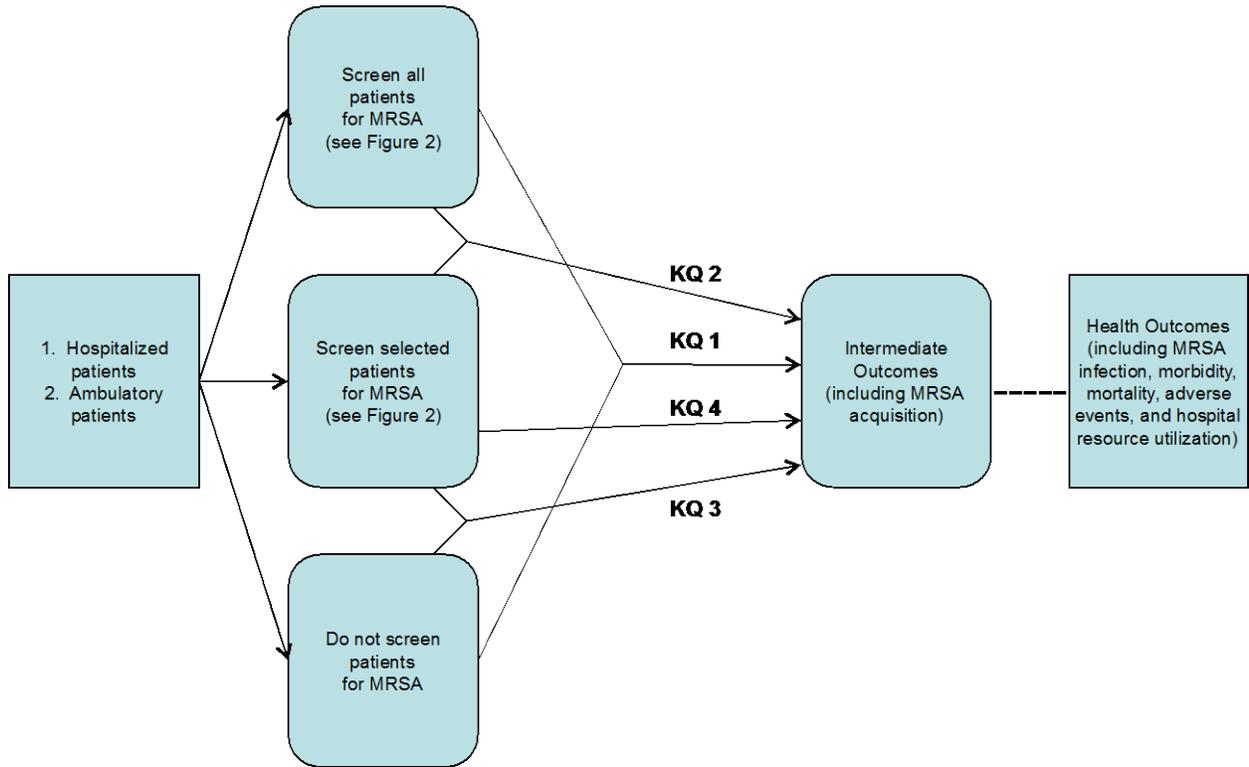
Comparator	No screening or screening of selected patient populations (targeted screening).
Outcomes	MRSA acquisition, MRSA infection, morbidity (including complications of MRSA infection), mortality, quality of care for non-infectious conditions, medical errors, adverse effects of screening and treatment including allergic reactions, non-allergic toxicities, and resistance to antimicrobials, and hospital resource utilization such as length of stay.
Timing	Intervention through follow-up.
Settings	Inpatient (hospital wards and intensive care units) and outpatient (ambulatory clinics, urgent care centers and emergency departments).

A comprehensive review evaluating the benefits and harms of screening for MRSA-carriage will identify areas of certainty and those that require additional prospective research.

Analytic Framework

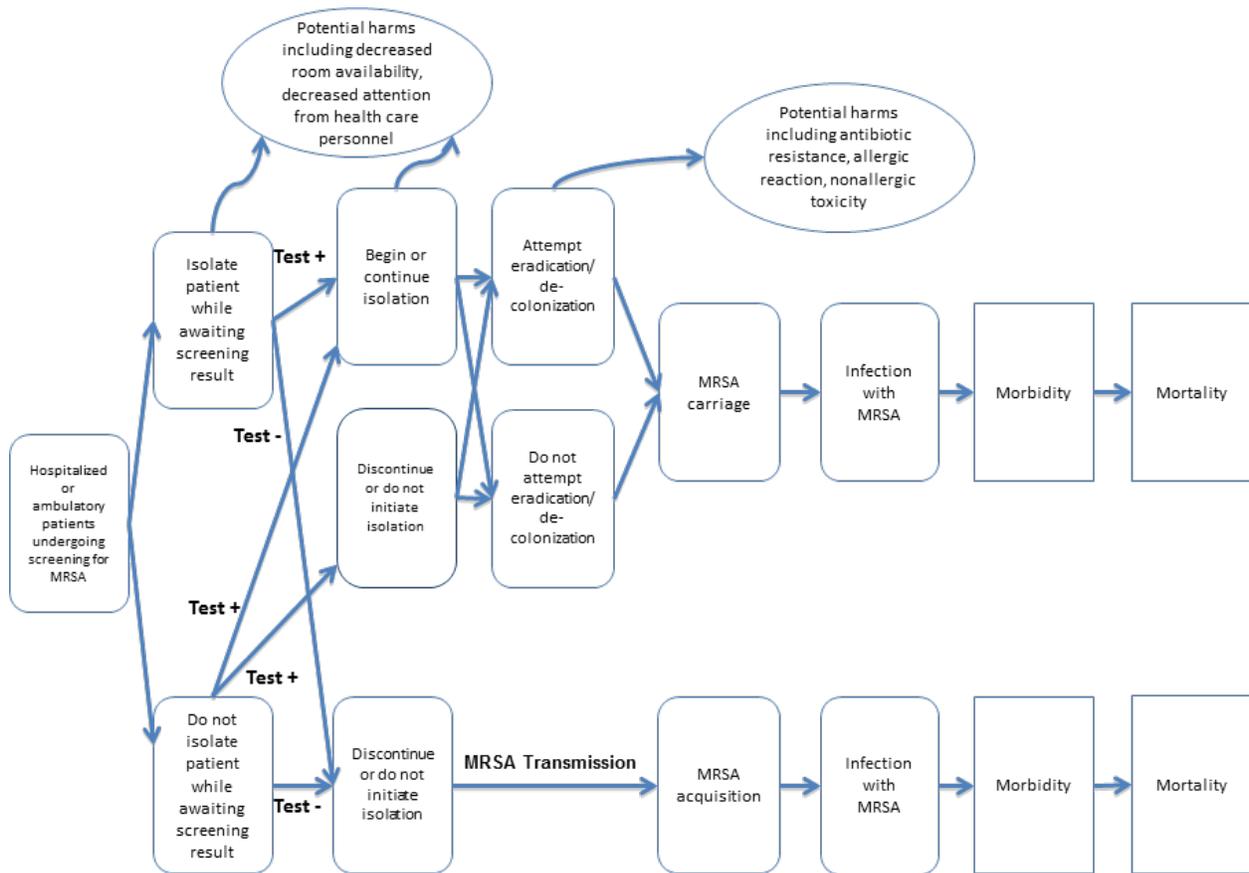
The analytic framework (Figure ES-1) depicts the effects of screening for MRSA-carriage on intermediate outcomes (including MRSA acquisition) and health outcomes (including MRSA infection, morbidity and mortality).

Figure ES-1. Analytic Framework for MRSA Screening



Abbreviations: KQ = key question; MRSA = methicillin-resistant *Staphylococcus aureus*.

Figure ES-2. Detailed Analytic Framework for MRSA Screening



Abbreviations: KQ = key question; MRSA = methicillin-resistant *Staphylococcus aureus*; Test + = positive MRSA-screening test result; Test - = negative MRSA-screening test result.

The detailed analytic framework (Figure ES-2) depicts the effects of screening for MRSA carriage in detail. Once screened, patients may or may not be isolated while waiting for screening test results. Once the screening test results are received, patients who screen positive may be isolated; patients who screen negative are not. Eradication/decolonization may be attempted in patients who screen positive. Intermediate outcomes of MRSA screening, including MRSA transmission and infection, are depicted in the figure. Health outcomes, including morbidity and mortality, are also depicted. The figure illustrates the potential harms of screening, including decreased room availability, decreased attention from health care personnel, antibiotic resistance, allergic reactions, and nonallergic toxicity.

Methods

Input from Stakeholders

This systematic review was developed by the Evidence-based Practice Center (EPC) with input from stakeholders. Stakeholders were broadly defined as anyone involved with making health care decisions, including patients, clinicians, professional and consumer organizations, and purchasers of health care. Individuals from various stakeholder groups were invited as Key Informants, Technical Experts, and/or Peer Reviewers to guide this systematic review.

Key informants are end-users of research. A Key Informant panel highlighted the controversies surrounding MRSA screening and the challenges inherent in a review of this topic. The Key Questions were then posted on the AHRQ website for public commentary. Input from the Key Informants panel and public were incorporated into the scope of the report and the analytic framework (Figures ES-1 and ES-2).

The Technical Expert Panel (TEP) reviewed the research protocol in two phases: 1) initial draft protocol; 2) revised protocol that incorporated the Panel's comments on the draft and findings of a preliminary literature search.

All potential Key Informants, Technical Experts, and Peer Reviewers were required to disclose any potential conflicts of interest in accordance with AHRQ policy. The AHRQ Task Order Officer and the EPC worked to balance, manage, or mitigate any potential conflicts of interest identified. Individuals who had conflicts of interest that precluded participation as informants, experts or reviewers were able to submit comments through the public comment mechanism. Writing and editing the report was solely the responsibility of the EPC.

Data Sources and Selection

MEDLINE® was searched from January 1, 1990 through September 1, 2011 for randomized and nonrandomized comparative studies. EMBASE® was searched from January 1, 1990 to September 1, 2011 for randomized controlled trials, nonrandomized comparative studies, and case series using similar search terms. The Cochrane Controlled Trials Register was searched without date restriction using the same search teams utilized for the MEDLINE® and EMBASE® searches. In addition, a search for systematic reviews was conducted in MEDLINE®, the Cochrane Database of Systematic Reviews, and the websites of the National Institute for Clinical Excellence, the National Guideline Clearinghouse, and the Health Technology Assessment Programme. The grey literature was also searched including in databases with regulatory information, clinical trial registries, abstracts and conference papers, grants and federally funded research, and manufacturing information.

The titles and abstracts were screened for studies that looked at MRSA acquisition, MRSA infection, morbidity, mortality, harms of screening, and resource utilization when screening for MRSA-carriage compared to no screening. A single reviewer made the decision about a full text review. Citations marked as uncertain were reviewed by a second reviewer for consideration of full text review. A third reviewer was consulted if necessary. We included randomized, controlled trials and nonrandomized comparative studies.

Data Extraction and Quality Assessment

Data were abstracted by a team of reviewers, and fact checked by another reviewer. If there were disagreements they were resolved through discussion among the review team. Categories of data elements were abstracted as follows: quality assessment (number of participants and flow of participants, treatment allocation methods, blinding, and independent outcome assessment), applicability and clinical diversity assessment (patient, diagnostic, and treatment characteristics), outcome assessment (primary and secondary outcomes, response criteria, follow-up frequency and duration, data analysis details).

Quality of included studies was assessed using the U.S. Preventive Services Task Force framework¹² based on the following criteria: assembly and maintenance of comparable groups, loss to follow-up, measurements (equal, reliable, and valid), clear definition of interventions, all important outcomes considered, and analysis (adjustment for potential confounders and intention-to-treat analysis). Three quality categories were used: good, fair, and poor. Quality of the abstracted studies was assessed by at least two independent reviewers, and the final quality rating was assigned by consensus adjudication.

Assessment of individual study quality was greatly informed by whether studies attempted to control for confounding or secular trends. Studies that used such analytic techniques are described as CCS studies, while those that did not are called non-CCS studies. Non-CCS studies used simple two-group statistical analyses. Observational studies that do not attempt to control for confounding or secular trends do not provide evidence that supports causal inference. The ratings of good, fair and poor quality are reserved for CCS studies. Comments will be made here about results from non-CCS studies, but they are not included in strength of evidence syntheses.

Data Synthesis and Analysis

We anticipated that the decision to incorporate formal data synthesis into this evidence review would be made after completing the formal literature search. Similarly we also anticipated that the decision to pool studies would be based on whether there were sufficient number of studies that were designed to ask similar questions and reported similarly defined outcomes. If a meta-analysis could be performed, subgroup and sensitivity analyses would be based on assessment of clinical diversity in available studies. The pooling method would involve inverse variance weighting and a random effects model.

The overall strength of evidence grade was determined in compliance with the *Methods Guide*¹³ and is based on a system developed by the Grading of Recommendations Assessment, Development and Evaluation (GRADE) Working Group.¹⁴ This system explicitly addressed the following domains: risk of bias, consistency, directness, and precision. The grade of evidence strength was classified into the following four categories: high, moderate, low, and insufficient. Specific outcomes and comparisons were rated depending on the evidence found in the literature. The grade rating was made by independent reviewers, and disagreements were resolved by consensus adjudication.

Results

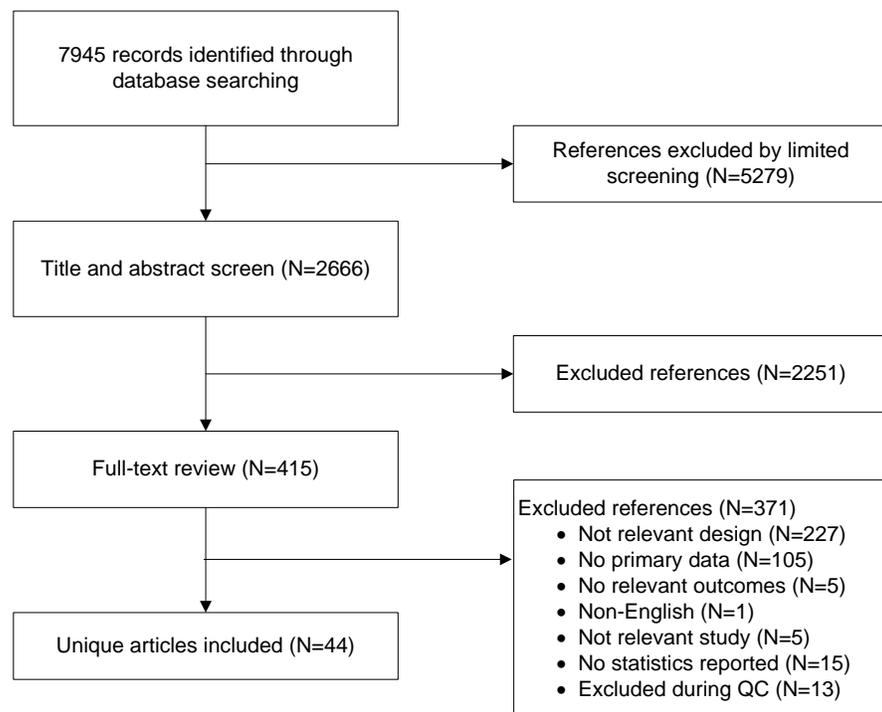
Overview

Overall, 44 studies were abstracted for this review. Two studies^{15, 16} reported outcomes that addressed key question 1, two studies^{15, 17} reported outcomes that addressed key question 2,

thirteen studies^{15, 18-29} reported outcomes that addressed key question 3A, thirteen studies³⁰⁻⁴¹ reported outcomes that addressed key question 3B, nine studies⁴²⁻⁴⁹ reported outcomes that addressed key question 3C and eight studies^{45, 50-56} reported outcomes that addressed key question 4. The emphasis is on health care-associated outcomes, because screening for MRSA-carriage in health care facilities is most proximately expected to impact health care-associated MRSA transmission and infection.

The 15 studies^{15-22, 30, 31, 42-45, 50} that attempted to control for confounding and/or secular trends (CCS studies) contributed to the SOE analysis across all four key questions. These studies had the potential to support causal inferences about the impact of MRSA screening on health outcomes, and therefore are included in the strength of evidence syntheses. The PRISMA diagram (Figure ES-3) depicts the flow of search screening and study selection.

Figure ES-3. PRISMA Diagram for Identified Published Literature



Key Question 1: Universal Screening for MRSA-Carriage Compared to No Screening

Two quasi-experimental CCS studies^{15, 16} described universal screening for methicillin-resistant *Staphylococcus aureus* (MRSA) carriage compared to no screening. The Robicsek study¹⁵ was judged to be of good quality. However, the Jain study¹⁶ was judged to be of poor quality.

Health Care-Associated MRSA Acquisition

Only the Jain study¹⁶ addressed this outcome. With universal screening for MRSA, this study showed a statistically significant reduction in health care-associated MRSA in the intensive care unit and in non-ICU settings.

Compared to no screening, the strength of evidence was insufficient that universal screening for MRSA-carriage decreases health care-associated MRSA acquisition based on the positive findings from a single, quasi-experimental before/after study. The risk of bias was judged to be high; the consistency of results is unknown; and the effect is imprecise.

Health Care-Associated MRSA Infection

Both the Robicsek study¹⁵ and the Jain study¹⁶ addressed this outcome. Compared to no screening, both studies found a statistically significant reduction in health care-associated MRSA infection with universal screening for MRSA. For the good quality study,¹⁵ the change in the rate of MRSA infection from a Poisson regression model was -69.6 percent with broad confidence intervals (95 percent CI: -89.2 to -19.6 percent). For the poor quality study,¹⁶ the relative reduction in the rate of MRSA infection was -62 percent in ICU settings and -45 percent in non-ICU settings. The p value for trend in both settings was <0.001.¹⁶

Compared to no screening, the strength of evidence was insufficient that universal screening for MRSA-carriage decreases health care-associated MRSA infection based on the moderate risk of bias and the lack of precision from two quasi-experimental studies.

Morbidity, Mortality, Harms and Resource Utilization

Because no studies addressed these outcomes, compared to no screening, the strength of evidence is insufficient to assess the effect of universal screening for MRSA-carriage on morbidity, mortality, harms or resource utilization.

Key Question 2: Universal Screening for MRSA-Carriage Compared to Screening of Selected Populations (Targeted Screening)

Two quasi-experimental CCS studies of good quality compared universal screening for MRSA carriage on hospital admission to screening of selected patient populations (targeted screening).^{15,17}

Table ES-1. Summary of Outcomes Measures and Strength of Evidence

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 ¹⁶	1,934,598	H	U	N	N	Insufficient
	MRSA Infection	2 QEX	Robicsek 2008 ¹⁵ Jain 2011 ¹⁶	112,985 1,934,598	M	Y	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 ¹⁵ Leonhardt 2011 ¹⁷	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 ²¹	4,056	M	N	N	N	Insufficient
		3 QEX	Holzmann-Pazgal 2011 ¹⁹ Huang 2006 ²⁰ Raineri 2007 ²²	3,097 Unclear 21,754; (166,877 [‡])					
	MRSA Infection	1 QEX	Robicsek 2008 ¹⁵	Unclear	L	U	Y	N	Insufficient
	MRSA Bacteremia or Blood Stream Infection	2 QEX	Robicsek 2008 ¹⁵ Huang 2006 ²⁰	Unclear	M	N	Y	N	Insufficient
	MRSA Surgical Site Infection	1 QEX	Robicsek 2008 ¹⁵	Unclear	L	U	Y	N	Insufficient
	Morbidity, Mortality, Harms, Resource Utilization	0	No studies	NA	NA	NA	NA	NA	Insufficient

Table ES-1. Summary of Outcomes Measures and Strength of Evidence (continued)

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 ³⁰	21,754	L	U	N	N	Insufficient
	MRSA infection	1 QEX-XR	Harbarth 2008 ³⁰	21,754	M	N	Y	N	Insufficient
		1 QEX	Muder 2008 ³¹	21,449 ⁺					
	MRSA Surgical Site Infection	1 QEX-XR	Harbarth 2008 ³⁰	21,754	M	N	Y	N	Insufficient
1 QEX		Muder 2008 ³¹	21,449 ⁺						
	Morbidity, Mortality, Harms, Resource Utilization	0	No Studies	NA	NA	NA	NA	Insufficient	
KQ3C Screening of High Risk Pts Vs No Screening	MRSA Transmission	2 QEX	Rodriguez-Bano 2010 ⁴⁵ Ellingson 2011 ⁴³	Unclear	H	N	N	N	Insufficient
	MRSA Infection	1 QEX	Harbarth 2000 ⁴⁴	506,012	H	U	Y	N	Insufficient
	MRSA Bacteremia/ Blood Stream Infection	3 QEX	Rodriguez-Bano 2010 ⁴⁵ Chowers 2009 Ellingson 2011 ⁴³	Unclear 377,945; (1,535,806 [‡]) Unclear	H	Y	Y	N	Insufficient
	MRSA Surgical Site Infection	1 QEX	Harbarth 2000 ⁴⁴	506,012	H	U	Y	N	Insufficient
		Morbidity, Mortality, Harms, Resource Utilization	0	No Studies	NA	NA	NA	NA	Insufficient
KQ4 Expanded screening vs. Limited Screening	MRSA Transmission	1 QEX	Rodriguez-Bano 2010 ⁴⁵	Unclear	H	U	N	N	Insufficient
	MRSA Infection	1 QEX	Chaberny 2008 ³⁰	219,124; (1,987,676 [‡])	H	U	N	N	Insufficient
	MRSA Bacteremia	1 QEX	Rodriguez-Bano 2010 ⁴⁵	Unclear	H	N	Y	N	Insufficient
		Morbidity, Mortality, Harms, Resource Utilization	0	No Studies	NA	NA	NA	NA	Insufficient

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

Health Care-Associated MRSA Acquisition

The strength of evidence to evaluate the effect of universal screening for MRSA-carriage compared to targeted screening on health care-associated MRSA transmission is insufficient, as no studies addressed this outcome.

Health Care-Associated MRSA Infection

Both CCS studies evaluated this outcome. While both studies showed a reduction in hospital-acquired MRSA infection with universal screening for MRSA carriage compared to targeted screening, only the Robicsek study showed a statistically significant reduction.

The strength of evidence to evaluate the effect of universal screening for MRSA-carriage compared to targeted screening on health care-associated MRSA infection was judged to be insufficient based on the moderate risk of bias, the lack of consistency and the imprecision of the study findings. Though both studies found a reduction in health care-associated MRSA infection with universal screening, the difference in statistical significance led us to conclude that the findings were inconsistent.

Morbidity, Mortality, Harms and Resource Utilization

Because no studies addressed these outcomes, the strength of evidence to evaluate the effect of universal screening for MRSA-carriage compared to targeted screening on morbidity, mortality, harms or resource utilization was judged to be insufficient.

Key Question 3A: MRSA Targeted Screening (ICU) versus No Screening

Six CCS studies^{15,18-22} and seven²³⁻²⁹ non-CCS studies described screening of ICU patients for MRSA-carriage compared to no screening. The Huskins study²¹ was a cluster randomized controlled trial and other studies^{15, 18-20, 22-29} utilized quasi-experimental designs. Of the CCS studies, the Robicsek¹⁵ and Huskins studies²¹ were of good quality, the Gould¹⁸ study was of fair quality, and the Huang,⁵⁷ Raineri,²² and Holzmann-Pazgal¹⁹ studies of poor quality.

Health Care-Associated MRSA Acquisition

One good quality study,²¹ three poor quality studies,^{19, 20, 22} and one non-CCS study²⁶ addressed this outcome. With targeted screening, the Huskins study²¹ found a non-statistically significant increase in health care-associated MRSA colonization or infection. However, the Huang, Raineri and Holzmann-Pazgal studies^{19, 20, 22} found statistically significant reductions in health care-associated colonization or infection. With screening, the non-CCS study by de la Cal and colleagues²⁶ found a statistically significant reduction in hospital-acquired MRSA colonization or infection with screening of ICU patients for MRSA-carriage.

The strength of evidence for screening of ICU patients for MRSA-carriage on MRSA acquisition was found to be insufficient based on the moderate risk of bias and the inconsistent and imprecise results.

Health Care-Associated MRSA Infection, Irrespective of Site

One good quality study¹⁵ and four^{24, 25, 27, 28} non-CCS studies addressed this outcome. The impact of screening for MRSA-carriage in the ICU on acquired MRSA infection was mixed. Compared to no screening, the good quality study¹⁵ found a reduction in hospital-acquired MRSA infection with screening of ICU patients for MRSA-carriage; however, this reduction was not statistically significant. In addition, compared to no screening, one²⁷ of the non-CCS studies found no statistically significant reduction in hospital-acquired MRSA infection with screening of ICU patients for MRSA-carriage. However, two^{24, 28} of the non-CCS studies found a statistically significant reduction in hospital-acquired MRSA infection with screening of ICU patients for MRSA-carriage. In addition, compared to no screening, one²⁵ of the non-CCS studies found a statistically significant reduction in hospital-acquired MRSA infection in the SICU, as well as in the pooled analysis of the SICU, MICU, and wards with screening for MRSA in the ICU, but no statistically significant reduction in hospital-acquired MRSA infection in the MICU or the wards.²⁵

The strength of evidence for the effect of screening of ICU patients on health care-associated MRSA infection was judged to be insufficient, based on the lack of statistically significant findings of a single, well conducted, quasi-experimental CCS study.¹⁵

Health Care-Associated MRSA Bacteremia or Bloodstream Infection

One good quality study,¹⁵ one poor quality study,²⁰ and one non-CCS study²⁶ addressed this outcome. The good quality study¹⁵ found no statistically significant reduction in the rate of acquired MRSA bloodstream infection with screening for MRSA in the ICU compared to no screening for MRSA. The poor quality study²⁰ found a statistically significant reduction in the trend of the hospital-associated incidence density of MRSA bloodstream infection in the ICU, non-ICU settings, and hospital wide with screening for MRSA in the ICU. In addition, this study²⁰ found a statistically significant reduction in the trend of the hospital-associated incidence of MRSA bloodstream infection hospital wide with screening for MRSA in the ICU. The non-CCS study²⁶ found a statistically significant reduction in the rate of acquired MRSA bacteremia with screening for MRSA in the ICU compared to no screening for MRSA.

The strength of evidence for the effect of screening of ICU patients for MRSA-carriage on health care-associated MRSA bacteremia or bloodstream infection was judged to be insufficient, based on the moderate risk of bias, lack of consistency and lack of precision. The risk of bias was deemed to be moderate because of the poor quality study²⁰ that did not report baseline group characteristics or whether its analysis controlled for confounders. The confidence intervals for the good quality study suggest lack of certainty about the direction of effect. Thus, the findings were judged to be inconsistent and imprecise.

Health Care-Associated MRSA Surgical Site Infection

One good quality study¹⁵ addressed this outcome. The Robicsek study found a reduction in hospital-associated surgical site infections with screening in the ICU compared to no screening; however, this reduction was not statistically significant.¹⁵

The strength of evidence for the effect of screening of ICU patients on health care-associated MRSA infection was judged to be insufficient, based on the lack of statistically significant findings from a single, well conducted, quasi-experimental study.¹⁵

Morbidity, Mortality, Harms and Resource Utilization

Because no studies addressed these outcomes, the strength of evidence to evaluate the effect of screening of ICU patients for MRSA-carriage on morbidity, mortality, harms or resource utilization was judged to be insufficient.

Key Question 3B: MRSA Targeted Screening (Surgical Patients) versus No Screening

Two^{30,31} CCS studies and 11 non-CCS studies described screening of surgical patients for MRSA compared to no screening. The Harbarth study³⁰ was a prospective, interventional cohort study with crossover design of good quality. The Muder study³¹ was a quasi-experimental before/after study design of poor quality. All of the 11 non-CCS studies employed a quasi-experimental before/after study design.

Health Care-Associated MRSA Acquisition

Only the study by Harbarth et al.,³⁰ evaluated this outcome. With targeted screening of surgical patients, Harbarth et al.,³⁰ found an increase in the rate ratio for MRSA acquisition to 1.1, but the confidence intervals included the null.

The strength of evidence for the effect of screening of surgical patients on health care-associated MRSA acquisition is insufficient based on the negative findings of a single, well conducted, quasi-experimental study.³⁰

Health Care-Associated MRSA Infection, Irrespective of Site

Two^{30,31} CCS studies and one⁵⁸ non-CCS study reported the effect of screening for MRSA-carriage in surgical wards on health care-associated infection.

With screening of surgical patients, Harbarth and colleagues³⁰ found the rates of MRSA infection were slightly higher with the intervention.

However, Muder and colleagues³¹ found that MRSA infection steadily declined in the intensive care unit and the surgical unit.

Sankar et al.,⁵⁸ reported that the proportion of patients with MRSA infection declined from 2.4 percent to 0.0 percent in an unadjusted analysis.

The strength of evidence for the effect of screening for MRSA-carriage in surgical patients on health care-associated MRSA infection was judged to be insufficient based on the moderate risk of bias, lack of consistency and lack of precision of the findings.

MRSA Surgical Site Infection

Two CCS studies and 10 non-CCS studies reported on MRSA surgical site infection. With screening in surgical patients, Harbarth³⁰ found an increase in MRSA surgical site infection³⁰ Muder³¹ found no difference in MRSA surgical site infection with screening of surgical patients. Compared to no screening, all of the non-CCS studies found a reduction in the rate of MRSA SSI with screening for MRSA-carriage in surgical patients. For six of these studies, the reduction was statistically significant.^{32, 33,35,39-41} For one study,³⁶ the reduction was statistically significant for one outcome, but not for another; and for three studies,^{34, 37,38} the reduction was not statistically significant.

The strength of evidence for the effect of screening for MRSA-carriage in surgical patients on MRSA surgical site infection was judged to be insufficient based on the moderate risk of bias and lack of precision of study findings. The risk of bias was deemed to be moderate because of the poor quality study¹⁶. The study findings were judged to be imprecise because of the lack of statistical significance for the poor quality study.

Morbidity

One non-CCS quasi-experimental study evaluated MRSA morbidity. Malde and colleagues³⁵ found a statistically significant decline in amputation rates for patients with elective admissions. For patients with emergency admissions, the rate of amputation declined, but this was not statistically significant.

Because no CCS studies addressed this outcome, the strength of evidence to evaluate the effect of screening for MRSA-carriage in surgical patients on morbidity was judged to be insufficient.

Mortality

One non-CCS quasi-experimental study reported on mortality rates among patients with MRSA colonization or infection. In the study by Malde and colleagues³⁵ for both elective and emergency admissions, mortality rates for patients with MRSA declined with screening.³⁵ However, these reductions were not statistically significant.

Because no CCS studies addressed this outcome, the strength of evidence to evaluate the effect of screening for MRSA-carriage in surgical patients on mortality was judged to be insufficient.

Harms

Because no studies addressed this outcome, the strength of evidence to evaluate the effect of screening of surgical patients for MRSA-carriage on harms was judged to be insufficient.

Resource Utilization

One non-CCS quasi-experimental study reported the impact of screening surgical patients for MRSA carriage on resource utilization. Sankar and colleagues⁵⁸ found that with screening, the mean length of hospital stay declined by almost one day. In unadjusted analysis, this result was found to be statistically significant.⁵⁸

Because no CCS studies addressed this outcome, the strength of evidence to evaluate the effect of screening for MRSA-carriage in surgical patients on resource utilization was judged to be insufficient.

Key Question 3C: MRSA Targeted Screening (High-Risk Patients) versus No Screening

Four CCS studies⁴²⁻⁴⁵ and five^{46-49, 59} non-CCS studies described screening of high-risk patients for MRSA-carriage compared to no screening. Of the CCS studies, one of the studies was of fair quality⁴⁵ and three⁴²⁻⁴⁴ were of poor quality.

All nine studies employed a quasi-experimental study design.

Health Care-Associated MRSA Acquisition

Two CCS studies^{43, 45} and one⁴⁸ non-CCS study evaluated health care-associated MRSA infection or colonization.

For the Rodriguez-Bano study,⁴⁵ the reported change in incidence of MRSA acquisition from a segmented regression analysis was -0.065 with confidence intervals that included zero.. However with screening, there was a statistically significant reduction in the trend of MRSA acquisition.⁴⁵ For the Ellingson study,⁴³ the percent change in the MRSA acquisition rate was -35.0 percent with wide confidence intervals that did not include zero. The Salaripour study⁴⁸ also found a statistically significant reduction in health care-associated MRSA infection with targeted screening.

The strength of evidence for the effect of targeted screening in high-risk patients on MRSA acquisition was judged to be insufficient based on the high risk of bias, lack of consistency and lack of precision.

Health Care-Associated MRSA Infection, Irrespective of Site

One⁴⁴ CCS study and two^{46, 49} non-CCS studies evaluated the impact of screening for MRSA-carriage in high-risk patients on health care-associated MRSA infection. All three studies showed a statistically significant reduction in health care-associated MRSA infection with screening of high-risk patients.^{44, 46, 49}

The strength of evidence for the effect of screening in high-risk patients on health care-associated MRSA infection, irrespective of site was judged to be insufficient based on the high risk of bias, unknown consistency and lack of precision given the single quasi-experimental before/after CCS study of poor quality that addressed this outcome.

Health Care-Associated MRSA Bacteremia or Bloodstream Infection

Three CCS studies^{42, 43, 45} and two non-CCS studies^{47, 49} addressed the impact of screening on rates of health care-associated MRSA bacteremia or bloodstream infection. The Rodriguez-Bano study⁴⁵ was of fair quality study and the Chowers study⁴² and Ellingson study⁴³ were of poor quality.

With segmented regression analysis, the Rodriguez-Bano study⁴⁵ reported a statistically significant reduction in the incidence and trend of MRSA bacteremia. The Ellingson study⁴³ reported a statistically significant reduction in incidence of MRSA bloodstream infection, but did not report confidence intervals. The Chowers study⁴² showed reductions in health care-associated MRSA bloodstream infection with all three components of the intervention. The reduction was statistically significant for one component, though not for the other two. The Wernitz⁴⁹ and Pan⁴⁷ studies showed statistically significant reductions in health care-associated MRSA bloodstream infection with screening of high-risk patients compared to no screening.

The strength of evidence for the effect of screening for MRSA-carriage in high-risk patients on health care-associated MRSA bacteremia or bloodstream infection was judged to be insufficient based on the high risk of bias and lack of precision of the three CCS studies that addressed this outcome. The risk of bias was determined to be high, given both study quality and design. The study findings are consistent, but imprecise given the variation in effect size.

MRSA Surgical Site Infection

Two studies addressed this outcome: one CCS study⁴⁴ and one⁵⁹ non-CCS study. Both the Harbarth⁴⁴ and Keshtgar⁵⁹ studies showed a statistically significant reduction in health care-associated MRSA surgical site infection with screening of high-risk patients compared to no screening.

The strength of evidence for the effect of screening for MRSA-carriage in high-risk patients on MRSA surgical site infection was judged to be insufficient based on the high risk of bias, unknown consistency and lack of precision of the single CCS study of poor quality that addressed this outcome.

Morbidity, Mortality, Harms and Resource Utilization

Because no studies addressed these outcomes, the strength of evidence to evaluate the effect of screening of high-risk patients for MRSA-carriage on morbidity, mortality, harms or resource utilization was judged to be insufficient.

Key Question 4: Expanded Targeted MRSA Screening versus Limited Targeted Screening

Eight quasi-experimental studies^{45, 50-56} described limited screening for MRSA-carriage compared to expanded screening. The studies by Chaberny⁵⁰ and Rodriguez-Bano⁴⁵ were CCS studies; the remaining six⁵¹⁻⁵⁶ were not.

The study by Rodriguez-Bano was judged to be of fair quality⁴⁵ and the study by Chaberny⁵⁰ was determined to be of poor quality.

Health Care-Associated MRSA Acquisition

Six studies evaluated health care-associated MRSA infection or colonization as an outcome. The study by Rodriguez-Bano⁴⁵ was a CCS study, while the studies by Eveillard,⁵¹ Trautmann,⁵⁵ Thompson,⁵⁴ Girou,⁵² and Schelenz⁵³ were not.

The Rodriguez-Bano study⁴⁵ showed reductions in the incidence and trend of health care-associated MRSA infection or colonization with expanded screening compared to limited screening. Though the reduction in trend was statistically significant, the reduction in incidence was not.⁴⁵ All five of the non-CCS studies showed a reduction in hospital-acquired MRSA infection with expanded targeted screening compared to limited targeted screening. The studies by Eveillard,⁵¹ Thompson,⁵⁴ Trautmann,⁵⁵ and Schelenz⁵³ showed a statistically significant reduction and the study by Girou⁵² did not.

Based on the high risk of bias due to the single CCS quasi-experimental study of fair quality, the unknown consistency and the lack of precision, the strength of evidence to evaluate the effect of expanded targeted screening compared to limited targeted screening on health care-associated MRSA acquisition was judged to be insufficient.⁴⁵

Health Care-Associated MRSA Infection, Irrespective of Site

One poor quality CCS study⁵⁰ and one non-CCS study⁵⁶ addressed this outcome. Chaberny⁵⁰ showed a statistically significant reduction in hospital-acquired MRSA infection with expanded screening compared to limited screening. West⁵⁶ showed a reduction in hospital-acquired MRSA

infection with expanded screening compared to limited screening; however, this reduction was not statistically significant.

Health Care-Associated MRSA Bacteremia or Bloodstream Infection

Three studies addressed this outcome. The study by Rodriguez-Bano⁴⁵ was a CCS study, while the studies by Thompson and by Trautmann were not.^{54,55}

The Rodriguez-Bano study⁴⁵ reported a reduction in hospital-acquired MRSA bacteremia with expanded targeted screening compared to limited targeted screening, but the confidence intervals included the null. The Thompson study⁵⁴ showed a statistically significant reduction in hospital-acquired MRSA intravenous catheter-associated septicemia with expanded targeted screening compared to limited targeted screening. The Trautmann study⁵⁵ showed no statistically significant reduction in hospital-acquired MRSA bacteremia with expanded targeted screening compared to limited targeted screening.

Based on the high risk of bias, lack of consistency and lack of precision, the strength of evidence to evaluate the effect of expanded targeted screening compared to limited targeted screening on health care-associated MRSA infection was judged to be insufficient.⁴⁵ One CCS study⁵⁰ addressed MRSA infection and one CCS study evaluated health care-associated bacteremia, a proxy for health care-associated infection.⁴⁵ The risk of bias was felt to be high due to the quality of the studies and the before/after designs. The findings are inconsistent and imprecise due to confidence intervals that included the null for one of the two studies.

Morbidity, Mortality, Harms and Resource Utilization

Because no studies addressed these outcomes, the strength of evidence to evaluate the effect of expanded screening for MRSA-carriage compared to limited screening on morbidity, mortality, harms or resource utilization was judged to be insufficient.

Discussion

Findings in Relationship to What is Already Known

At least two previous systematic reviews have evaluated the impact of screening for MRSA-carriage. McGinagle et al.⁶⁰ concluded that there were significant gaps in the evidence that precluded definitive recommendations about the effectiveness of screening for MRSA-carriage. After meta-analysis, Tacconelli et al.⁶¹ found a statistically significant reduction in the risk of MRSA bloodstream infection, but not surgical site infection.

The conclusions of the present report are not substantially different than those reached in the previous systematic reviews, although there are some differences in the interpretation of the findings. In all three reports, the paucity of rigorous, well-controlled studies employing uniform or even standardized microbiological and infection control techniques serves as a critical limitation. The present review includes a much larger set of published studies for assessment. In addition, this comparative effectiveness review utilized a more rigorous standard for grade of evidence than did the prior reviews.

Guidelines and Public Policy

The 2006 Guidelines for the Management of Multidrug-Resistant Organisms in Healthcare Settings published by the CDC Healthcare Infection Control Practices Advisory Committee

(HICPAC)⁶² include active surveillance screening as a recommended control strategy for multi-drug resistant organisms (MDRO), including MRSA. This document recommends that such interventions should be implemented when the frequency of MDRO infections have not decreased despite the use of more routine control measures.

The 2003 Society for Healthcare Epidemiology of America (SHEA) Guidelines for Preventing Nosocomial Transmission of Multidrug-Resistant Strains of *Staphylococcus aureus* and *Enterococcus*⁶³ take a more affirmative stand regarding the deployment of MRSA screening. The authors recommend that active surveillance cultures and contact precautions be implemented to prevent the spread of epidemiologically significant antibiotic-resistant pathogens. The guidelines further advise that these measures “should be implemented in all types of health care facilities throughout the system.”

A subsequent SHEA position paper,⁶⁴ stepped back from advocating for mandatory screening, citing concerns about the importance of institutional risk assessment and possible unintended consequences of mandatory and widespread screening.

The strength of the available evidence and the findings of this review find the evidence is insufficient to support or refute the recommendations adopted by the CDC HICPAC or the SHEA Guidelines.

Applicability

An important limitation of the available evidence regarding MRSA screening relates to heterogeneity in the nature of the interventions performed. By its nature, MRSA screening itself would not be expected to impact the frequency of subsequent transmission or infection. Rather, clinical outcomes are influenced by the application of additional infection control interventions in response to the detection of colonization, including more rigorous hand hygiene, barrier precautions, environmental cleaning, and antimicrobial decolonization. That these interventions are often deployed as part of a “bundle” further limit the conclusions that can be drawn about the attributable benefit of screening compared to any other component of the intervention.

A number of the included studies provided insufficient information about the full scope of interventions deployed in conjunction with screening for MRSA-carriage, especially those measures implemented in response to the new detection of MRSA colonization. For example, while decolonization for MRSA-positive patients may not have been recommended as part of the MRSA screening intervention, most studies did not address whether or not decolonization was specifically prohibited. As a result, the measured effect of the screening strategy may have been influenced by the application of uncontrolled and unmeasured interventions targeting MRSA colonization. In addition, the included studies rarely assessed adherence to the interventions, leaving uncertainty about whether the failure of screening to impact clinical outcomes can be attributed to poor practitioner compliance with the intervention.

In addition, included studies often failed to examine the impact of other concurrent infection-prevention efforts with the potential to affect the measured impact of screening for MRSA-carriage. Campaigns to reduce the frequency of vascular device infections, initiatives to improve hand hygiene, and interventions to promote an institutional culture of safety have been shown to influence the frequency of many health care-associated infections, including those caused by MRSA. Therefore, their omission may be important.

The vast majority of included studies employed a quasi-experimental study design, largely an observational before/after design. The use of historical controls is subject to confounding due to epidemiological trends that contribute to variation in the incidence of infectious diseases over

time. Even large studies, conducted across multiple geographic sites and clinical settings, can be influenced by these secular trends.¹⁶ While such changes over time may reflect statistical variation alone, changes in disease incidence also may be due to outbreaks of infection, deviations and departures from best practice, the widespread dissemination of new prevention practices, changes in antibiotic prescribing, seasonal influences, or even the application of other interventions that influence transmission or infection. Unless these epidemiologic trends are identified and accounted for, they may influence the perception of the effectiveness of screening for MRSA-carriage.

Implications for Clinical and Policy Decision-making

Insufficient evidence is currently available to determine the effectiveness of screening for MRSA-carriage on MRSA transmission, MRSA infection, morbidity or mortality. Thus, there is insufficient evidence to support the routine implementation of screening for MRSA-carriage as part of organizational infection control in all settings. Decision-making is further hindered by 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. This, in turn, may decrease the number of patients who can be served locally, regionally and nationally. However, even in the absence of these data, other factors may compel hospital leaders to recommend screening for MRSA-carriage. For example, where MRSA infection affects a large number of patients, the resultant infections are severe, and other infection control strategies have been unable to check the spread of infection, the deployment of a screening program may be sensible, even in light of the limited available evidence. In essence, this advice mirrors that offered in the CDC HICPAC guidelines.²⁴

Limitations of the Clinical Effectiveness Review Process

Determining the scope of the review posed an important challenge. The decision was made to be inclusive in considering the available literature, in which observational studies were overrepresented. In the same vein, contributors to this review were challenged to negotiate a rational and justifiable framework for presenting the many included observational studies. To this end, the decision was made to recognize the importance of the use of statistical methods to attempt to control for confounding or secular trends. The results section particularly highlights those studies that employed regression analysis or time series analysis.

Limitations of the Evidence Base, Research Gaps and Future Research Opportunities

The available evidence is limited by inconsistency in the definition, application and measurement of the interventions commonly bundled together with MRSA screening. Future research must take a more uniform approach to the testing strategy utilized (e.g., PCR vs. culture), test turnaround time, management of patients before screening test results are known, transmission prevention strategy (e.g., contact precautions), and the use of decolonization therapy. In addition, future research should quantify and account for the potential bias introduced by epidemiologic trends, as well as the influence of concomitant infection prevention strategies and interventions.

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 is absolutely critical.

Ideally, future studies will compare the effectiveness of screening strategies that employ different interventions, alone and in combination. In essence, this work will entail examining each element of an intervention bundle in order to accurately determine the benefit or harm that can be attributed to it. For example, it is possible that a single component of an intervention (such as the decolonization of patients found through screening to be MRSA-positive) may independently produce a significant clinical benefit.

The cluster randomized controlled trial is increasingly recognized as the optimal design for testing and evaluating the impact of infection prevention strategies. In this approach, rather than randomizing individual patients, wards or units are randomized to the intervention or control groups. This approach reduces the bias introduced into even large multicenter observational epidemiologic studies. The cluster randomized controlled trial, used sparingly in the MRSA screening literature to date,²¹ offers the highest standard in study design and execution and should be adopted as an expected standard on the part of grant committees, journal editors and reviewers.

Precise estimates of the impact of screening for MRSA-carriage on morbidity and mortality are lacking. To allow meaningful assessment of these crucial health outcomes, future studies will need to enroll sufficient numbers of patients to be adequately powered to detect any effect. Thus, large multicenter trials will be needed.

Perhaps most importantly, to determine the comparative effectiveness of screening for MRSA-carriage, the harms of screening must be clearly delineated. 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.

Conclusions

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

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Introduction

Background and Objectives for the Systematic Review

Methicillin-resistant *Staphylococcus aureus* (MRSA) first emerged as a clinically relevant human pathogen more than 3 decades ago.¹ The aggressive 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 (which further compromise host defenses) created a favorable environment for dissemination. MRSA emerged as an important cause of health care–associated infections, particularly central line-associated bloodstream infection, ventilator-associated pneumonia, and surgical site infection. Despite the adoption of a number of measures to prevent spread, the incidence of MRSA infection at most U.S. hospitals has steadily increased over the past 20 years.² Complicating matters, the management of infection caused by MRSA remains a challenge for clinicians. A number of analyses suggest that MRSA infections are associated with increased mortality and cost of care when compared with those due to strains that are susceptible to methicillin. A meta-analysis by Cosgrove and colleagues³ identified a 2-fold increased risk of death associated with methicillin resistance. Engemann and colleagues⁴ documented a significantly higher risk of poor outcomes and increased expense in managing patients with surgical site infection due to MRSA when compared with patients infected with antibiotic-susceptible strains. Even the availability of newer pharmaceutical agents with specific activity against MRSA, including linezolid and daptomycin, has not lessened the burden of MRSA for patients and clinicians. The widespread use of these agents has been limited in part because of toxicity, expense, and uncertainty as to optimal indications.⁵

The management and control of MRSA has been further complicated by dramatic changes in the epidemiology of transmission and infection observed over the past 2 decades. Specifically, *S. aureus* strains resistant to methicillin, once exclusively linked to hospital care, have increasingly been detected among patients in the community who lack conventional risk factors for MRSA infection (such as prior antimicrobial therapy or invasive procedures).^{6, 7} These so-called community-associated MRSA (CA-MRSA) strains have demonstrated a predilection to affect specific populations. Clusters among schoolchildren and competitive athletes have been extensively described in both the scientific literature and the mass media.^{5, 8} CA-MRSA infection often manifests in characteristic clinical patterns—including aggressive skin and soft tissue infections (typically arising from an initial lesion often mistaken by patients and clinicians for a spider bite) and necrotizing pneumonia.⁹ Extensive investigation has demonstrated a number of unique genetic and pathogenic features of CA-MRSA isolates that may provide insight into the epidemiology of these bacteria. CA-MRSA strains typically share a distinctive methicillin-resistance cassette that helps to explain the characteristic susceptibility of these strains to non-beta-lactam antimicrobial agents such as clindamycin and trimethoprim/sulfamethoxazole.¹⁰ In addition, CA-MRSA isolates commonly overexpress a particular set of virulence factors, including the Panton-Valentine leukocidin.¹¹ While the specific relationship between these features and the unique clinical and epidemiological characteristics of CA-MRSA remain to be elucidated, the importance of these strains continues to grow. CA-MRSA has increasingly been linked to outbreaks of infection in hospitals and health care facilities, and there is some evidence that these strains are now the dominant cause of staphylococcal disease in some settings.¹²

Conventional strategies for the control of MRSA (whether hospital- or community-associated) have focused on the prevention of spread from patient to patient (horizontal transmission). It is generally acknowledged that environmental contamination and airborne transmission could plausibly play a minor role in transmission.^{13, 14} However, the overwhelming majority of staphylococcal spread (and of MRSA) likely comes about through a chain of transmission linking a colonized or infected patient and a previously unaffected patient by way of the hands or personal items of health care workers. With this in mind, the most common tools used to prevent the spread of MRSA involve the disruption of these points of contact.

The effectiveness of hand hygiene in preventing the spread of MRSA has been most convincingly demonstrated in quasi experimental observational studies in which hand hygiene-promotion campaigns were associated with subsequent reductions in the incidence of MRSA among hospitalized patients. Pittet and colleagues¹⁵ demonstrated a significant reduction in MRSA bloodstream infections in one especially robust investigation. The benefit of hand hygiene appears to be consistent, whether the use of soap and water or alcohol-based hand rubs is promoted.¹⁶ The ease of adherence associated with the latter method suggests that this approach may be especially fruitful.

While hand hygiene remains the cornerstone of MRSA transmission-control efforts, the continued spread of the pathogen after initial introduction in most facilities has prompted efforts to identify more robust and effective strategies. The use of personal protective equipment—including the donning of gowns and gloves when interacting with patients colonized or infected with MRSA and the assignment of such patients to single rooms or to a room with a group of affected patients—has been widely promoted and adopted. Such isolation precautions now stand as the centerpiece in most authoritative guidelines regarding MRSA control.¹⁷ Despite the broad consensus associated with the use of personal protective equipment for MRSA prevention, the specific evidence in support of this practice remains somewhat limited and indirect. Jernigan and colleagues¹⁸ noted a significant decrease in the risk of MRSA transmission when isolation precautions were implemented in a pediatric unit. However, the fact that the study was conducted in the midst of a MRSA outbreak in the unit raises questions about the suitability of generalizing these findings to other circumstances, including settings in which MRSA is endemic. Moreover, a number of studies have examined the role of specific elements of isolation precautions (specifically, the use of gowns vs. gloves) with mixed results.¹⁹

Given the continued dissemination of MRSA at most U.S. hospitals, it is clear that these measures, as presently deployed, have been insufficient to check the spread of MRSA and other antibiotic-resistant pathogens. Much of the blame for this underperformance can likely be attributed to the poor adoption of these measures at most health care facilities. When rigorously assessed, adherence to hand hygiene standards is especially disappointing; many hospitals report a compliance rate of less than 50 percent among health care workers. The situation with personal protective equipment use and adherence to isolation precautions is difficult to know, as compliance has been less commonly studied and reported. However, a recent report²⁰ found that despite the use of an electronic flag denoting the need for isolation precautions in the records of inpatients at an urban academic medical center, only 58 percent of such patients were placed in a private room and had appropriate signage posted on the door to the room. Other analyses of actual compliance with the donning of gowns and gloves have been similarly disappointing.

A further important limitation of these approaches—and specifically the use of isolation precautions—relates to the potential negative consequences of these measures. A series of studies have associated isolation precautions with worsened outcomes in terms of safety and

patient satisfaction.²¹ In addition, questions have been raised about 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. While the methodology employed in some of these studies has been questioned, no rigorous definitive analysis has been completed to exonerate isolation precautions.²²

Based on the failure of conventional control strategies 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 colorfully referred to as “search and destroy,” identifies contacts of colonized and infected patients in an effort to intercede to prevent dissemination.²³ While such draconian 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 U.S. Particular attention has been given to the potential value of active surveillance screening for MRSA. Because routine clinical cultures may identify as few as 18 percent of patients overtly infected with antibiotic-resistant organisms such as MRSA, there exists a large reservoir of patients who are silent carriers of these organisms. These individuals may serve as a reservoir for further transmission. With active surveillance, microbiological samples are obtained from at-risk patients even in the absence of signs or symptoms of infection in an effort to identify the underlying population of colonized individuals. In most cases, this involves the collection of a nasal swab, as the nares have been identified as a common sanctuary site for MRSA in colonized individuals. At some centers, additional sites may be sampled, depending on the population under examination (e.g., the umbilicus of newborns; the sites of invasive devices or wounds). By detecting the larger population of colonized individuals, at the very least conventional precautions can be implemented in a broader and a more timely manner so as to interrupt horizontal transmission of MRSA. Detection of colonized patients also permits consideration of more aggressive interventions, including attempts at microbiological eradication or decolonization, as is discussed later.

The specific evidence in support of active surveillance for MRSA has been promising, although a number of questions remain regarding the suitability of this approach in some settings and populations. Some of the most compelling evidence for the effectiveness of active surveillance in controlling the spread of antibiotic-resistant organisms came from experience with vancomycin-resistant *Enterococcus* (VRE). Rectal screening for this pathogen was associated with decreased transmission at the level of individual units and wards,²⁴ whole hospitals,²⁵ and even across an entire region.²⁶ For MRSA, a number of fairly rigorous studies have tested the hypothesis that identification of asymptomatic carriers can result in decreased MRSA transmission. Huang and colleagues²⁷ reported their experience of adding active surveillance screening of patients in the intensive care unit to an already comprehensive control strategy (including hand hygiene promotion) and a bundle of interventions to prevent central line-associated bloodstream infection. Only the addition of active surveillance resulted in a statistically significant decline in the incidence of MRSA bloodstream infections.²⁷ In perhaps the most widely cited report of active surveillance for MRSA, Robicsek and colleagues²⁸ describe the impact of a staged implementation of screening, first among patients in an intensive care unit and ultimately involving all patients admitted to a three-hospital health care system in the Chicago suburbs. With this approach, the prevalence and density of MRSA disease fell significantly among all patients. However, this is not to say that the experience with active surveillance has been universally effective. Harbarth and colleagues²⁹ found that active

surveillance screening of surgical patients was not associated with a reduction in surgical site infections in a crossover-design study at a large Swiss center. Thus, questions remain not only about the effectiveness of active surveillance for MRSA-carriage, but also about whether screening should be applied to all patient populations (universal screening) or to selected populations (targeted screening).

A number of methodological issues have been raised about many of the studies of active MRSA surveillance, including both those that seem to support the practice and those that do not. These questions also reflect the methodological uncertainty about deploying the strategy in actual clinical practice. One key issue relates to the microbiological testing method applied. Early on, most surveillance programs relied on conventional culture methods. This approach, while reliable and familiar in the hands of most clinical laboratories, is plagued by the necessity of delayed availability of final results, in as much as culturing, subculturing, and formal susceptibility testing can require up to 5 to 6 days in some laboratories. Advances in culture methodology, including the use of chromogenic growth media, can shorten this waiting period, but still do not typically provide clinicians with information regarding the need for isolation precautions until a day or more after the samples are collected. Most recently, the advent of reliable and commercially available polymerase chain reaction techniques offer the promise of exceptionally rapid turnaround time for MRSA detection (often less than several hours). Farr has argued that without standardization and optimization to ensure rapid results from screening, comparisons regarding the relative effectiveness of active surveillance for MRSA are limited.³⁰ Some of the concerns about delayed screening results can be obviated by adopting a policy of early implementation of isolation precautions for all screened patients with the aim to discontinue these measures for those patients who test negative (irrespective of the assay employed). This so-called “guilty until proven innocent” approach, while sound from an epidemiological perspective, has presented logistical challenges at centers where the physical plant limits the availability of rooms and beds for such empirical isolation.

Determining the optimal approach once patients are identified as colonized with MRSA presents an even larger challenge to assessing the effectiveness of active MRSA surveillance. The impact of screening is likely to be exceptionally sensitive to the measures deployed once MRSA carriers are identified. As has been noted, adherence to basic prevention measures, such as hand hygiene and the use of personal protective equipment, is inconsistent in most settings in which compliance has been measured. Nonetheless, these very practices are central to the effectiveness of any active surveillance program. Simply stated, knowing which patients are colonized with MRSA should not be expected to affect the frequency of spread if adherence to transmission-control strategies remains inadequate. Surprisingly, even the most robust investigations of the effectiveness of active surveillance have not routinely described the frequency of compliance with hand hygiene and use of personal protective equipment. Similarly, other more intensive measures may dramatically affect the impact of a MRSA-screening program. For example, efforts to decolonize or eradicate MRSA from carrier patients through the use of systemic or topical antimicrobial agents should have an important effect on the likelihood of transmission. This practice has been applied in a number of settings for both MRSA and staphylococcal disease in general.³¹ The results have been mixed, depending on the population under study, and the risk for emerging antibiotic resistance as the result of such efforts remains a concern. With this in mind, to try to determine the impact of a screening program without detailed information about the deployment of decolonization measures is an important limitation

to the available studies and has engendered considerable confusion among clinicians and policymakers.

In light of the promising, but limited evidence in support of active MRSA surveillance and in consideration of the important methodological questions previously noted, a systematic review of the evidence appears to be both justified and timely. The importance of gaining a better understanding of the evidence is further highlighted by the increasing demand for better control of MRSA and a higher standard for prevention of hospital-acquired infections in general. Policymakers both within and outside of the U.S. health care system have heeded the degree of public concern surrounding these issues. The control of MRSA and other antibiotic-resistant bacteria has been highlighted as a likely target for pay-for-performance initiatives on the part of the U.S. Government and a number of private payers. The Joint Commission has highlighted the issue by identifying a National Patient Safety Goal regarding the control and prevention of antibiotic resistance. Perhaps most telling, some state jurisdictions in the U.S. have already mandated screening for MRSA. In some cases, these legislative mandates have been issued even in the face of direct opposition from clinical experts in the field.³² It seems evident that the public and scientific debate regarding the merits and potential negative consequence of widespread MRSA screening will benefit from a systematic review of the available evidence.

Objective

The objective of this systematic review was to synthesize comparative studies that examined the benefits or harms of screening for Methicillin-resistant *Staphylococcus aureus* (MRSA) carriage in the inpatient or outpatient settings. 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 ICU, patients admitted for a surgical procedure, or patients at high-risk of MRSA colonization or infection) 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 patient population included all ambulatory patients (outpatients) and hospitalized patients (inpatients).

Key Questions

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 to no screening on:

- Intermediate outcomes such as MRSA transmission (as measured by new acquisition events)?
- Health outcomes such as the incidence of 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?

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 to screening of selected patient populations (targeted screening) on:

- Intermediate outcomes such as MRSA transmission (as measured by new acquisition events)?
- Health outcomes such as the incidence of 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?

Key Question 3A

Among ambulatory or hospitalized patients, what are the effects of screening ICU patients for MRSA-carriage (screen, isolate, eradicate/decolonize) – when compared to no screening on:

- Intermediate outcomes such as MRSA transmission (as measured by new acquisition events)?
- Health outcomes such as the incidence of 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?

Key Question 3B

Among ambulatory or hospitalized patients, what are the effects of screening surgical patients for MRSA-carriage (screen, isolate, eradicate/decolonize) – when compared to no screening on:

- Intermediate outcomes such as MRSA transmission (as measured by new acquisition events)?
- Health outcomes such as the incidence of 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?

Key Question 3C

Among ambulatory or hospitalized patients, what are the effects of screening high-risk patients for MRSA-carriage (screen, isolate, eradicate/decolonize) – when compared to no screening on:

- Intermediate outcomes such as MRSA transmission (as measured by new acquisition events)?
- Health outcomes such as the incidence of 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?

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 to a limited screening strategy on:

- Intermediate outcomes such as MRSA transmission (as measured by new acquisition events)?
- Health outcomes such as the incidence of 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?

PICOTS (Patient, Intervention, Comparator, Outcome, Timing, and Setting) for the Key Questions

Patients	All ambulatory patients (outpatients) and all hospitalized patients (inpatients). In addition, the following subpopulations were evaluated: 1) patients admitted to an intensive care unit; 2) patients undergoing surgical procedures; and 3) patients at high-risk of MRSA colonization or infection.
Intervention	A MRSA screening strategy applied to all patients in a setting (universal screening) or applied to particular wards, units or patients (targeted screening) that includes: <ol style="list-style-type: none">1) MRSA screening using a testing modality (typically PCR) with rapid turnaround (results available on the same day as the testing is performed) or2) MRSA screening using a testing modality with intermediate turnaround (results available next day to 2 days after testing performed) or3) MRSA screening using a testing modality (typically culture) with a longer turnaround time (results available greater than 2 days after testing performed) And that may include: <ol style="list-style-type: none">1) Isolation and/or2) Eradication/decolonization.
Comparator	No screening or screening of selected patient populations (targeted screening).
Outcomes	MRSA acquisition, MRSA infection, morbidity (including complications of MRSA infection), mortality, quality of care for non-infectious conditions, medical errors, adverse effects of screening and treatment including allergic reactions, non-allergic toxicities, and resistance to antimicrobials and hospital resource utilization such as length of stay.
Timing	Intervention through follow-up.

Settings Inpatient (hospital wards and intensive care units) and outpatient (ambulatory clinics, urgent care centers and emergency departments).

A comprehensive review evaluating the benefits and harms of screening for MRSA-carriage will identify areas of certainty and those that require additional prospective research.

Methods

Methodological practices followed in this review were derived from the Agency for Healthcare Research and Quality (AHRQ) Methods Guide for Effectiveness and Comparative Effectiveness Reviews³³ (hereafter referred to as the “Methods Guide”) and its subsequent updates.

Topic Development and Refinement

Key questions were reviewed and refined as needed by the Evidence-based Practice Center (EPC) with input from Key Informants and the Technical Expert Panel (TEP) to assure that the questions were specific and explicit about what information was being reviewed. In addition, for Comparative Effectiveness reviews, the key questions were posted for public comment and finalized by the EPC after review of the comments.

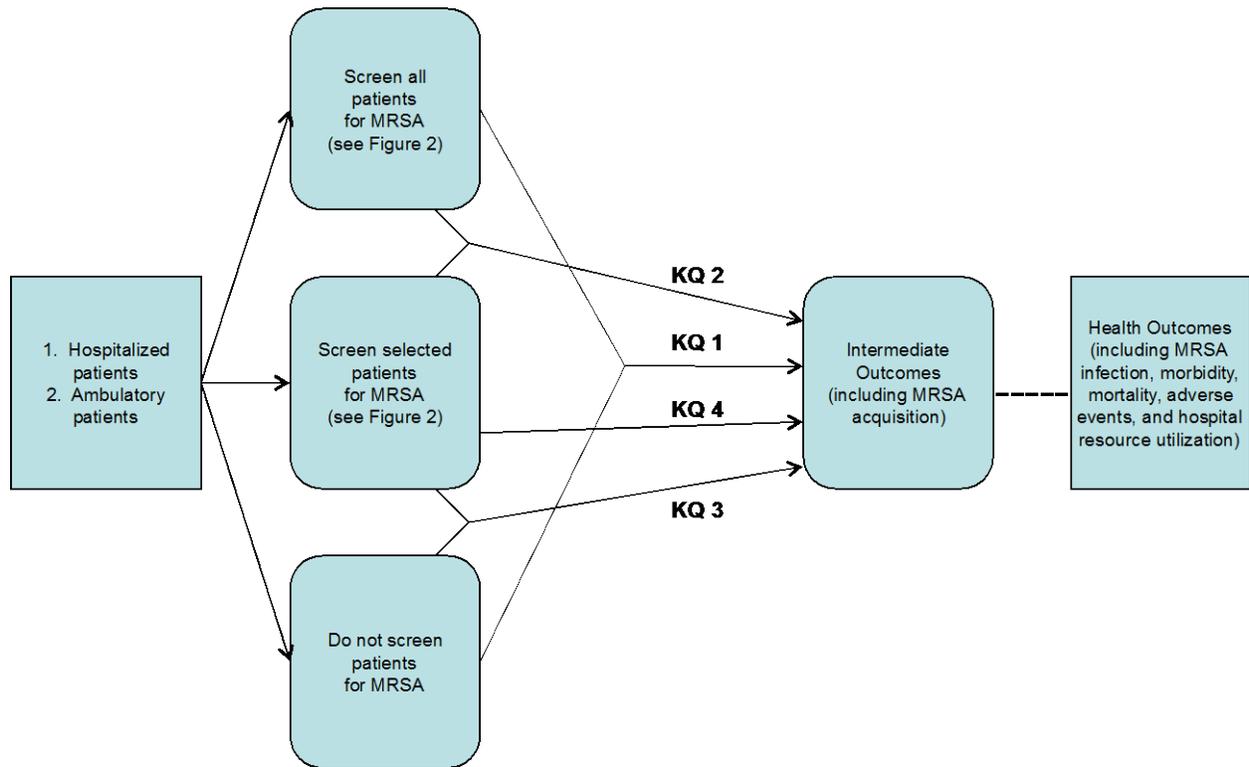
Key Informants are the end users of research, including patients and caregivers, practicing clinicians, relevant professional and consumer organizations, purchasers of health care, and others with experience in making health care decisions. Within the EPC program, the Key Informant role is to provide input into identifying the Key Questions for research that will inform health care decisions. The EPC solicited input from Key Informants when developing questions for systematic review or when identifying high priority research gaps and needed new research. Key Informants were not involved in analyzing the evidence or writing the report and have not reviewed the report, except as given the opportunity to do so through the peer or public review mechanism.

Key Informants had to disclose any financial conflicts of interest greater than \$10,000 and any other relevant business or professional conflicts of interest. Because of their role as end-users, individuals were invited to serve as Key Informants and those who presented without potential conflicts were retained. The AHRQ Task Order Officer (TOO) and the EPC worked to balance, manage, or mitigate any potential conflicts of interest identified.

Analytic Framework

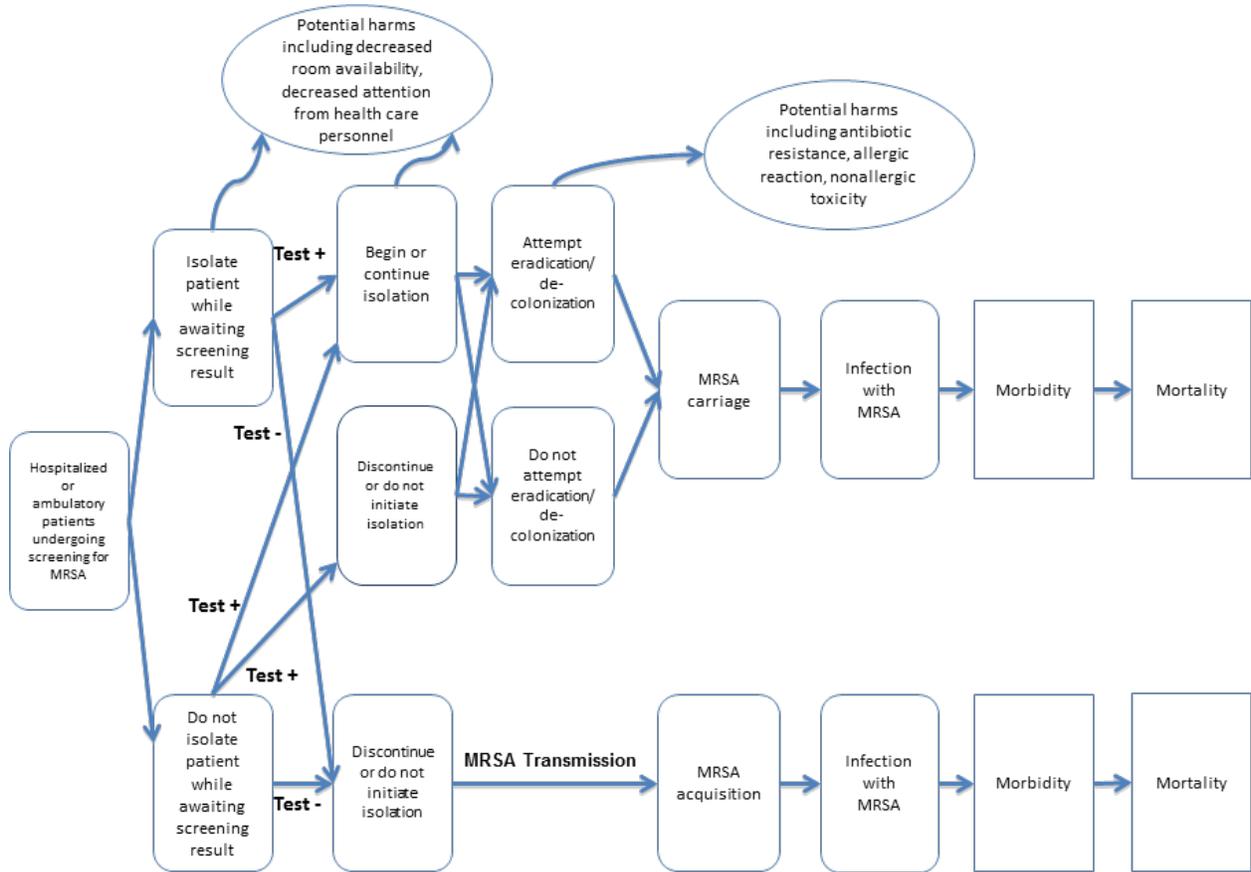
Figure 1 and Figure 2 depict the effects of MRSA screening on intermediate outcomes (including MRSA acquisition) and health outcomes (including infection, morbidity and mortality).

Figure 1. Analytic Framework for MRSA Screening



Abbreviations: KQ = key question; MRSA = methicillin-resistant *Staphylococcus aureus*.

Figure 2. Detailed Analytic Framework for MRSA Screening



Abbreviations: KQ = key question; MRSA = methicillin-resistant *Staphylococcus aureus*;
 Test + = positive MRSA-screening test result; Test - = negative MRSA-screening test result.

Literature Search Strategy

The databases listed below were searched for citations. The full search strings and strategies can be found in Appendix A. The search was limited to literature published from 1990 to the present because this is the evidence most applicable to current practice. The search was limited to the English-language literature because in past projects, our EPC has found the inclusion of non-English language literature did not yield sufficient high quality information to justify the resources required for translation.

- MEDLINE® (January 1, 1990, to September 1, 2011)
- EMBASE® (January 1, 1990, to September 1, 2011)
- Cochrane Controlled Trials Register (to September 1, 2011)

To identify systematic reviews, we searched MEDLINE®, the Cochrane Database of Systematic Reviews, and the Web sites of the National Institute for Clinical Excellence, Guidelines.gov, and the NHS Health Technology Assessment Programme. We followed the recommendations of the Agency for Healthcare Research and Quality in its *Methods Guide* about inclusion of results from previously conducted meta-analyses and systematic reviews.³³ Our search strategy used the National Library of Medicine's Medical Subject Headings (MeSH®) keyword nomenclature developed for MEDLINE® and adapted for use in other databases. The searches were limited to humans. We searched the Cochrane Controlled Trials Register using the same search teams utilized for the MEDLINE® and EMBASE® searches.

The TEP and individuals and organizations providing peer review were asked to inform the project team of any studies relevant to the key questions that were not included in the draft list of selected studies.

We searched indexed, electronically searchable conference abstracts by subject heading for the following conferences from the past 5 years: ICAAC (Interscience Conference on Antimicrobial Agents and Chemotherapy), Infectious Disease Society of America, Society for Healthcare Epidemiology of America, Association of Professionals in Infection Control and Epidemiology, American College of Physicians, Pediatric Infectious Diseases Society, European Society of Clinical Microbiology and Infectious Diseases, International Society of Infectious Diseases, European Society of Infectious Diseases, British Society of Infectious Diseases, Australasian Society of Infectious Diseases, International Sepsis Forum, and European Society of Intensive Care Medicine.

We reviewed Scientific Information Packets from the Scientific Resource Center and grey literature from the U.S. Food and Drug Administration Web site and ClinicalTrials.gov. We include those studies that have gone through a process equivalent to journal peer review.

In the course of this project, our EPC transitioned from EndNote® or ProCite® databases to use of Distiller SR®. Therefore, search results were initially stored in an EndNote9® database, subsequently transferred to Distiller SR®. In an initial screen of titles and abstracts, study selection criteria were applied by a single reviewer who marked each citation as: 1) eligible for review as a full-text article; 2) ineligible for full-text review; or 3) uncertain. Citations marked as uncertain were reviewed by a second reviewer and resolved by consensus opinion; and when necessary, discordant opinions will be resolved by a third reviewer. Throughout the title/abstract screening and study selection processes, reviewer training and quality control procedures were applied to achieve accuracy. Forms to facilitate title and abstract review were pilot tested during reviewer training.

Inclusion and Exclusion Criteria

We included randomized, controlled studies and nonrandomized, comparative studies (observational, case-control, and cohort studies) of populations, comparisons, interventions, and outcomes that were not adequately studied in controlled trials. We also used observational studies to assess comparative effectiveness in populations not well represented in randomized controlled trials. To classify observational study designs, we used the system developed by Briss and colleagues.³⁴ Studies were included that have these design characteristics and meet descriptions included under Population(s), Interventions, Comparators, Outcomes, Timing and Settings. Additionally, studies were excluded that: 1) did not describe any statistical analysis; or 2) report a relevant outcome only as a frequency without a denominator.

Study Selection

Final study selection criteria were applied to full-text articles to determine inclusion in the systematic review in the same manner as applied to title and abstract screening. Records of the reason for exclusion for each paper retrieved in full-text, but excluded from the review (Appendix B), were kept in the EndNote9® and Distiller SR® databases. Forms to facilitate full-text screening were pilot tested during reviewer training.

Search Strategies for Grey Literature

The EPC staff conducted a systematic search of the following grey literature sources to identify unpublished studies or studies published in journals that are not indexed in major bibliographic citation database in accordance with guidance from Effective Health Care Scientific Resource Center. The search strategies can be found in Appendix A.

1. Regulatory Information
 - a. U.S. Food and Drug Administration (www.FDA.gov)
2. Clinical Trial Registries
 - a. ClinicalTrials.gov
 - b. Current Controlled Trials
 - c. Clinical Study Results
 - d. World Health Organization (WHO) Clinical Trials
3. Abstracts and Conference Papers
 - a. Conference Papers Index
 - b. Scopus
 - c. Interscience Conference on Antimicrobial Agents and Chemotherapy (ICAAC)
 - d. The Infectious Disease Society of America (IDSA)
 - e. The Society for Healthcare Epidemiology of America (SHEA)
 - f. The Association of Professionals in Infection Control and Epidemiology (APIC)
 - g. The American College of Physicians (ACP)
 - h. The Pediatric Infectious Diseases Society (PIDS)
 - i. The European Society of Clinical Microbiology and Infectious Diseases (ESCMID)
 - j. The International Society of Infectious Diseases (ISID)
 - k. The Australasian Society of Infectious Diseases (ASID)
 - l. The International Sepsis Forum (ISF)
 - m. The European Society of Intensive Care Medicine (ESICM)

4. Grants and Federally Funded Research
 - a. NIH RePORTER (a searchable database of federally funded biomedical research projects conducted at universities, hospitals, and other research institutions)
 - b. HSRPROJ (a database providing access to ongoing grants and contracts in health services research)
 - c. AHRQ GOLD (an online searchable database of AHRQ grants, working papers and HHS recovery act projects)
5. Manufacturer database: Industry stakeholders were invited to submit the following types of information for possible inclusion as evidence:
 - A current product label;
 - Published randomized controlled trials and observational studies relevant to the clinical outcomes; and
 - Unpublished randomized controlled trials and observational studies relevant to the clinical outcomes.

These sources were searched using sensitive searches similar to the searches in bibliographic databases, except for the following:

- Regulatory information: The FDA website was searched for 510(k) decision summary documents related to devices used for diagnosis of MRSA- Xpert MRSA SA/SSTI, Xpert MRSA SA/BC, Xpert MRSA, GeneOhm MRSA assay and BBL ChromAgar MRSA.
- For clinical registries, NIH RePORTER, HSRPROJ, and AHRQ GOLD searches were limited to completed studies only.
- For abstracts and conferences, studies published prior to 2006 were excluded.

Data Extraction and Data Management

Data Elements

Using Distiller SR® software, the following data elements from the intervention studies were abstracted, or recorded as not reported (see Appendixes C, D, and E). The data elements to be abstracted were defined in consultation with the TEP and included the following:

- Quality Assessment:
 - Number of participants and flow of participants through steps of study
 - Treatment allocation methods (including concealment)
 - Use of blinding
 - Prospective vs. retrospective
 - Use of independent outcome assessor
 - Additional elements are described below under Assessment of Methodological Quality of Individual Studies
- Assessment of Applicability & Clinical Diversity:
 - Patient characteristics, including
 - Age
 - Sex
 - Race/ethnicity
 - Disease and type

- Disease duration
- Other prognostic characteristics (e.g., comorbidities and other potential confounders and/or effect modifiers)
- Setting
 - Outpatient
 - Inpatient
- Diagnostic and Treatment Characteristics, including
 - Type of assay used to screen for MRSA and its turnaround time
 - Decision-making for diagnosis and/or treatment
 - Antibiotic usage
 - Other treatment modalities
 - Duration of observation
- Outcome Assessment:
 - Identified primary outcome
 - Identified secondary outcomes
 - Response criteria
 - Follow-up frequency and duration
 - Data analysis details:
 - Statistical analyses (statistical test/estimation results)
 - Test used
 - Summary measures
 - Sample variability measures
 - Precision of estimate
 - p values
 - Regression modeling techniques
 - Model type
 - Candidate predictors and methods for identifying candidates
 - Univariate analysis results
 - Selected predictors and methods for selecting predictors
 - Testing of assumptions
 - Inclusion of interaction terms
 - Multivariable model results
 - Discrimination or validation methods and results
 - Calibration or “goodness-of-fit” results

Evidence Tables

Templates for evidence tables were created in Microsoft Excel® and Microsoft Word® after data were downloaded from Distiller SR®. Forms to facilitate data abstraction were pilot tested during implementation of quality control to achieve accuracy. One reviewer performed primary abstraction of all data elements into the evidence/abstraction tables, and a second reviewer reviewed the articles and evidence tables for accuracy (see Appendix F, Data Abstraction Tables). Disagreements were resolved by discussion, and if necessary, by consultation with a third reviewer. When small differences occurred in quantitative estimates of data from published figures, the values were obtained by averaging the estimates of the two reviewers.

Quality Assessment of Individual Studies

Definition of Ratings Based on Criteria

In adherence with the *Methods Guide*,³³ the general approach to grading individual comparative studies was that used by the U.S. Preventive Services Task Force.³⁵ According to this approach, studies lacking control for confounding would be considered fatally flawed and therefore of poor quality. The quality of the abstracted studies and the body of evidence was assessed by two independent reviewers. Discordant quality assessments were resolved with input from a third reviewer, if necessary.

- The quality of studies was assessed on the basis of the following criteria:
 - Initial assembly of comparable groups: adequate randomization, including concealment and whether potential confounders (e.g., other concomitant care) were distributed equally among groups
 - Maintenance of comparable groups (includes attrition, crossovers, adherence, contamination)
 - Important differential loss to follow-up or overall high loss to follow-up
 - Measurements: equal, reliable, and valid (includes masking of outcome assessment)
 - Clear definition of interventions
 - All important outcomes considered
 - Analysis: adjustment for potential confounders, intention-to-treat analysis
- The rating of intervention studies encompasses the three quality categories described here.
 - *Good*: Meets all criteria; comparable groups are assembled initially and maintained throughout the study (follow-up at least 80 percent); reliable and valid measurement instruments are used and applied equally to the groups; interventions are spelled out clearly; all important outcomes are considered; and appropriate attention is given to confounders in analysis. In addition, for randomized, controlled trials, intention to treat analysis is used.
 - *Fair*: Studies graded as “fair” if any or all of the following problems occur, without the fatal flaws noted in the “poor” category below: In general, comparable groups are assembled initially but some question remains whether some (although not major) differences occurred with follow-up; measurement instruments are acceptable (although not the best) and generally applied equally; some but not all important outcomes are considered; and some but not all potential confounders are accounted for. Intention-to-treat analysis is done for randomized, controlled trials.
 - *Poor*: Studies graded as “poor” if any of the following fatal flaws exists: Groups assembled initially are not close to being comparable or maintained throughout the study; unreliable or invalid measurement instruments are used or not applied at all equally among groups (including not masking outcome assessment); and key confounders are given little or no attention. For randomized, controlled trials, intention-to-treat analysis is lacking.
- The quality of included nonrandomized comparative intervention studies was also assessed based on a selection of items proposed by Deeks et al.,³⁶ to inform the approach used by the U.S. Preventive Services Task Force,³⁵ as follows:
 - Was sample definition and selection prospective or retrospective?

- Were inclusion/exclusion criteria clearly described?
- Were participants selected to be representative?
- Was there an attempt to balance groups by design?
- Were baseline prognostic characteristics clearly described and groups shown to be comparable?
- Were interventions clearly specified?
- Were participants in treatment groups recruited in the same time period?
- Was there an attempt by investigators to allocate participants to treatment groups in an attempt to minimize bias?
- Were concurrent/concomitant treatments clearly specified and given equally to treatment groups?
- Were outcome measures clearly valid, reliable and equally applied to treatment groups?
- Were outcome assessors blinded?
- Was the length of follow-up adequate?
- Was attrition below an overall high level (less than 20 percent)?
- Was the difference in attrition between treatment groups below a high level (less than 15 percent)?
- Did the analysis of outcome data incorporate a method for handling confounders such as statistical adjustment?

Assessment of individual study quality was greatly informed by whether studies attempted to control for confounding or secular trends. Studies that used such analytic techniques are described as CCS studies, while those that did not are called non-CCS studies. Non-CCS studies used simple two-group statistical analyses. Observational studies that do not attempt to control for confounding or secular trends do not provide evidence that supports causal inference. The ratings of good, fair and poor quality are reserved for CCS studies. Comments will be made here about results from non-CCS studies, but they are not included in strength of evidence syntheses.

Data Synthesis

Because of the heterogeneity of the data, this evidence review did not perform formal data synthesis through meta-analysis. If a meta-analysis could have been performed, subgroup and sensitivity analyses would have been based on assessment of clinical diversity in available studies. Anticipated subgroups included patients at high-risk for MRSA, including those with end-stage renal disease and those residing in long-term care facilities. The *Methods Guide*³³ and the paper by Owens and colleagues³⁷ was used to rate the strength of the overall body of evidence.

Assessment of Applicability

Applicability of findings in this review was assessed within the EPICOT framework (Evidence, Population, Intervention, Comparison, Outcome, Timestamp). Selected studies were assessed for relevance against target populations, interventions of interest, and outcomes of interest.

Grading the Body of Evidence for Each Key Question

The system used for rating the strength of the overall body of evidence was developed by the Agency for Healthcare Research and Quality for its Methods Guide,^{33, 37} based on a system developed by the GRADE Working Group.³⁸ This system explicitly addresses the following domains: risk of bias, consistency, directness, and precision. The grade of evidence strength is classified into the following four categories:

- High: High confidence that the evidence reflects the true effect. Further research is very unlikely to change our confidence in the estimate of effect.
- Moderate: Moderate confidence that the evidence reflects the true effect. Further research may change our confidence in the estimate of effect and may change the estimate.
- Low: Low confidence that the evidence reflects the true effect. Further research is likely to change our confidence in the estimate of effect and is likely to change the estimate.
- Insufficient: Evidence is either unavailable or does not permit estimation of an effect.
- Additional domains such as strength of association, publication bias, coherence, dose-response relationship, and residual confounding were assessed when appropriate.

Peer Review, Public Commentary, and Technical Expert Panel

Peer reviewers will be invited to provide written comments on the draft report based on their clinical, content, or methodological expertise. Peer review comments on the preliminary draft of the report will be considered by the EPC in preparation of the final draft of the report. Peer reviewers have not participated in the writing or editing of the final report or other products. The synthesis of the scientific literature presented in the final report will not necessarily represent the views of individual reviewers. The dispositions of the peer review comments will be documented and published three months after the publication of the evidence report.

Potential reviewers will have to disclose any financial conflicts of interest greater than \$10,000 and any other relevant business or professional conflicts of interest. Invited peer reviewers cannot have any financial conflict of interest greater than \$10,000. Peer reviewers who disclose potential business or professional conflicts of interest will be able to submit comments on draft reports through the public comment mechanism.

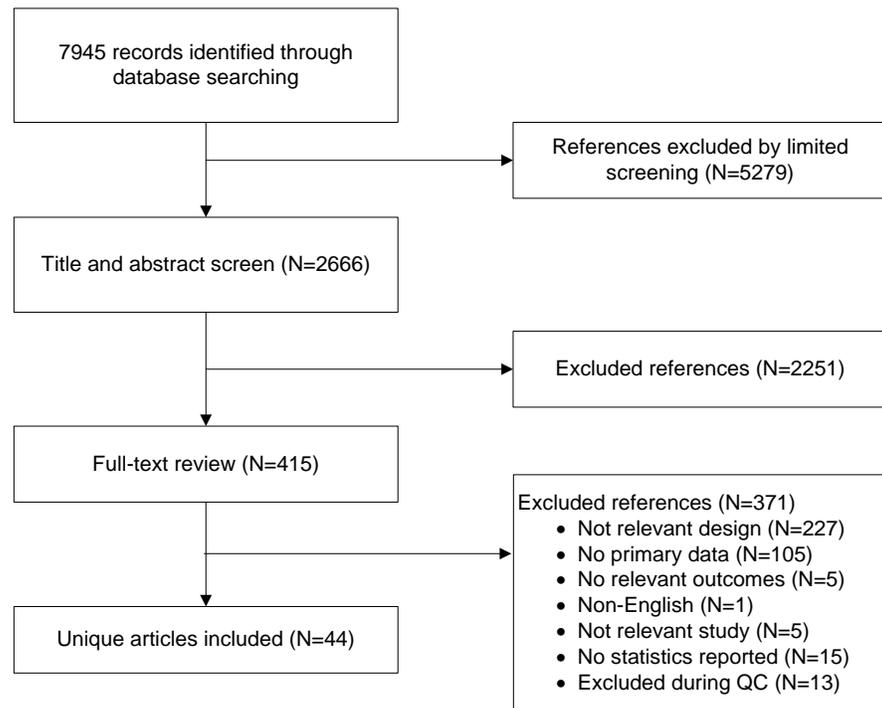
A Technical Expert Panel (TEP) was formed to provide consultation on the development of the protocol and evidence tables for the review. Ad hoc clinical questions were also addressed to the TEP.

Results

Literature Search

Of the 7,945 records identified through the literature search, we limited screening to those references that contained the terms “screen* OR surveil*” in title or abstract. Of the references that did not contain the key textwords, none met eligibility criteria. Of the remaining 2,666 records, 1,630 were excluded at various stages of screening and 44 records were included. The PRISMA diagram (Figure 3) depicts the flow of search screening and study selection.

Figure 3. PRISMA Diagram for Identified Published Literature



Grey Literature Search

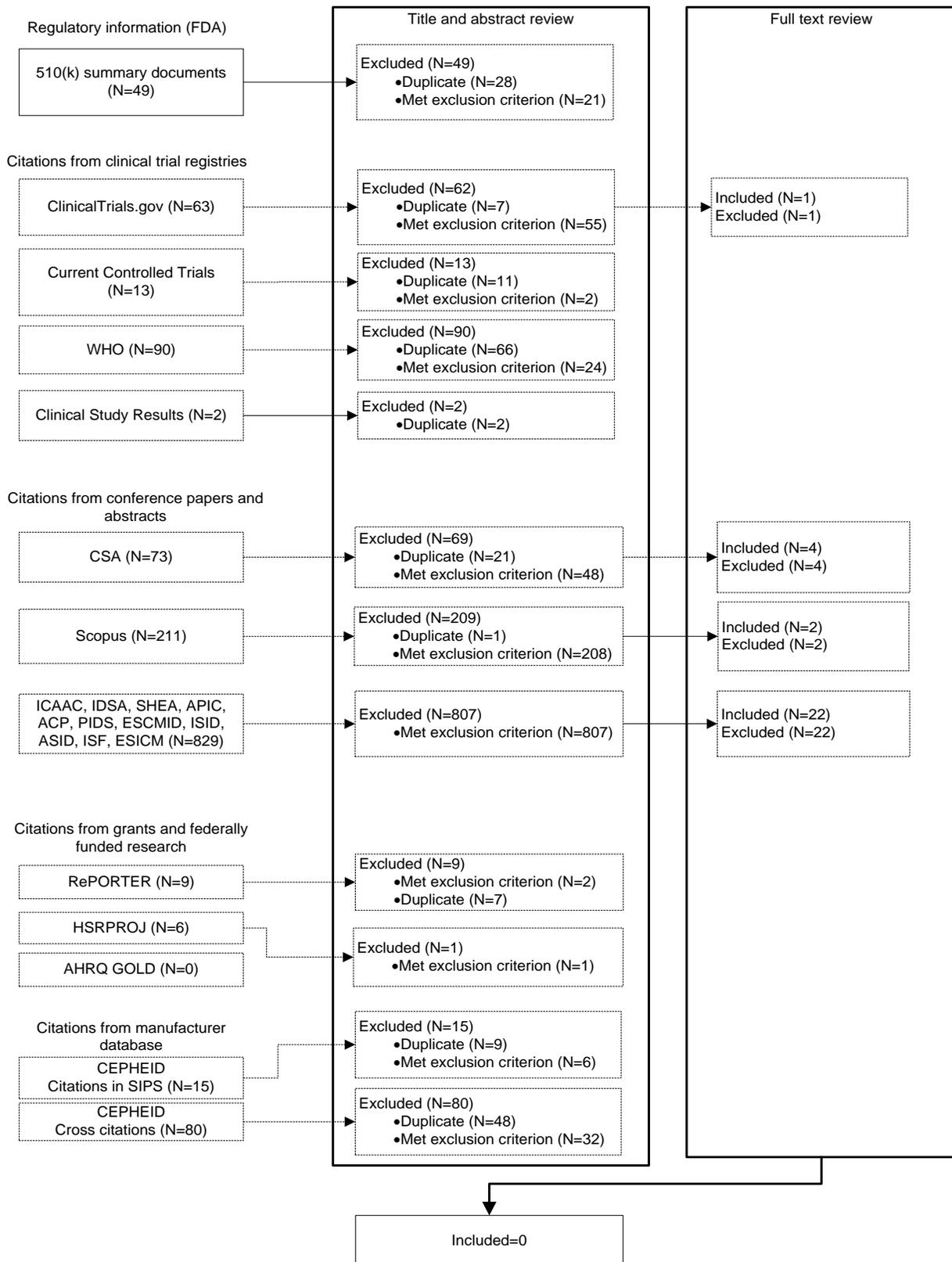
We evaluated the results of the grey literature search with results summarized in Figure 4.

- **Regulatory Information:** The search yielded 49 studies from the 510(k) summaries obtained for MRSA; the assays included Xpert MRSA SA/SSTI, Xpert MRSA SA/BC, Xpert MRSA, GeneOhm MRSA assay and BBL ChromAgar MRSA. All 49 citations were excluded—28 were duplicates and 21 met one or more exclusion criterion. No new studies were identified from this source.
- **Clinical trial registries:** Citations for published articles linked to trials registered at ClinicalTrials.gov were included. The search yielded 168 clinical trials, of which, 167 were excluded during the title and abstract screen—86 were duplicate (literature citations already included in the reference database) and 81 met one or more exclusion criterion (e.g., did not compare MRSA screening versus an

alternative or noncomparative trial). One reference was reviewed in full-text and was excluded according to the study protocol.

- **Abstracts and Conference Papers:** The search yielded 1,113 citations, of which, 1,085 were excluded during the title and abstract screen—22 references were duplicate and 1,063 met one or more exclusion criterion. Twenty-eight references were reviewed by a third team member in full-text and all were excluded according to the study protocol.
- **Grants and federally funded research:** The search yielded 15 citations and all 15 were excluded—3 were duplicates and 13 met one or more exclusion criterion.
- **Manufacturer database (SIPs):** In response to requests, scientific information packets (SIPs) were received from CEPHEID. The submissions consisted of descriptive text supported by 15 citations. No abstracts or unpublished data were provided by the company. Of the 15 references, 13 were excluded during abstract and title screen—9 were duplicate and 4 met one or more exclusion criterion. The remaining two references were evidence reports—one from the Canadian Agency for Drugs and Technologies in Health (CADTH) and one from ECRI Institute. Further, the CADTH report was cross-referenced to another relevant CADTH report and hence was included in the full-text review. The full-text review of these three evidence reports yielded 80 references. Of these, all 80 were excluded—48 were duplicates and 32 met one or more exclusion criterion.

Figure 4. PRISMA Diagram for Identified Grey Literature



Overview of Studies Included in the Present Review

Overall, 44 studies were abstracted for this review. They are summarized in Table 1. Two studies^{28, 39} reported outcomes that addressed key question 1, two studies^{28, 40} reported outcomes that addressed key question 2, 13 studies^{27, 28, 41-51} reported outcomes that addressed key question 3A, 13 studies^{29, 52-62} reported outcomes that addressed key question 3B, 9 studies⁶³⁻⁷⁰ reported outcomes that addressed key question 3C and 8 studies^{66, 71-77} reported outcomes that addressed key question 4. The 15 studies^{27-29, 39-44, 52, 63-66, 71} that attempted to control for confounding and/or secular trends (CCS studies) contributed to the SOE analysis across all six key questions. These studies had the potential to support causal inferences about the impact of MRSA screening on health outcomes, and therefore are included in the strength of evidence syntheses. The quality of the studies that attempted to control for confounding and/or secular trends (CCS studies) was subsequently rated as good, fair or poor. Good quality studies reported baseline group characteristics, considered and analyzed at least one important (i.e., health care-associated) outcome, and conducted appropriate analysis (tested for trend, addressed autocorrelation, and included at least one confounder in the analysis). Poor quality studies failed to conduct appropriate analysis (e.g., did not test for trend in both control and intervention periods or did not report including at least one confounder in the analysis). Fair quality studies did not meet the criteria for good quality studies or for poor quality studies. The remaining 29 studies that did not attempt to control for confounding and/or secular trends (non-CCS studies) cannot support causal inferences and are therefore excluded from the strength of evidence syntheses. These studies performed simple two-group statistical analyses. Comments are given in this Results section contrasting the pattern of results from the non-CCS studies relative to the CCS studies.

Table 1. Overview of abstracted studies

A. CCS, Good Quality, used in SOE synthesis

Author, Year	Design	KQ1	KQ2	KQ3A	KQ3B	KQ3C	KQ4	HCA Acq	HCA Inf	HCA Site Inf	HCA /Imp Acq	HCA/ Imp Inf	HCA/ Imp Site Inf
Harbarth, et al., 2008 ²⁹	QEX-CG, X-OVER				•			•	•	•			
Huskins, et al., 2011 ⁴³	RCT			•				•					
Leonhardt, et al., 2011 ⁴⁰	QEX-CG		•						•				
Robicsek, et al., 2008 ²⁸	QEX-BA	•	•	•					•	•			

B. CCS, Fair Quality, used in SOE synthesis

Author, Year	Design	KQ1	KQ2	KQ3A	KQ3B	KQ3C	KQ4	HCA Acq	HCA Inf	HCA Site Inf	HCA /Imp Acq	HCA/ Imp Inf	HCA/ Imp Site Inf
Gould, et al., 2007 ⁴¹	QEX-ITS			•							•		
Rodriguez-Bano, et al., 2010 ⁶⁰	QEX-ITS					•	•	•		•			

C. CCS, Poor Quality, used in SOE synthesis

Author, Year	Design	KQ1	KQ2	KQ3A	KQ3B	KQ3C	KQ4	HCA Acq	HCA Inf	HCA Site Inf	HCA /Imp Acq	HCA/ Imp Inf	HCA/ Imp Site Inf
Chaberny, et al., 2008 ⁷¹	QEX-BA						•		•		•		
Chowers, et al., 2009 ⁶³	QEX-ITS					•				•			
Ellingson, et al., 2011 ⁶⁴	QEX-ITS					•		•		•			
Harbarth, et al., 2000 ⁶⁵	QEX-BA					•			•	•			
Holzmann-Pazgal, et al., 2011 ⁴²	QEX-BA			•				•					
Huang, et al., 2006 ²⁷	QEX-ITS			•				•		•			
Jain, et al., 2011 ³⁹	QEX-BA	•						•	•	•			
Muder, et al., 2008 ⁵²	QEX-BA				•				•	•			
Raineri, et al., 2007 ⁴⁴	QEX-BA			•				•					

Table 1. Overview of abstracted studies (continued)

D. Non-CCS, Poor Quality, not used in SOE synthesis

Author, Year	Design	KQ1	KQ2	KQ3A	KQ3B	KQ3C	KQ4	HCA Acq	HCA Inf	HCA Site Inf	HCA /Imp Acq	HCA/ Imp Inf	HCA/ Imp Site Inf
Blumberg and Klugman, 1994 ⁴⁵	QEX-BA			•									•
Bowler, et al., 2010 ⁶⁷	QEX-BA					•			•				
Boyce, et al., 2004 ⁴⁶	QEX-BA			•					•				
Clancy, et al., 2006 ⁴⁷	QEX-BA			•					•				
de la Cal, et al., 2004 ⁴⁸	QEX-BA			•				•		•			
Eveillard, et al., 2006 ⁷²	QEX-BA						•	•					
Girou, et al., 2000 ⁷³	QEX-BA						•	•					
Jog, et al., 2008 ⁵⁵	QEX-BA				•					•			
Keshtgar, et al., 2008 ⁷⁸	QEX-BA					•				•			
Kim DH, et al., 2010 ⁵⁴	QEX-BA				•					•			
Kurup, et al., 2010 ⁴⁹	QEX-BA			•					•				
Lipke and Hyott 2010 ⁵⁵	QEX-BA				•					•			
Malde, et al., 2006 ⁵⁶	QEX-BA				•					•			
Nixon, et al., 2006 ⁵⁷	QEX-BA				•					•			
Pan, et al., 2005 ⁶⁸	QEX-BA					•				•			
Pofahl, et al., 2009 ⁵⁸	QEX-BA				•					•			
Salaripour, et al., 2006 ⁶⁹	QEX-BA					•		•					
Sankar, et al., 2005 ⁷⁹	QEX-BA				•				•				
Schelenz, et al., 2005 ⁷⁴	QEX-BA						•	•					
Simmons 2011 ⁵⁰	QEX-BA			•					•				
Sott, et al., 2001 ⁵⁹	QEX-BA				•					•			
Souweine, et al., 2000 ⁵¹	QEX-BA			•							•		
Supriya, et al., 2009 ⁶⁰	QEX-BA				•					•			
Thomas, et al., 2007 ⁶¹	QEX-BA				•					•			
Thompson, et al., 2009 ⁷⁵	QEX-BA						•	•		•			
Trautmann, et al., 2007 ⁷⁶	QEX-BA						•	•		•			
Walsh, et al., 2011 ⁶²	QEX-BA				•					•			
Wernitz, et al., 2005 ⁷⁰	QEX-BA					•			•	•			
West, et al., 2006 ⁷⁷	QEX-BA						•		•				

Acq: Acquisition; BA: Before after; CCS: attempted to control for confounding or secular trends; HCA: Health Care-Associated; Imp: Imported; Inf: Infection; ITS: Interrupted time series; KQ: Key question; MRSA: Methicillin-resistant *Staphylococcus aureus*; NR: Not reported; QEX: Quasi-experimental; RCT: Randomized controlled trial; SOE: Strength of evidence; X-over: Cross over

Key Question 1

Universal Screening for MRSA-Carriage Compared to No Screening

Overview

This section describes the literature that evaluates universal screening for MRSA-carriage compared to no screening. After an overview of the literature, the results are described for each outcome: MRSA acquisition, MRSA infection, morbidity, mortality, harms, and resource utilization. The emphasis in this chapter is on outcomes describing health care-associated events. Health care-associated outcomes are the primary outcomes of interest because screening for MRSA-carriage in health care facilities is most proximately expected to impact health care-associated MRSA transmission and infection. Table 2 summarizes the studies reviewed for Key Question 1.

Table 2. KQ1: Health care-associated MRSA acquisition and infection

Outcome	Study	Quality	Statistical Result	Synthesis
HCA acquisition	Jain et al. ³⁹	Poor	SS ↓	SOE=insufficient
HCA infection	Robicsek et al. ²⁸	Good	SS ↓	SOE=insufficient
	Jain et al. ³⁹	Poor	SS ↓	

HCA = Health care associated; KQ = Key Question; SOE = strength of evidence; SS = statistically significant

Two studies^{28, 39} described universal screening for methicillin-resistant *Staphylococcus aureus* (MRSA) carriage compared to no screening. Both studies attempted to use statistical methods to control for confounding and/or secular trends. Both of the studies utilized quasi-experimental study designs. The Robicsek study²⁸ was judged to be of good quality overall. However, the Jain study³⁹ was judged to be of poor quality overall because it did not report baseline group characteristics and did not report whether its analysis controlled for confounders.

Both studies were conducted in multihospital organizations of acute care hospitals. The Jain study³⁹ occurred in Veterans Affairs hospitals, while the Robicsek study²⁸ occurred in academic and community hospitals. Both had a large number of subjects. The Robicsek study²⁸ specified the sample size for the intervention group (n=73,464) and for the control group (39,521). The Jain study³⁹ specified the sample size for the intervention group (n=1,934,598), but not for the control group.

For both of the studies, the interventions included at least one intervention in addition to universal screening for MRSA carriage. For the good quality study, the intervention was nasal surveillance for MRSA colonization on the first day of hospitalization for all patients, as well as decolonization (with intranasal antimicrobials and topical antimicrobial washes) for those patients who tested positive for MRSA.²⁸ For the poor quality study, the intervention was a MRSA bundle including surveillance for nasal colonization with MRSA for all patients within 24 hours of admission to the hospital, all patients not already known to be colonized or infected with MRSA transferred from one unit to another within the hospital, and all patients not already known to be colonized or infected with MRSA on discharge from the hospital; contact precautions for patients colonized or infected with MRSA; hand hygiene; and an institutional

culture change wherein infection control became the responsibility of everyone who had patient contact.³⁹ One of the studies utilized polymerase chain reaction (PCR) to screen patients for MRSA²⁸ and one³⁹ utilized either culture or PCR to screen patients for MRSA carriage. For both of the studies, the control condition consisted of no screening.

The primary outcome of the both the studies was the rate of health care-associated MRSA infection. For the Jain study,³⁹ the primary outcome was the rate of health care-associated MRSA infections. For the Robicsek study,²⁸ the primary outcome was the aggregate health care-associated rate of MRSA infection in the hospital.

The infection control practices differed for MRSA-positive patients during the intervention and control periods. Both studies recommended no action for patients awaiting test results for the intervention or control groups. However, both studies recommended more intensive actions for MRSA-positive patients in the intervention group than for MRSA-positive patients in the control group. In the Robicsek study,²⁸ the MRSA-positive intervention group received isolation or cohorting, barrier precautions, dedicated equipment for staff use, and decolonization (with intranasal antimicrobials and topical antimicrobial washes). For its MRSA-positive control group, the Jain study²⁸ recommended isolation or cohorting, barrier precautions, and dedicated equipment for staff use, but no decolonization. For its MRSA-positive intervention group, one study³⁹ recommended contact precautions, hand washing, and repeat assays. For its MRSA-positive control group, this study recommended no action. Only the Robicsek study²⁸ described the turnaround time for testing (0.67 day).

Results by Outcome

Health Care-Associated MRSA Acquisition

Health care-associated MRSA acquisition is measured by MRSA colonization or by MRSA colonization or infection that is health care-associated, rather than imported. Only one poor quality study³⁹ addressed this outcome. This study by Jain et al.,³⁹ defined health care-associated MRSA colonization or infection as a positive sample for MRSA obtained more than 48 hours after admission from a patient not previously known to be colonized or infected with MRSA. Patients not known to be colonized or infected with MRSA who were readmitted to the hospital within 48 hours after discharge and were found to be positive at the time of readmission were also considered to have a transmission event. With universal screening for MRSA, this study showed a statistically significant reduction in health care-associated MRSA in the intensive care unit (-17 percent relative risk reduction) and in non-ICU settings (-21 percent relative risk reduction).

Strength of Evidence

Overall, compared to no screening, the strength of evidence was assessed as insufficient that universal screening for MRSA-carriage decreases health care-associated MRSA acquisition based on the positive findings from a single, quasi-experimental before/after study. The risk of bias was judged to be high based on the one poor quality study with a quasi-experimental before/after study design. Because only one study evaluated this outcome, the consistency of these results is unknown and the effect was judged to be imprecise. Moreover, health care-associated MRSA acquisition is an indirect outcome measure.

Health Care-Associated MRSA Infection

One good quality study²⁸ and one poor quality study³⁹ addressed health care-associated MRSA infection overall. In their definition of hospital-acquired infection, both studies included infection that had occurred more than two days after admission. The Robicsek study²⁸ defined infection as the sum total of all bloodstream infections (positive blood culture in the absence of a positive clinical culture from another site), respiratory tract infections (positive respiratory culture, compatible chest radiograph and decision to treat), urinary tract infections (positive urine culture and decision to treat or growth of more than 100,000 colony-forming units/mL plus at least 50 leukocytes per high-power field), and surgical site infections (positive culture of a surgical site). Infections were considered hospital-associated if they occurred more than two days after admission and within 30 days of discharge. The Jain study³⁹ defined health care-associated MRSA infection according to the Center for Disease Control and Prevention's (CDC's) National Healthcare Safety Network (NHSN) guidelines with three modifications: 1) the diagnosis of MRSA infection required a positive culture; 2) a positive culture was considered to be imported if it was obtained within 48 hours after admission; 3) a positive clinical culture obtained from a patient in whom infection was not present or incubating at the time of admission as defined by NHSN criteria was considered to be health care-associated if it was obtained more than 48 hours after admission.

Compared to no screening, both studies found a statistically significant reduction in health care-associated MRSA infection with universal screening for MRSA. For the good quality study,²⁸ the change in the rate of MRSA infection from a Poisson regression model was -69.6 percent with broad confidence intervals (95 percent CI: -89.2 to -19.6 percent). For the poor quality study,³⁹ the relative reduction in the rate of MRSA infection was -62 percent in ICU settings and -45 percent in non-ICU settings. The p value for trend in both settings was <0.001.³⁹

Strength of Evidence

Overall, compared to no screening, the strength of evidence was assessed as insufficient that universal screening for MRSA-carriage decreases health care-associated MRSA infection based on the moderate risk of bias and the lack of precision from two quasi-experimental studies. The risk of bias was judged to be moderate based on one good quality quasi-experimental study with a limited time series design²⁸ and one³⁹ poor quality quasi-experimental study with a before/after design. Because both studies found a statistically significant reduction in health care-associated MRSA infection with screening, the results are consistent. Health care-associated MRSA infection is a direct outcome measure. The effect of universal MRSA screening was judged to be imprecise as the results have not been replicated by a second study of good or fair quality.

Morbidity, Mortality, Harms and Resource Utilization

Results

No studies addressed these outcomes.

Strength of Evidence

Because no studies addressed these outcomes, compared to no screening, the strength of evidence is insufficient to assess the effect of universal screening for MRSA-carriage on morbidity, mortality, harms or resource utilization.

Summary Strength of Evidence Across Key Question 1

A summary of the main syntheses for this question follows in Table 3.

Table 3. Strength of evidence for studies comparing universal screening versus no screening

Strategies Compared	Outcome	No of Studies [§]	Risk of Bias	Consistency	Directness	Precision	Overall Grade
Universal screening vs. No screening	MRSA Transmission	1 QEX (N=1,934,598) Jain 2011 ³⁹	High	Unknown	Indirect	Imprecise	Insufficient
	MRSA Infection	2 QEX (N= 112,985) Robicsek 2008 ²⁸ (N=1,934,598) Jain 2011 ³⁹	Moderate	Consistent	Direct	Imprecise	Insufficient

QEX: Quasi-experimental; NA: Not applicable

[§]CCS studies

Key Question 2

Universal Screening for MRSA-Carriage Compared to Screening of Selected Patient Populations (Targeted Screening)

Overview

This section describes the literature that evaluates universal screening for MRSA-carriage compared to screening of selected patient populations (targeted screening). After an overview of the literature, the body of evidence is described for each outcome measure: MRSA acquisition, MRSA infection, morbidity, mortality, harms, and resource utilization. The emphasis in this chapter is on outcomes describing health care-associated events. Health care-associated outcomes are the primary outcomes of interest because screening for MRSA-carriage in health care facilities is most proximately expected to impact health care-associated MRSA transmission and infection. Table 4 summarizes the studies reviewed for Key Question 2.

Table 4. KQ2: Health care-associated MRSA infection

Outcome	Study	Quality	Statistical Result	Synthesis
HCA infection	Robicsek et al. ²⁸	Good	SS ↓	SOE=insufficient
	Leonhardt et al. ⁴⁰	Good	NS	

HCA = Health care associated; KQ = Key Question; NS = nonsignificant; SOE = strength of evidence; SS = statistically significant

Two quasi-experimental studies compared universal screening for MRSA carriage on hospital admission to screening of selected patient populations (targeted screening).^{28,40} Both of these studies used statistical methods to attempt to control for confounders and/or secular trends. The overall quality of both studies^{28,40} was rated as good. Both of the studies utilized a quasi-experimental study design; the study by Leonhardt and colleagues was a case-control study⁴⁰ and the study by Robicsek and colleagues²⁸ was a limited time series design. The sample sizes ranged from 15,049 to 77,856. The aggregate number of subjects across studies was at least 92,905.

As its comparison group, the Robicsek study²⁸ evaluated screening of patients admitted to the ICU. The Leonhardt study⁴⁰ evaluated screening of high-risk patients, including those admitted to the ICU as its comparison group. In its high-risk group, this study also included patients with a history of MRSA infection or colonization; those with a history of prior hospitalization, including transfers, within the past 6 months; patients from long-term care facilities and correctional institutes; patients receiving hemodialysis; and selected orthopedic and cardiothoracic surgery patients.

The Robicsek study²⁸ conducted follow-up for MRSA disease for 180 days after discharge, though patients in the intervention group were followed for less than 180 days if they were discharged in the final 180 days of the study period. The Leonhardt study⁴⁰ did not specify the duration of follow-up.

Both of the studies utilized PCR to screen for MRSA carriage. Turnaround times for screening results were reported for the Robicsek study,²⁸ but not for the Leonhardt study.⁴⁰ The Robicsek study²⁸ found the turnaround time to be 2.5 days for the control period and 0.67 day for the intervention period.

The Robicsek study²⁸ cited aggregate hospital-associated MRSA infection rate as its primary outcome. This study included several secondary outcomes including rates of health care-associated MRSA and MSSA bacteremia, rates of aggregate MRSA infections occurring up to 180 days after discharge, and adherence to MRSA surveillance. The Leonhardt study⁴⁰ cited the clinical effectiveness and the cost benefit of universal screening versus targeted screening for MRSA as its primary outcome.

The infection control practices used to care for MRSA-positive patients differed between intervention and control group patients for the Robicsek study²⁸ but were the same for the Leonhardt study.⁴⁰ For MRSA-positive patients in the intervention group, Robicsek et al.²⁸ utilized contact isolation and decolonization (with nasal antimicrobials and topical antimicrobial washes). However, MRSA-positive patients in the control group received contact isolation without decolonization. For MRSA-positive patients in both intervention and control groups, Leonhardt et al.,⁴⁰ utilized contact isolation and when appropriate, perioperative decolonization and antibiotic prophylaxis.

The infection control practices used to care for patients while waiting for screening tests results were the same for intervention and control group patients for both studies. Robicsek et

al.,²⁸ utilized no interventions during this time period. Leonhardt et al.,⁴⁰ recommended contact isolation for patients previously known to be MRSA positive.

Results by Outcome

Health Care-Associated MRSA Acquisition

Health care-associated MRSA acquisition is measured by MRSA colonization or by MRSA colonization or infection that is health care-associated, rather than imported.

Results

No studies addressed this outcome.

Strength of Evidence

No studies addressed this outcome. Therefore, the strength of evidence to evaluate the effect of universal screening for MRSA-carriage compared to targeted screening on health care-associated MRSA transmission was judged to be insufficient.

Health Care-Associated MRSA Infection

Results

While both studies showed a reduction in hospital-acquired MRSA infection with universal screening for MRSA carriage compared to targeted screening, only the Robicsek study showed a statistically significant reduction. Using a segmented Poisson regression, Robicsek et al.,²⁸ found that the rate of hospital-acquired MRSA infection declined by 52.4 percent (CI: 9.3 to 78.3 percent) in the universal screening group compared to the targeted screening group. Leonhardt et al.,⁴⁰ showed a 0.12 percent reduction in hospital-acquired infection with universal screening compared to targeted screening. However, this reduction was not statistically significant ($p=0.23$), nor was the difference in difference ($p=0.34$).

The definitions of hospital-acquired infection differed between the two studies. One study⁴⁰ defined an infection as hospital acquired if it occurred on or after day 4 of hospitalization. The other study²⁸ defined an infection as hospital acquired if it occurred more than 48 hours after admission and 30 days or less after discharge.

Strength of Evidence

Overall, the strength of evidence to evaluate the effect of universal screening for MRSA-carriage compared to targeted screening on health care-associated MRSA infection was judged to be insufficient based on the moderate risk of bias and the imprecision of the study findings. The risk of bias was judged to be moderate as two good quality quasi-experimental studies, one²⁸ a limited time series design and one⁴⁰ a case control study, addressed this outcome. For one study, the targeted screening strategy was screening for MRSA-carriage in ICU patients²⁸ and for the other, targeted screening was performed in high-risk patients.⁴⁰ With universal screening, both studies found a reduction in health care-associated MRSA infection. However, the reduction in the Robicsek²⁸ study was statistically significant and Leonhardt⁴⁰ was not. Thus the results were inconsistent. Both studies measured MRSA infection, a direct outcome measurement. Because of

the difference in statistical significance between the two studies, the findings were deemed imprecise.

Morbidity, Mortality, Harms, and Resource Utilization

Results

No studies addressed these outcomes.

Strength of Evidence

Because no studies addressed these outcomes, the strength of evidence to evaluate the effect of universal screening for MRSA-carriage compared to targeted screening on morbidity, mortality, harms or resource utilization was judged to be insufficient.

Summary Strength of Evidence Across Key Question 2

A summary of the main syntheses for this question follows in Table 5.

Table 5. Strength of evidence for studies comparing universal screening versus screening in selected patient population

Strategies Compared	Outcome	No of Studies [§]	Risk of Bias	Consistency	Directness	Precision	Overall Grade
Universal Vs Screening of Selected Patients	MRSA Transmission	No studies	NA	NA	NA	NA	Insufficient
	MRSA Infection	2 QEX (N=128,334) (Robicsek 2008, ²⁸ Leonhardt 2011 ⁴⁰)	Moderate	Inconsistent	Direct	Imprecise	Insufficient

QEX: Quasi-experimental; NA: Not applicable

[§]CCS studies

Key Question 3A

Screening of ICU Patients for MRSA-Carriage Compared to No Screening

Overview

This section describes the literature that evaluates screening of ICU patients for MRSA-carriage compared to no screening. After an overview of the literature, the results are described for each outcome: MRSA acquisition, MRSA infection, morbidity, mortality, harms, and resource utilization. Within the category of MRSA infection, we also include results for MRSA bacteremia or bloodstream infection and for MRSA surgical site infection, as some studies present these outcomes rather than the broader outcome of MRSA infection irrespective of site. The emphasis in this chapter is on outcomes describing health care-associated events. Health care-associated outcomes are the primary outcomes of interest because screening for MRSA-carriage in health care facilities is most proximately expected to impact health care-associated MRSA transmission and infection. Strength of evidence syntheses presented here include only

studies that attempted to control for confounding and/or secular trends (CCS studies). Because studies that use simple two-group statistical analyses cannot support causal inferences, those studies that did not attempt to control for confounding and/or secular trends (non-CCS studies) were excluded from the strength of evidence analysis. Following the strength of evidence syntheses, we comment on the pattern of results seen in studies that did not attempt to control for confounding and/or secular trends (non-CCS studies). Table 6 summarizes the studies reviewed for Key Question 3A.

Table 6. KQ3A: Health care-associated MRSA acquisition, infection, bacteremia, or surgical-site infection

Outcome	Study	Quality	Statistical Result	Synthesis
HCA acquisition	Huskins ⁴³	Good	NSS ↑	SOE=insufficient
	Huang ²⁷	Poor	SS ↓	Comment: Results more favorable than the good quality Huskins study, however causal inference is not possible.
	Raineri ⁴⁴	Poor	SS ↓	
	Holzmann-Pazgal ⁴²	Poor	SS ↓	
de la Cal ⁴⁸	Non-CCS	SS ↓		
HCA infection	Robicsek ²⁸	Good	NSS ↓	SOE=insufficient
	Clancy ⁴⁷	Non-CCS	SS ↓/ NSS ↓	Comment: Results more consistently favorable than Robicsek, however causal inference is not possible.
	Boyce ⁴⁶	Non-CCS	SS ↓	
	Kurup ⁴⁹	Non-CCS	NSS ↓	
Simmons ⁵⁰	Non-CCS	Significant ↓		
HCA bacteremia/ blood stream infection	Robicsek ²⁸	Good	NSS ↓	SOE=insufficient
	Huang ²⁷	Poor	SS ↓	Comment: Results more consistently favorable than Robicsek, however causal inference is not possible.
	de la Cal ⁴⁸	Non-CCS	SS ↓	
HCA surgical site infection	Robicsek ²⁸	Good	NSS ↓	

CCS = study attempted to control for confounding and/or secular trends; HCA = Health care-associated; KQ = Key Question; NSS = nonstatistically significant; SOE = strength of evidence; SS = statistically significant

Thirteen studies described screening of ICU patients for MRSA-carriage compared to no screening. Six of the studies^{28,27,41-44} used statistical methods to attempt to control for confounders or secular trends and seven⁴⁵⁻⁵¹ did not. Of the studies that used statistical methods to attempt to control for confounders or secular trends, the Robicsek²⁸ and Huskins⁴³ studies were judged to be of good quality overall, the Gould⁴¹ study was judged to be of fair quality, and the Huang,¹³ Raineri and Holzmann-Pazgal⁴² studies were judged to be of poor quality. The Gould study⁴¹ was rated as fair quality because it did not report on a purely health care-associated outcome. The Huang study²⁷ was rated as poor quality because it did not report baseline group characteristics and whether the analysis controlled for confounders. The Raineri study⁴⁴ was rated as poor quality because it did not report adjusting for any confounders. The Holzmann-Pazgal study⁴² was rated as poor quality because though it controlled for the confounding influence of hand hygiene compliance and for trend during the intervention period,

it did not address trend during the pre-intervention period. Seven studies did not use statistical methods to attempt to control for confounders or secular trends.⁴⁵⁻⁵¹

Of the good quality studies, Huskins⁴³ was a cluster randomized, controlled trial and Robicsek²⁸ utilized a before/after quasi-experimental design. The Gould study, a study of fair quality, utilized a quasi-experimental interrupted time series design.⁴¹ Of the poor quality studies, all three utilized a quasi-experimental study design. The Huang study²⁷ utilized an interrupted time series design and the other two studies^{42, 44} utilized a before/after design. Of the studies that did not use statistical methods to attempt to control for confounders and/or secular trends (non-CCS studies), all seven studies⁴⁵⁻⁵¹ utilized a before/after design.

In terms of sample size, both of the good quality studies^{28, 43} specified the sample size for the intervention group and for the control group. Among the good quality studies, the range in sample size for the intervention group was 1,615–39,521; the range in sample size for the control group was 2,441–40,392. The total sample size for the good quality studies^{28, 43} was 83,969. For the fair quality study, the sample size for the control group was 1,232, the sample size for the intervention group was 1,421, and the total sample size was 2,653.^{41, 42} Of the poor quality studies, two^{42, 44} specified the sample size and one²⁷ did not. Among the poor quality studies, the range in sample size for the intervention group was 2367-3311; the range in sample size for the control group was 667-730. The total sample size for the poor quality studies was 7,075. For the good, fair and poor quality studies combined, the total sample size was 86,622.

Of the studies that did not use statistical methods to attempt to control for confounders and/or secular trends (non-CCS studies), two of seven specified the sample size for the intervention group and for the control group.^{45, 48} Four non-CCS studies^{46, 47, 49, 50} specified the sample size for the intervention group, but not for the control group. One⁵¹ of the non-CCS studies did not specify the sample size for the intervention group or for the control group. Of the non-CCS studies, the range in sample size for the intervention group was 351–2,605; the range in sample size for the control group was 140–2,315. For the non-CCS studies, the total sample size including patients in both the intervention and control groups was at least 9,369.

All 13 studies evaluated patients in the intensive care unit (ICU). The Holzmann-Pazgal study⁴² focused its intervention on the pediatric ICU (PICU). The Blumberg study⁴⁵ also evaluated patients in a pediatric oncology unit.

The MRSA screening interventions could be divided into two general categories: multicomponent MRSA screening interventions or MRSA screening alone. The interventions in both good quality studies^{28, 43} consisted of MRSA screening alone. The fair quality study⁴¹ consisted of a multicomponent intervention. For the study by Gould et al.,⁴¹ the intervention consisted of surveillance cultures of the nares, throat, axillae, and groin on admission to the ICU, decolonization for all patients (with intranasal antimicrobials and topical antimicrobials), isolation, decolonization for MRSA-positive patients, and barrier nursing for MRSA-positive patients. Of the poor quality studies, two^{27, 44} were multicomponent interventions and one⁴² consisted of screening for MRSA carriage alone. The intervention from Huang and colleagues²⁷ included four sequential interventions: 1) a campaign to increase sterile barrier precautions during central venous catheter placement; 2) the hospitalwide institution of alcohol-based hand rubs; 3) a hand hygiene campaign; and 4) nasal surveillance for MRSA in all ICU patients on admission and weekly throughout the ICU stay. The intervention from Raineri et al.,⁴⁴ included two interventions. The first intervention included active surveillance for MRSA (a nasal swab on admission to the ICU and every 3 days throughout the ICU stay), contact precautions (gloves and hand hygiene, with gowns and masks reserved for procedures at risk for MRSA transmission),

decolonization of carriers (with intranasal antimicrobials and topical antimicrobials), repeat testing after treatment, and additional treatment for those patients who continued to test positive. Staff education was provided throughout the intervention. The second intervention included all of the components of the first intervention, as well as the movement of the ICU to a new ward where isolation or cohorting could be performed.

Of the studies that did not use statistical methods to control for confounders and/or secular trends (non-CCS studies), three^{45, 48, 51} were multicomponent interventions, and four^{46, 47, 49, 50} consisted of screening for MRSA-carriage alone. One⁴⁸ of the non-CCS studies included two interventions. For the study by de la Cal et al.,⁴⁸ the first intervention consisted of surveillance samples from the nose, throat, rectum, tracheostomy and pressure sores, on admission to the ICU and weekly throughout the ICU stay. Enteral vancomycin was administered to those found to be MRSA positive. The second intervention also included surveillance samples from the nose, throat, rectum, tracheostomy, and pressure sores, on admission to the ICU and weekly throughout the ICU stay. In addition, all patients expected to require mechanical ventilation for three or more days received enteral vancomycin and selective digestive decontamination with oral and intravenous antibiotics. In addition, vancomycin paste was administered topically to the oropharynx, tracheostomy site, and pressure sores 4 times a day. Vancomycin solution was administered via nasogastric tube 4 times a day. Patients were washed with a topical antimicrobial solution twice a week.

The Souweine study⁵¹ used an intervention that included surveillance cultures (on admission to the ICU, weekly throughout the ICU stay, and at discharge from the ICU), isolation procedures (handwashing, gown and gloves, cleansing patients), attempted eradication of MRSA nasal carriage with mupirocin, and staff education. The Blumberg study⁴⁵ also utilized a multicomponent intervention. This intervention included screening of staff at study onset and six months later, screening of patients at study onset followed by sampling of new patients three times a week, decolonization and repeat assays.

Of the good quality studies, the Robicsek study²⁸ utilized PCR to screen patients for MRSA and the Huskins study⁴³ utilized culture. The fair quality study utilized culture to screen patients for MRSA.⁴¹ Of the poor quality studies, all three^{27, 42, 44} utilized culture to screen patients for MRSA. Of the studies that did not use statistical methods to attempt to control for confounders and/or secular trends (non-CCS studies) five utilized culture to screen patients for MRSA,^{45-48, 51} one⁵⁰ utilized PCR to screen patients for MRSA, and one⁴⁹ utilized culture to screen some patients for MRSA and PCR to screen other patients for MRSA.

For all of the studies, the control condition consisted of no screening.

The primary outcomes for the majority of the studies included health care-associated MRSA acquisition (either colonization, infection or both colonization and infection). There were several distinctive primary outcomes of interest. For the Huskins study,⁴³ the primary outcome was the ICU-level incidence of new events of colonization or infection with MRSA or vancomycin-resistant *Enterococcus* (VRE). The inclusion of VRE was unusual among the 13 studies. Almost all of the studies focused on outcomes that were documented in the ICU. However, for the Robicsek study,²⁸ the primary outcome was the aggregate rate of MRSA infection in the hospital and for the Simmons study,⁵⁰ the primary outcomes were the ICU-acquired MRSA rate, and the hospital-wide MRSA rate. The Blumberg study⁴⁵ included the identification and treatment of MRSA-positive staff and patients as a primary outcome of interest. For the Huang study,²⁷ the primary outcome was rates of MRSA bacteremia.

Of the studies of fair or good quality, the Huskins study⁴³ and the Gould study⁴¹ recommended actions for patients in the intervention group before test results were known, but no actions for patients in the control group before test results were known. The Huskins study⁴³ recommended universal gloving and contact precautions for those patients infected or colonized with MRSA or VRE during the prior year. The Gould study⁴¹ recommended topical and intranasal antimicrobials while awaiting test results. In contrast, the Robicsek study²⁸ recommended no action for patients in either the intervention group or the control group before test results were known. None of the poor quality studies^{42, 44} recommended action before test results were known for patients in the intervention group or the control group.

The majority of poor quality studies (four of seven) took no action before test results were known for patients in the intervention group or the control group. Two of the poor quality studies recommended actions for patients in the intervention group while awaiting test results. The Souweine study⁵¹ recommended isolation for patients transferred from another ICU while awaiting test results. For the first half of the intervention period, the Kurup study⁴⁹ recommended no action for patients while awaiting test results; in the second half of the intervention period however, this study recommended topical antimicrobial washes for patients while awaiting test results.

Once a patient was found to be MRSA-positive, all of the good quality^{28, 43} and fair quality studies^{42, 43} recommended the same action for these patients in the intervention group as for those in the control group. All of these studies^{28, 41-43} recommended isolation and barrier precautions. In addition, the Robicsek study²⁸ recommended dedicated equipment for staff use. Of the poor quality studies, only one⁴² recommended the same action for MRSA-positive patients in the intervention group as in the control group. The Holzman-Pazgal study⁴² recommended isolation and barrier precautions for MRSA-positive patients in both the intervention and control groups. In contrast, two^{27, 44} of the poor quality studies recommended different actions for MRSA-positive patients in the intervention and control groups. Huang et al.,²⁷ recommended contact precautions for MRSA-positive patients in the intervention group and no action for MRSA-positive patients in the control group. Raineri et al.,⁴⁴ recommended contact precautions (hand hygiene and gloves; gowns and masks when performing procedures at risk for MRSA transmission), intranasal and topical antimicrobials, and repeat assays for MRSA-positive patients in the first and second intervention groups. In addition, this study⁴⁴ recommended isolation and cohorting for MRSA-positive patients in the second intervention group. No action was recommended for MRSA-positive patients in the control group.⁴⁴

None of the seven studies that did not use statistical methods to attempt to control for confounding and/or secular trends (non-CCS studies) recommended precisely the same action for MRSA-positive patients in the intervention group as in the control group. Two of the non-CCS studies^{47, 50} recommended similar actions for MRSA-positive patients in the intervention and control groups. The Clancy study⁴⁷ recommended isolation or cohorting, barrier precautions, handwashing compliance checks, contact isolation compliance checks, and repeat assays for MRSA-positive patients in the intervention group. Isolation or cohorting and barrier precautions were recommended for MRSA-positive patients in the control group.⁴⁷ In another non-CCS study, Simmons and colleagues⁵⁰ recommended contact isolation, potential decolonization (with intranasal antimicrobials), and repeat assays for MRSA-positive patients in the intervention group. Contact isolation, potential decolonization (type unspecified), and repeat assays were recommended for MRSA-positive patients in the control group. Five^{45, 46, 48, 49, 51} of the seven non-CCS studies recommended different interventions for MRSA-positive patients in the

intervention group than in the control group. de la Cal et al.,⁴⁸ recommended isolation or cohorting, barrier precautions, topical antimicrobials, oral or intravenous antimicrobials, and hand washing for MRSA-positive patients in the intervention group. Isolation or cohorting, barrier precautions and hand washing were recommended for MRSA-positive patients in the control group.⁴⁸ Boyce et al.,⁴⁶ recommended contact precautions for MRSA-positive patients in the intervention group, but no intervention was recommended for MRSA-positive patients in the control group.

Souweine et al.,⁵¹ recommended isolation or cohorting, barrier precautions, intranasal antimicrobials, topical antimicrobial washes, hand washing, and repeat assays for MRSA-positive patients in the intervention group. In addition, all soiled articles, moist body substances, and waste were wrapped in double bags before removal from patient rooms.⁵¹ No interventions were recommended for MRSA-positive patients in the control group.⁵¹ Blumberg et al.,⁴⁵ recommended isolation or cohorting for patients admitted to the ICU (not for those admitted to the pediatric oncology unit), barrier precautions, intranasal antimicrobials, topical antimicrobial washes, and alcohol-based hand rubs for MRSA-positive patients in the intervention group. In addition, cohort nursing was attempted for MRSA-positive patients in the intervention group.⁴⁵ No interventions were recommended for MRSA-positive patients in the control group.⁴⁵ Kurup et al.,⁴⁹ recommended isolation or cohorting, topical antimicrobial washes, and repeat assays for MRSA-positive patients in the intervention group. No interventions were recommended for MRSA-positive patients in the control group.⁴⁹

Of the studies of good, fair or poor quality, four of the six reported test turnaround time.^{27, 28, 42, 43} The Robicsek study described the turnaround time as 2.5 days²⁸ and the Huskins study as 5.2 days \pm 1.4 days.⁴³ The Huang study²⁷ and Holzmänn-Pazgal study⁴² described test turnaround time as two days. One⁵⁰ of the non-CCS studies reported test turnaround time. The Simmons study⁵⁰ described the turnaround time as 12 hours.

Results by Outcome

Health Care-Associated MRSA Acquisition

Health care-associated MRSA acquisition is measured by MRSA colonization or by MRSA colonization or infection that is health care-associated, rather than imported. One good quality study,⁴³ three poor quality studies,^{27, 42, 44} and one study⁴⁸ that did not attempt to use statistical methods to attempt to control for confounding and/or secular trends (non-CCS study) addressed this outcome. The Huskins study⁴³, a good quality study, was a cluster randomized controlled trial and the poor quality studies^{27, 42, 44, 48} and the non-CCS study⁴⁸ utilized quasi-experimental designs.

The definitions of hospital-associated infection differed from study to study. The Huskins study⁴³ defined hospital-associated as a positive-MRSA sample 2 or more days after admission to the ICU in a patient whose ICU length of stay was at least 3 days with no history of colonization or infection in the prior year, no positive clinical culture within two days after admission to the ICU, and a negative surveillance culture within 2 days of admission to the ICU. The Huang study²⁷ defined hospital-associated infection as a first-ever MRSA-positive sample more than 2 days after admission if not previously hospitalized at that institution within the prior year, or at any time during the hospital admission if hospitalized at that institution in the prior year. The Raineri study⁴⁴ defined ICU-associated as a MRSA-positive isolate identified at least 48 hours after admission in patients with no previous MRSA isolate documented and at least one

negative screen from the ICU. The Holzmann-Pazgal study⁴² defined hospital-acquired as the initial isolation of MRSA in any specimen obtained more than 48 hours after admission. The non-CCS study⁴⁸ defined colonization or infection as hospital-associated if the MRSA-positive sample was obtained more than 72 hours after admission.

Compared to no screening, the good quality study⁴³ found a non-statistically significant increase in health care-associated MRSA colonization or infection with screening for MRSA-carriage in the ICU. However, the poor quality studies^{27, 42, 44, 48} found a statistically significant reduction in hospital-acquired MRSA colonization or infection with screening for MRSA-carriage in the ICU as did the non-CCS study.⁴⁸

Strength of Evidence

Four studies^{27, 42-44} that used statistical methods to attempt to control for confounding and/or secular trends (CCS-studies) evaluated the impact of screening for MRSA-carriage in ICU patients on health care-associated MRSA transmission. One of these studies was a good quality, cluster randomized controlled trial⁴³, while the other three studies were quasi-experimental before/after studies of poor quality. For the group of studies, the risk of bias was deemed to be moderate because of the three studies that utilized before/after designs and did not adequately analyze for confounding or secular trends. With targeted screening, the Huskins study⁴³ found a non-statistically significant increase in health care-associated MRSA colonization or infection. However, the Huang,²⁷ Raineri⁴⁴ and Holzmann-Pazgal⁴² studies found statistically significant reductions in health care-associated colonization or infection. Because the studies found divergent results, the findings are inconsistent. The studies assessed hospital-associated transmission by measuring both colonization and infection, an indirect outcome measure by definition. The effect of screening for MRSA-carriage in ICU patients was judged to be imprecise, given the lack of consistency of the data. The strength of evidence for screening of ICU patients for MRSA-carriage on MRSA acquisition was found to be insufficient based on the moderate risk of bias, inconsistent and imprecise results.

Comment, Non-CCS Studies

One study⁴⁸ that did not attempt to use statistical methods to control for confounders and/or secular trends (non-CCS study) evaluated the impact of screening for MRSA-carriage in the ICU on health care-associated MRSA transmission. With screening, the non-CCS study by de la Cal and colleagues⁴⁸ found a statistically significant reduction in hospital-acquired MRSA colonization or infection with screening of ICU patients for MRSA-carriage.

Health Care-Associated MRSA Infection, Irrespective of Site

One good quality study²⁸ and four^{46, 47, 49, 50} studies that did not use statistical methods to attempt to control for confounders and/or secular trends (non-CCS studies) addressed this outcome. The definitions of hospital-associated MRSA infections were diverse. The Robicsek study²⁸ defined infection as the sum total of all bloodstream infections (positive blood culture in the absence of a positive clinical culture from another site), respiratory tract infections (positive respiratory culture, compatible chest radiograph and decision to treat), urinary tract infections (positive urine culture and decision to treat or growth of more than 100,000 colony-forming units/mL plus at least 50 leukocytes per high-power field), and surgical site infections (positive culture of a surgical site). Infections were considered to be hospital associated if they occurred more than 2 days after admission and within 30 days of discharge. The Clancy study⁴⁷ defined

hospital-associated infection as the first clinical specimen (ordered to evaluate for infection) positive for MRSA more than 72 hours after admission. The Simmons study⁵⁰ defined hospital-associated MRSA rates using the National Nosocomial Infection Surveillance system. The study by Boyce and colleagues⁴⁶ utilized CDC criteria to define hospital-associated infection. Patients were considered to have a hospital-associated MRSA infection if the infection began more than 3 days after admission to the ICU in a patient with no prior history of MRSA. The Kurup study⁴⁹ utilized CDC criteria to define infection. Patients were considered to have a hospital-associated MRSA infection if the first MRSA isolate from any source was recovered more than 24 hours after ICU admission in a patient with no known prior history of MRSA.⁴⁹

The impact of screening for MRSA-carriage in the ICU on acquired MRSA infection was mixed. Compared to no screening, the good quality study²⁸ found a reduction in hospital-acquired MRSA infection with screening of ICU patients for MRSA-carriage (rate difference - 1.46 [95 percent CI: -3.43 to 0.51]); however, this reduction was not statistically significant. In addition, compared to no screening, one⁴⁹ of the non-CCS studies found no statistically significant reduction in hospital-acquired MRSA infection with screening of ICU patients for MRSA-carriage. However, two^{46,50} of the non-CCS studies found a statistically significant reduction in hospital-acquired MRSA infection with screening of ICU patients for MRSA-carriage. In addition, compared to no screening, one⁴⁷ of the non-CCS studies found a statistically significant reduction in hospital-acquired MRSA infection in the SICU, as well as in the pooled analysis of the SICU, MICU, and wards with screening for MRSA in the ICU. However, this same study⁴⁷ found no statistically significant reduction in hospital-acquired MRSA infection in the MICU or the wards.⁴⁷

Strength of Evidence

One study²⁸ that used statistical methods to attempt to control for confounding and/or secular trends addressed this outcome. The risk of bias for this good quality quasi-experimental study was judged to be low.²⁸ With screening, the study²⁸ found a reduction in health care-associated MRSA infection (rate difference -1.46; 95 percent CI: -3.43 to 0.51); however, this reduction was not statistically significant. As only one CCS study evaluated this outcome, the consistency of the findings is unknown. MRSA infection is a direct outcome measure. The study findings were judged to be imprecise because data were available from only one study. The strength of evidence for the effect of screening of ICU patients on health care-associated MRSA infection was judged to be insufficient, based on the lack of statistically significant findings of a single, well conducted, quasi-experimental study.²⁸

Comment, Non-CCS Studies

Four studies that did not use statistical methods to attempt to control for confounding and/or secular trends (non-CCS studies) evaluated the impact of screening for MRSA-carriage in the ICU on health care-associated MRSA infection, regardless of site.^{46, 47, 49, 50} Compared to no screening, all of these studies demonstrated a reduction in health care-associated MRSA infection with screening of ICU patients for MRSA-carriage. For two^{46, 50} of these studies, the reduction was statistically significant, while for one⁴⁹ of the studies it was not. For another⁴⁷ of the non-CCS studies, the reduction was statistically significant in some settings, but not in others.

Health Care-Associated MRSA Bacteremia or Bloodstream Infection

One good quality study²⁸, one poor quality study,²⁷ and one study⁴⁸ that did not use statistical methods to attempt to control for confounders and/or secular trends (non-CCS study) addressed this outcome. The good quality study²⁸ by Robicsek, which also reported MRSA infection irrespective of site, defined bloodstream infection as a positive blood culture in the absence of a positive clinical culture from another site. Infections were considered to be hospital associated if they occurred more than 2 days after admission and within 30 days of discharge. The poor quality study²⁷ defined hospital-associated cases as those with a first-ever MRSA-positive blood culture more than 2 days after admission if not previously hospitalized at that institution within the prior year, or at any time during the hospital admission if hospitalized at that institution in the prior year. The non-CCS study⁴⁸ used the term “positive diagnostic sample” rather than infection to avoid bias in the definition of some infections (e.g., ventilator-associated pneumonia). Diagnostic samples (those performed for reasons other than surveillance) were considered hospital associated if the sample was obtained more than 72 hours after admission.

The good quality study²⁸ found no statistically significant reduction in the rate of acquired MRSA bloodstream infection with screening for MRSA in the ICU compared to no screening for MRSA. Compared to no screening for MRSA, the poor quality study²⁷ found a statistically significant reduction in the trend of the hospital-associated incidence density of MRSA bloodstream infection in the ICU, non-ICU settings, and hospital wide with screening for MRSA in the ICU. In addition, this study²⁷ found a statistically significant reduction in the trend of the hospital-associated incidence of MRSA bloodstream infection hospital wide with screening for MRSA in the ICU. The non-CCS study⁴⁸ found a statistically significant reduction in the rate of acquired MRSA bacteremia (including bloodstream infection) with screening for MRSA in the ICU compared to no screening for MRSA.

Strength of Evidence

The strength of evidence for the effect of screening of ICU patients for MRSA-carriage on health care-associated MRSA bacteremia or bloodstream infection was judged to be insufficient, based on the moderate risk of bias, lack of consistency and lack of precision. Of the two CCS studies one was a good quality, quasi-experimental limited time series design²⁸ and the other was a poor quality quasi-experimental before/after study.²⁷ For the group of studies, the risk of bias was deemed to be moderate because of the poor quality study that did not report baseline group characteristics or whether its analysis controlled for confounders. While both studies reported a reduction in MRSA bacteremia or bloodstream infection with screening, the good quality study had nonsignificant results. Thus, the findings were judged to be inconsistent. MRSA infection is a direct outcome measure. The study findings were judged to be imprecise because of the lack of consistency of study findings.

Comment, Non-CCS Studies

One non-CCS study⁴⁸ evaluated the impact of screening for MRSA-carriage in the ICU on health care-associated MRSA bacteremia or bloodstream infection. Compared to no screening, this study⁴⁸ found a statistically significant reduction in the rate of acquired MRSA bacteremia (including bloodstream infection) with screening for MRSA in the ICU.

Health Care-Associated MRSA Surgical Site Infection

One good quality study²⁸ addressed this outcome. The Robicsek study found a reduction in hospital-associated surgical site infections with screening in the ICU compared to no screening; however, this reduction was not statistically significant.²⁸ With screening, the study found no statistically significant reduction in health care-associated MRSA infection (rate difference - 0.77; 95 percent CI: -1.85 to 0.30).

Strength of Evidence

One good quality, quasi-experimental study evaluated this outcome.²⁸ The risk of bias for this study was judged to be low. As only one study evaluated this outcome, the consistency of the findings is unknown. MRSA infection is a direct outcome measure. The study findings were judged to be imprecise because data were available from only one study. The strength of evidence for the effect of screening of ICU patients on health care-associated MRSA infection was judged to be insufficient, based on the lack of statistically significant findings from a single, well conducted, quasi-experimental study.²⁸

Morbidity, Mortality, Harms and Resource Utilization

Results

No studies addressed these outcomes.

Strength of Evidence for Screening of ICU Patients for MRSA-Carriage on Morbidity, Mortality, Harms and Resource Utilization

Because no studies addressed these outcomes, the strength of evidence to evaluate the effect of screening of ICU patients for MRSA-carriage on morbidity, mortality, harms or resource utilization was judged to be insufficient.

Summary Strength of Evidence Across Key Question 3A

A summary of the main syntheses for this question follows in Table 7.

Table 7. Strength of evidence for studies comparing screening of ICU patients versus no screening

Strategies Compared	Outcome	No of Studies§	Risk of Bias	Consistency	Directness	Precision	Overall Grade
Screening of ICU Risk Pts Vs No Screening	MRSA Transmission	1 RCT (N=4,056) (Huskins 2011 ⁴³) 3 QEX (N=3097) (Holzmann-Pazgal 2011 ⁴²) (N=Unclear) (Huang 2006 ²⁷) (N=21,754; 166,877 [‡]) (Raineri 2007 ⁴⁴)	Moderate	Inconsistent	Indirect	Imprecise	Insufficient
	MRSA Infection	1 QEX (N=Unclear) (Robicsek 2008 ²⁸)	Low	Unknown	Direct	Imprecise	Insufficient
	MRSA Bacteremia or Blood Stream Infection	2 QEX (N=Unclear) (Robicsek 2008 ²⁸) (N=Unclear) (Huang 2006 ²⁷)	Moderate	Inconsistent	Direct	Imprecise	Insufficient
	MRSA Surgical Site Infection	1 QEX (N=Unclear) (Robicsek 2008 ²⁸)	Low	Unknown	Direct	Imprecise	Insufficient

[‡] Patient days; ICU: Intensive care unit; NA: Not applicable; QEX: Quasi-experimental; RCT: Randomized controlled trial

[§] CCS studies

Key Question 3B

Screening of Surgical Patients for MRSA-Carriage Compared to No Screening

Overview

This section describes the literature that evaluates screening surgical patients for MRSA-carriage compared to no screening. After an overview of the literature, the results are described for each outcome measure: MRSA acquisition, MRSA infection, morbidity, mortality, harms, and resource utilization. Within the category of MRSA infection, we also include results for MRSA surgical site infection, as some studies present this outcome rather than the broader outcome of MRSA infection, irrespective of site. The emphasis in this chapter is on outcomes describing health care-associated events. Health care-associated outcomes are the primary outcomes of interest because screening for MRSA-carriage in health care facilities is most proximately expected to impact health care-associated MRSA transmission and infection. Strength of evidence syntheses presented here include only studies that attempted to control for

confounding and/or secular trends (CCS studies). Because studies that use simple two-group statistical analyses cannot support causal inferences, those studies that did not attempt to control for confounding and/or secular trends (non-CCS studies) were excluded from the strength of evidence analysis. Following the strength of evidence syntheses, we comment on the pattern of results seen in studies that did not attempt to control for confounding and/or secular trends (non-CCS studies). Table 8 summarizes the studies reviewed for Key Question 3B.

Table 8. KQ3B: Health care-associated MRSA acquisition, infection, or surgical site infection

Outcome	Study	Quality	Statistical Result	Synthesis
HCA acquisition	Harbarth ²⁹	Good	NS ↑	SOE=insufficient
HCA infection	Harbarth ²⁹	Good	NS	SOE=insufficient
	Muder ⁵²	Poor	SS ↓	
	Sankar ⁷⁹	Non-CCS	SS ↓	
HCA surgical site infection	Harbarth ²⁹	Good	NS ↑	SOE=insufficient Comment: Results from non-CCS studies more consistently favorable than CCS studies, however causal inference is not possible
	Muder ⁵²	Poor	SS ↓	
	Jog ⁵³	Non-CCS	SS ↓	
	Kim ⁵⁴	Non-CCS	SS ↓	
	Lipke ⁵⁵	Non-CCS	SS ↓	
	Malde ⁵⁶	Non-CCS	SS ↓	
	Nixon ⁵⁷	Non-CCS	SS ↓	
	Pofahl ⁵⁸	Non-CCS	NS ↓	
	Sott ⁵⁹	Non-CCS	NS ↓	
	Supriya ⁶⁰	Non-CCS	SS ↓	
	Thomas ⁶¹	Non-CCS	SS ↓	
Walsh ⁶²	Non-CCS	SS ↓		

HCA = Health care-associated; KQ = Key Question; NS = nonsignificant; SOE = strength of evidence; SS = statistically significant

Thirteen studies described screening surgical patients for MRSA compared to no screening. Two^{29,52} of the studies attempted to use statistical methods to control for confounding and/or secular trends; eleven did not. The Harbarth study²⁹ was a prospective, interventional cohort study with crossover design. This study²⁹ was judged to be of good quality overall. The Muder study⁵² was a quasi-experimental before/after study design. This study⁵² was judged to be of poor quality, as it did not report baseline group characteristics, addressing autocorrelation, and whether its analysis controlled for confounders. Of the 11 studies that did not use statistical methods to attempt to control for confounding and/or secular trends, all employed a quasi-experimental before/after study design.

All thirteen studies evaluated patients admitted to the hospital for a surgical procedure. There was considerable variation in the type of surgical patient targeted for screening. Three studies^{29,52,58} included patients across a broad and inclusive range of surgeries. Four studies^{54,57,59,79} focused on orthopedic surgery patients and two studies^{53,62} focused on cardiothoracic surgery patients. The remaining four studies included very specific surgical patient populations (e.g., head and neck cancer). Two^{56,57} of the studies specifically included protocols for patients admitted for emergency surgery. The 13 studies were all conducted in Europe or the U.S. (one Swiss study, five U.S. studies, and seven U.K. studies).

The MRSA screening protocol varied between studies, as did the infection control practices that accompanied screening. In terms of the MRSA screening protocol, four studies^{29,53,54,58} utilized PCR to screen for MRSA and the remaining nine studies utilized culture. While waiting for screening test results, three studies^{52,56,60} utilized contact isolation and two studies^{53,57} initiated MRSA eradication by topical antimicrobial wash and/or intranasal antibiotics. The

remaining eight studies did not initiate special procedures while waiting for screening results. Once patients were found to be MRSA positive, studies varied in the number of interventions applied. The most intensive combination included four elements (contact isolation, intranasal antibiotics, topical antimicrobials, and adjustment in systemic antibiotics) at the time of surgery for five studies.^{29, 53, 54, 56, 61} Two studies^{59, 79} used a protocol with intranasal antibiotics, topical antimicrobials, and adjustment in systemic antibiotics, but did not describe contact isolation procedures. The study by Nixon⁵⁷ used a combination of contact isolation, topic antimicrobial wash, and adjusted systemic antibiotics. The remaining 5 studies used two or fewer procedures in various combinations.

The control arms of each of the thirteen studies included no systematic screening for MRSA. However, the infection control practices of the control groups did vary considerably especially in cases where an individual with MRSA was identified during routine care. In the study by Harbarth et al.,²⁹ control period patients found to have MRSA were treated just as they were in the intervention periods with a combination of isolation, intranasal antibiotics, topical antimicrobial wash, and adjusted use of systemic antibiotic prophylaxis. In the study by Nixon,⁵⁷ again, intranasal antibiotics and topic antimicrobial wash were used. Walsh and colleagues⁶² isolated patients with MRSA and adjusted the use of systemic antibiotic prophylaxis. Three other studies^{53, 58, 60} described isolating or cohorting patients found to have MRSA during control periods. Most studies provided very little specific information about routine care for patients without MRSA during control periods.

Study durations were divided into control periods and intervention periods of varying lengths. Five studies had observation periods of multiple years.^{52, 56, 58, 61, 62} Two studies^{29, 57} had observation periods less than 1 year. The remaining six studies had observation periods of 1 year. Seven studies^{53-55, 57, 58, 61, 62} identified MRSA surgical site infection (SSI) rates as the primary endpoint of interest. Three studies^{29, 60, 79} used broader MRSA endpoints such as MRSA infection rates. One study⁵² identified MRSA infection rates and MRSA SSI as the primary endpoints. Malde et al.,⁵⁶ identified wound infection and major limb amputation as primary endpoints. Sott et al.,⁵⁹ identified postoperative sepsis associated with MRSA as the primary endpoint.

Results by Outcome

Health Care-Associated MRSA Acquisition

Health care-associated MRSA acquisition is measured by MRSA colonization or by MRSA colonization or infection that is health care-associated, rather than imported.

Results

Only the study by Harbarth et al.,²⁹ a good quality study with a crossover design, specifically evaluated the incidence of nosocomial MRSA acquisition which included both new infection and colonization. With targeted screening of surgical patients, Harbarth et al.,²⁹ found an increase in the rate ratio for MRSA acquisition to 1.1, but the confidence intervals were wide and not significant (95 percent CI: 0.8-1.4).

Strength of Evidence

The strength of evidence for the effect of screening of surgical patients on health care-associated MRSA acquisition was judged to be insufficient based on the nonsignificant findings of a single, well conducted, quasi-experimental study.²⁹ The study was felt to have a low risk of bias, but the consistency of its finding is unknown. The study assessed hospital-associated transmission by measuring both colonization and infection, an indirect outcome measure by definition. The study findings were judged to be imprecise because data were available from only one study.

Health Care-Associated MRSA Infection, Irrespective of Site

Three studies reported the effect of MRSA screening in surgical wards on health care-associated MRSA infection. Two^{29, 52} of these studies used statistical methods to attempt to control for confounders and/or secular trends and one⁷⁹ did not.

For the Harbarth study,²⁹ infection was defined as hospital-acquired if it occurred more than 48 hours after admission and less than 72 hours after discharge from the surgical service. This endpoint was assessed among patients with previously known or newly identified MRSA carriage. With screening of surgical patients, Harbarth and colleagues²⁹ found no reduction in the rate of acquired MRSA infection. In fact, the rate of MRSA infection was slightly higher in the intervention group than in the control group (1.11/1000 patient days vs. 0.91/1000 patient days).²⁹ This analysis adjusted for colonization pressure, antibiotic selection pressure, use of alcohol-based hand rubs, temporal trends, and clustering.

For the Muder study,⁵² health care-associated MRSA infection was based on CDC definitions. Using a segmented Poisson regression, Muder and colleagues⁵² found that MRSA infection steadily declined in the intensive care unit (1.56/1000 patient days pre, 0.63/1000 patient days post) and the surgical unit (5.45/1000 patient days pre, 1.35/1000 patient days post).

Sankar et al.,⁷⁹ did label MRSA outcomes as hospital-acquired infection but did not provide a specific definition. Sankar et al.,⁷⁹ reported that the proportion of patients with MRSA infection declined from 2.4 percent (4/164) to 0.0 percent (0/231) in an unadjusted analysis.

Strength of Evidence

The strength of evidence for the effect of screening for MRSA-carriage in surgical patients on health care-associated MRSA infection was judged to be insufficient based on the moderate risk of bias, lack of consistency and lack of precision of the findings. Two CCS studies evaluated the impact of screening for MRSA-carriage on surgical patients on health care-associated MRSA infection.^{29, 52} The Harbarth study²⁹ was a prospective, interventional cohort study with crossover design. This study²⁹ was judged to be of good quality overall. The Muder study⁵² was a quasi-experimental before/after study design. This study⁵² was judged to be of poor quality, as it did

not report baseline group characteristics, addressing autocorrelation, or whether its analysis controlled for confounders. For the group of studies, the risk of bias was deemed to be moderate because of the poor quality study that did not report baseline group characteristics, addressing autocorrelation, or whether its analysis controlled for confounders. With screening in surgical patients, Harbarth and colleagues found no reduction in MRSA infection, in fact the rate was slightly higher.²⁹ On the other hand, the Muder study⁵² found that with screening, MRSA infection steadily declined in the intensive care unit. The results are inconsistent. MRSA infection is a direct outcome. The evidence was judged to be imprecise.

Comments, Non-CCS Studies

One non-CCS study⁷⁹ evaluated the impact of screening for MRSA-carriage in surgical patients on health care-associated MRSA infection. Compared to no screening, this study⁷⁹ found a statistically significant reduction in the rate of health care-associated MRSA infection with screening for MRSA in surgical patients

MRSA Surgical Site Infection

Twelve of 13 surgical ward studies reported on MRSA surgical site infection. For three studies, surgical site infection (SSI) due to MRSA was attributed to surgery if it was documented within 30 days following the surgical procedure.^{29, 52, 54} These three studies also defined MRSA acquisition with some specificity. The Harbarth study,²⁹ a good quality study, found no difference in the rate of MRSA surgical site infection after adjustment for covariates. With screening in surgical patients, Harbarth and colleagues found a nonsignificant increase in MRSA surgical site infection (rate ratio 1.2; 95 percent CI: 0.8-1.7). The Muder study,⁵² a poor quality CCS study, found no difference in the trends for MRSA SSI (1.91 percent control; 1.91 percent intervention; $p=0.60$ for trend).⁵² On the other hand, Kim and colleagues⁵⁴, in a non-CCS study, found a significant reduction in the proportion of surgical patients experiencing MRSA SSI.

The remaining nine of the 12 surgical ward studies, all non-CCS studies, that addressed MRSA SSI varied in their specific definition of a MRSA surgical site infection. Three of the studies mentioned criteria for identifying MRSA SSI such as the Nosocomial Infection Surveillance System criteria.^{55, 58, 62} Three studies^{57, 59, 61} required both signs of an infected wound and a positive wound swab for MRSA to identify a MRSA SSI. Two studies^{53, 60} did not provide a definition for MRSA surgical site infection. One study⁵⁶ used a markedly different definition of MRSA surgical site infection than the other studies. In this study, investigators quantified the rate of wound infections among patients with known MRSA colonization or infection.

In all nine of these studies, the point estimates for MRSA SSI rates were lower in screening periods in comparison to control periods. In six out of nine studies, these differences in rates were statistically significant. For two studies,^{58, 59} the reductions were not statistically significant. In the Nixon⁵⁷ and Malde⁵⁶ studies, MRSA SSI rates were lower during screening periods for both emergent and elective surgery patients.

Strength of Evidence

The strength of evidence for the effect of screening for MRSA-carriage in surgical patients on MRSA surgical site infection was judged to be insufficient based on the moderate risk of bias and lack of precision of study findings. Two CCS studies evaluated the impact of screening for MRSA-carriage on surgical patients on health care-associated MRSA infection.^{29, 52} The

Harbarth study²⁹ was a prospective, interventional cohort study with crossover design. This study²⁹ was judged to be of good quality overall. The Muder study⁵² was a quasi-experimental before/after study design. This study⁵² was judged to be of poor quality, as it did not report baseline group characteristics, addressing autocorrelation, or whether its analysis controlled for confounders. The results are consistent, as neither study found a reduction in MRSA surgical site infection with screening for MRSA-carriage in surgical patients. MRSA surgical site infection is a direct outcome. The evidence was judged to be imprecise because of the lack of statistical significance for both studies.

Comment, Non-CCS Studies

Ten non-CCS studies evaluated the impact of screening for MRSA-carriage in surgical patients on health care-associated MRSA infection. Compared to no screening, all of the non-CCS studies found a reduction in the rate of MRSA SSI with screening for MRSA-carriage in surgical patients. For six of these studies, the reduction was statistically significant.^{53, 54, 56, 60-62} For one study⁵⁷ the reduction was statistically significant for one outcome, but not for another; and for three studies,^{55, 58, 59} the reduction was not statistically significant.

Morbidity

No studies that used statistical methods to attempt to control for confounders and/or secular trends evaluated the impact of screening for MRSA-carriage in surgical patients on morbidity. However, one non-CCS quasi-experimental study formally evaluated MRSA morbidity. Malde and colleagues⁵⁶ were specifically interested in major limb amputations among patients who were found to have MRSA colonization or infection. From the Malde study,⁵⁶ amputation rates declined significantly from 27.8 percent to 9.0 percent for patients with elective admissions. For patients with emergency admissions, the rate of amputation did decline from 50.0 percent to 38.8 percent, but this was not statistically significant.

Strength of Evidence

Because no studies that used statistical methods to attempt to control for confounders and/or secular trends addressed this outcome, the strength of evidence to evaluate the effect of screening for MRSA-carriage in surgical patients on morbidity was judged to be insufficient.

Comment, Non-CCS Studies

One study that did not use statistical methods to attempt to control for confounders and/or secular trends addressed this outcome. With screening, Malde and colleagues⁵⁶ found a statistically significant reduction in amputation rates from 27.8 percent to 9.0 percent for patients admitted electively. For patients with emergency admissions, the rate of amputation declined from 50.0 percent to 38.8 percent, but this was not statistically significant.⁵⁶

Mortality

Results

No studies that used statistical methods to attempt to control for confounders and/or secular trends evaluated the impact of screening for MRSA-carriage in surgical patients on mortality.

However, one non-CCS quasi-experimental study reported on mortality rates among patients with MRSA colonization or infection.

In the study by Malde and colleagues⁵⁶ for both elective and emergency admissions, mortality rates for patients with MRSA declined with screening.⁵⁶ However, these reductions were not statistically significant.

Strength of Evidence

Because no studies that used statistical methods to attempt to control for confounders and/or secular trends addressed this outcome, the strength of evidence to evaluate the effect of screening for MRSA-carriage in surgical patients on mortality was judged to be insufficient.

Comment, Non-CCS Studies

One study⁵⁶ that did not use statistical methods to attempt to control for confounders and/or secular trends addressed this outcome. With screening, Malde and colleagues⁵⁶ found reductions in mortality for patients admitted electively or emergently. However, these reductions were not statistically significant.⁵⁶

Harms

Results

No studies addressed this outcome.

Strength of Evidence for Screening of Surgical Patients for MRSA-Carriage on Harms

Because no studies addressed this outcome, the strength of evidence to evaluate the effect of screening of surgical patients for MRSA-carriage on harms was judged to be insufficient.

Resource Utilization

Results

No studies that used statistical methods to attempt to control for confounders and/or secular trends evaluated the impact of screening for MRSA-carriage in surgical patients on resource utilization. However, one non-CCS quasi-experimental study reported the impact of screening surgical patients for MRSA carriage on resource utilization. Sankar and colleagues⁷⁹ found that with screening, the mean length of hospital stay declined by almost one day. In unadjusted analysis, this result was found to be statistically significant.⁷⁹

Strength of Evidence

Because no studies that used statistical methods to attempt to control for confounders and/or secular trends addressed this outcome, the strength of evidence to evaluate the effect of screening for MRSA-carriage in surgical patients on resource utilization was judged to be insufficient.

Comments, Non-CCS Studies

One study⁷⁹ that did not use statistical methods to attempt to control for confounders and/or secular trends addressed this outcome. With screening, Sankar and colleagues⁷⁹ found a

reduction in the mean length of hospital stay of almost one day. In unadjusted analysis, this result was found to be statistically significant.⁷⁹

Summary Strength of Evidence Across Key Question 3B

A summary of the main syntheses for this question follows in Table 9.

Table 9. Strength of evidence for studies comparing screening of surgical patients versus no screening

Strategies Compared	Outcome	No of Studies [§]	Risk of Bias	Consistency	Directness	Precision	Overall Grade
Screening of Surgical Pts Vs No Screening	MRSA Transmission	1 QEX - crossover design (N=21,754) (Harbarth 2008 ²⁹)	Low	Unknown	Indirect	Imprecise	Insufficient
	MRSA infection	1 QEX - crossover design (N=21,754) (Harbarth 2008 ²⁹) 1 QEX (N=21,449 [‡]) (Muder 2008 ⁵²)	Moderate	Inconsistent	Direct	Imprecise	Insufficient
	MRSA Surgical Site Infection	1 QEX - crossover design (N=21,754) (Harbarth 2008 ²⁹) 1 QEX (N=21,449 [‡]) (Muder 2008 ⁵²)	Moderate	Inconsistent	Direct	Imprecise	Insufficient

[‡] Patient days ;QEX: Quasi-experimental

[§]CCS Studies

Key Question 3C

Screening of High-Risk Patients for MRSA-Carriage Compared to No Screening

Overview

This section describes the literature that evaluates screening of high-risk patients for MRSA-carriage compared to no screening. After an overview of the literature, the results are described for each outcome measure: MRSA acquisition, MRSA infection, morbidity, mortality, harms, and resource utilization. Within the category of MRSA infection, we also include results for MRSA bacteremia or bloodstream infection and for MRSA surgical site infection, as some studies present these outcomes rather than the broader outcome of MRSA infection irrespective

of site. The emphasis in this chapter is on outcomes describing health care-associated events. Health care-associated outcomes are the primary outcomes of interest because screening for MRSA-carriage in health care facilities is most proximately expected to impact health care-associated MRSA transmission and infection. Strength of evidence syntheses presented here include only studies that attempted to control for confounding and/or secular trends (CCS studies). Because studies that use simple two-group statistical analyses cannot support causal inferences, those studies that did not attempt to control for confounding and/or secular trends (non-CCS studies) were excluded from the strength of evidence analysis. Following the strength of evidence syntheses, we comment on the pattern of results seen in studies that did not attempt to control for confounding and/or secular trends (non-CCS studies). Table 10 summarizes the studies reviewed for Key Question 3C.

Table 10. KQ3C: Health care-associated MRSA acquisition, infection, bacteremia, or surgical site infection

Outcome	Study	Quality	Statistical Result	Synthesis
HCA acquisition	Rodriguez-Bano ⁶⁶	Fair	NS ↓	SOE=insufficient Comment: Causal inference is not possible based on non-CCS studies
	Ellingson ⁶⁴	Poor	SS ↓	
	Salaripour ⁶⁹	Non-CCS	SS ↓	
HCA infection	Harbarth ⁶⁵	Poor	SS ↓	SOE=insufficient
	Bowler ⁶⁷	Non-CCS	SS ↓	
	Wernitz ⁷⁰	Non-CCS	SS ↓	
HCA bacteremia/ blood stream infection	Rodriguez-Bano ⁶⁶	Fair	NS	SOE=insufficient Comment: Causal inference is not possible based on non-CCS studies
	Chowers ⁶³	Poor	SS ↓	
	Ellingson ⁶⁴	Poor	SS ↓	
	Wernitz ⁷⁰	Non-CCS	SS ↓	
	Pan ⁶⁸	Non-CCS	SS ↓	
HCA surgical site infection	Harbarth ⁶⁵	Poor	SS ↓	SOE=insufficient Comment: Causal inference is not possible based on non-CCS studies
	Keshtgar ⁷⁸	Non-CCS	SS ↓	

HCA = Health care-associated; KQ = Key Question; NS = nonsignificant; SOE = strength of evidence; SS = statistically significant

Nine studies described screening of high-risk patients for MRSA-carriage compared to no screening. Four of these studies⁶³⁻⁶⁶ attempted to use statistical methods to control for confounding and/or secular trends (CCS studies) and five^{67-70, 78} did not (non-CCS studies). Of the CCS studies, one of the studies was of fair quality⁶⁶ and three⁶³⁻⁶⁵ were of poor quality. The Rodriguez-Bano⁶⁶ study was determined to be of fair quality because it used indirect control of confounders rather than statistical adjustment within the segmented regression analysis. The Chowers study⁶³ and the Ellingson study⁶⁴ were judged to be of poor quality as they did not report baseline group characteristics or whether their analysis controlled for confounders. The Harbarth study⁶⁵ was also determined to be of poor quality as it did not report baseline group characteristics, addressing autocorrelation, or whether its analysis controlled for confounders.

All nine studies employed a quasi-experimental study design. The study by Rodriguez-Bano and colleagues, which was of fair quality⁶⁶ utilized an interrupted times series design, as did the studies by Ellingson and colleagues⁶⁴ and by Chowers and colleagues,⁶³ two of the poor quality

studies. The other studies utilized a before/after study design. In terms of clinical setting, all nine studies evaluated hospitalized patients. Four of the studies took place in teaching hospitals, two in community hospitals, one in a regional referral hospital, and one in a Veterans Affairs hospital.

“Screening of high-risk patients” was defined differently across studies. The study by Rodriguez-Bano and colleagues⁶⁶ evaluated the screening of patients on high-risk wards as well as high-risk patients. Of the poor quality studies, the studies by Ellingson⁶⁴ and Harbarth⁶⁵ evaluated screening of patients on high-risk wards; and the study by Chowers,⁶³ evaluated screening of high-risk patients. Of the non-CCS studies, the study by Keshtgar⁷⁸ evaluated screening of patients on high-risk wards; the studies by Salaripour,⁶⁹ Wernitz⁷⁰ and Bowler⁶⁷ evaluated screening of high-risk patients; and the study by Pan⁶⁸ evaluated screening of patients on high-risk wards as well as high-risk patients. The studies varied in their execution of the MRSA screening protocol and the infection control practices that accompanied screening. Seven studies utilized culture to screen patients for MRSA. The Keshtgar study⁷⁸ utilized PCR to screen patients for MRSA. The Chowers study⁶³ first utilized culture and then utilized PCR to screen patients for MRSA.

The study by Rodriguez-Bano and colleagues⁶⁶ included MRSA bacteremia as a primary outcome. The other studies reported diverse primary endpoints ranging from nosocomial MRSA⁶⁹ to MRSA bloodstream infection.^{64, 68}

Of the studies that used statistical methods to attempt to control for confounders and/or secular trends (CCS studies), the studies by Rodriguez-Bano and colleagues⁶⁶ and by Chowers and colleagues⁶³ reported test turnaround time. For the Rodriguez-Bano study,⁶⁶ the reported turnaround time was described as 37 to 51 hours after culture was performed. The Chowers study⁶³ reported turnaround time as 2 to 4 days after culture was performed and 24 hours after PCR was performed. Of the non-CCS studies, one reported test turnaround time and four did not. The Keshtgar study⁷⁸ noted the time from sample collection to receipt in lab was 13.7 hours (9.78-15.1), from receipt in the lab to obtaining the result 21.8 hours (21.0-22.5), and from obtaining result to calling the service with the result 1.03 hours (0.83-1.41).

The Pan study⁶⁸ reported the compliance rate for contact precautions (203/370 patients or 55 percent overall, 62 percent for those known to be MRSA positive during the hospitalization). None of the other eight studies reported the compliance rate for contact precautions.

Beyond MRSA screening, the intervention protocols varied considerably in their infection control practices. For one of its interventions, the study by Rodriguez-Bano and colleagues⁶⁶ took no specific action for patients awaiting test results in the intervention group or control group. For the other of its interventions, this study⁶⁶ recommended preemptive isolation of readmitted patients previously colonized with MRSA for intervention group patients before the results of screening tests returned, but not for control group patients. Of the other three CCS studies, two^{63, 64} took no specific action for patients awaiting test results in the intervention or control groups. The exception was the study by Harbarth et al.⁶⁵ The Harbarth study⁶⁵ recommended preemptive isolation of patients previously known to be colonized or infected with MRSA for the intervention group, but not for the control group. For the five non-CCS studies, three studies⁶⁷⁻⁶⁹ took no specific action for patients awaiting test results in the intervention or control groups. The exceptions were the studies by Wernitz et al.⁷⁰ and Keshtgar et al.⁷⁸ The Wernitz study⁷⁰ recommended isolation, barrier precautions and topical antimicrobial wash for all potential MRSA carriers pending screening test results. The same protocol took place for control group patients awaiting test results. The Keshtgar study⁷⁸ recommended intranasal

antimicrobials and topical antimicrobial washes for patients who required emergency surgery before the screening test results returned.

Once a patient was found to be MRSA-positive, the Rodriguez-Bano study⁶⁶ recommended different actions for MRSA-positive patients in the intervention group in comparison to the control group. In this study,⁶⁶ MRSA-positive patients in the intervention group received contact precautions and decolonization (intranasal antimicrobials, topical antimicrobial washes) as well as dedicated patient care equipment and disinfection of surfaces and devices. MRSA-positive patients in the control group also received contact precautions, dedicated patient care equipment and disinfection of surfaces and devices, but did not receive decolonization. One of the non-CCS studies, the Wernitz study⁷⁰ recommended the same action for MRSA-positive patients in the intervention group and in the control group. For the Harbarth,⁶⁵ Chowers,⁶³ Salaripour,⁶⁹ and Pan studies,⁶⁸ steps were taken to isolate and decolonize MRSA-positive patients in the intervention group but no interventions were recommended for MRSA-positive patients in the control group. For the Bowler⁷¹ and Keshtgar studies,⁷² decolonization was recommended for MRSA-positive patients in the intervention group, but not for MRSA-positive patients in the control group. In the Ellingson study,⁶⁴ MRSA-positive patients in the intervention group received contact precautions and unspecified hand hygiene, while MRSA-positive patients in the control group received no specific intervention.

The control arms of each of the nine studies included no systematic screening for MRSA. However, the infection control practices of the control groups did vary especially in cases where an individual with MRSA was identified during routine care. As mentioned above, the Wernitz study⁷⁰ decolonized patients found to be MRSA positive in their control groups.

Results by Outcome

Health Care-Associated MRSA Acquisition

Health care-associated MRSA acquisition is measured by MRSA colonization or by MRSA colonization or infection that is health care-associated, rather than imported. Three studies evaluated health care-associated MRSA infection or colonization as an outcome. Two^{64, 66} of these studies used statistical methods to attempt to control for confounders and/or secular trends (CCS studies) and one⁶⁹ did not (non-CCS study). Of the CCS studies, the Rodriguez-Bano study was determined to be of fair quality⁶⁶ and the Ellingson study was determined to be of poor quality.⁶⁴ Definition of this acquired outcome varied across studies. The Rodriguez-Bano study⁶⁶ defined cases as health care-associated if the first sample yielding MRSA was obtained more than 3 calendar days after hospital admission or if the first sample yielding MRSA was obtained from an ambulatory patient with an identified association with recent health care delivery. The Ellingson study⁶⁴ defined cases as health care-associated if a positive, clinical MRSA culture result was obtained at least 48 hours after admission to an acute care unit or if the patient was transferred, within 48 hours after transfer to another unit. Cases were excluded as nonincident if a positive clinical culture result could be identified anywhere in the laboratory information system (including long-term care and outpatient settings) within the prior year. The Salaripour study⁶⁹ defined cases as health care-associated if a positive culture result was obtained more than 72 hours after admission.

In terms of findings, for the Rodriguez-Bano study,⁶⁶ the reported change in incidence of MRSA acquisition from a segmented regression analysis was -0.065 with confidence intervals

that included zero (change in incidence after second intervention -0.053 to 0.182). Considering the baseline rate of 0.55/1000 patient days, this change in incidence rate would be equivalent to a relative risk reduction of -11.8 percent. The reported change in trend in incidence of MRSA acquisition was -0.045 (95 percent CI: -0.062 to -0.029; $p < 0.001$).⁶⁶ In univariate analysis, compared to no screening, both interventions showed a reduction in MRSA colonization or infection, though this reduction was not statistically significant.⁶⁶ For the Ellingson study,⁶⁴ the percent change in the MRSA acquisition rate was -35.0 percent with wide confidence intervals that did not include zero (pre- to post-intervention change -57.2 percent to -1.1 percent). The Salaripour study⁶⁹ also found a statistically significant reduction in health care-associated MRSA infection with targeted screening (-0.18 per 1000 patient-days, a 30 percent reduction).

Strength of Evidence

The strength of evidence for the effect of targeted screening in high-risk patients on MRSA acquisition was judged to be insufficient based on the high risk of bias, lack of consistency and lack of precision. Two CCS studies addressed this outcome. One found a nonsignificant reduction in the incidence of MRSA acquisition with screening,⁶⁶ while the other reported a wide confidence interval that achieved statistical significance.⁶⁴ Based on the quality of these two quasi-experimental studies, the risk of bias was judged to be high. Though the point estimates for both studies suggest a reduction in health care-associated MRSA acquisition with screening, because the confidence intervals for the change in the incidence of MRSA acquisition for the fair quality study include the null, the findings are inconsistent. The studies assessed hospital-associated transmission by measuring both colonization and infection, an indirect outcome measure by definition. The findings are imprecise as they lack consistency.

Comment, Non-CCS Study

One study⁶⁹ that did not use statistical methods to attempt to control for confounders and/or secular trends addressed this outcome. With screening of high-risk patients, the Salaripour study⁶⁹ demonstrated a statistically significant reduction in health care-associated MRSA colonization or infection.

Health Care-Associated MRSA Infection, Irrespective of Site

Results

Three studies^{65, 67, 70} evaluated the impact of screening for MRSA-carriage in high-risk patients on health care-associated MRSA infection. One⁶⁵ of these studies used statistical methods to attempt to control for confounders and/or secular trends (CCS study) and two^{67, 70} did not. All three studies defined health care-associated MRSA infection as clinical signs of infection 48 hours or more after admission, with MRSA isolated as the causative pathogen. All studies showed a statistically significant reduction in health care-associated MRSA infection with screening of high-risk patients compared to no screening.

Strength of Evidence

The strength of evidence for the effect of screening in high-risk patients on health care-associated MRSA infection, irrespective of site was judged to be insufficient based on the high risk of bias, unknown consistency and lack of precision. One CCS study showed a statistically significant reduction in health care-associated MRSA infection with targeted screening compared

to no screening. The risk of bias was determined to be high, given the single quasi-experimental before/after study of poor quality. The consistency of the findings is unknown, given the single study that addressed this outcome. MRSA infection is a direct outcome measure. The study findings were judged to be imprecise because data were available from only one study.

Comment, Non-CCS Studies

Two studies that did not use statistical methods to attempt to control for confounders and/or secular trends (non-CCS studies) evaluated this outcome.⁶⁷ Compared to no screening, both studies showed a statistically significant reduction in health care-associated MRSA infection with screening of high-risk patients.^{67, 70}

Health Care-Associated MRSA Bacteremia or Bloodstream Infection

Five studies addressed the impact of screening on rates of health care-associated MRSA bacteremia or bloodstream infection. Three of these studies^{63, 64, 66} used statistical methods to attempt to control for confounders and/or secular trends (CCS studies) and two^{68, 70} did not (non-CCS studies). Of the CCS studies, the Rodriguez-Bano study⁶⁶ was determined to be of fair quality study and the Chowers study⁶³ and Ellingson study⁶⁴ were of poor quality. The Rodriguez-Bano study⁶⁶ measured MRSA bacteremia and defined cases as health care-associated if the first sample yielding MRSA was obtained more than 3 calendar days after hospital admission or if the first sample yielding MRSA was obtained from an ambulatory patient with an identified association with recent health care delivery. The Ellingson,⁶⁴ Wernitz⁷⁰ and Pan⁶⁸ studies defined cases as health care-associated if a positive, clinical MRSA culture result was obtained at least 48 hours after admission. In addition, the Ellingson study⁶⁴ also considered a case health care-associated if the patient was transferred and the positive clinical MRSA culture result was obtained within 48 hours after transfer to another unit. Cases were excluded as nonincident if a positive clinical culture result could be identified anywhere in the laboratory information system (including long-term care and outpatient settings) within the prior year. The Chowers study⁶³ defined bacteremia as health care-associated if a positive blood culture result was obtained from blood drawn 48 hours or more after admission, or from blood drawn at admission from any patient who had been admitted to the study hospital during the prior year.

With segmented regression analysis, the fair quality study by Rodriguez-Bano and colleagues⁶⁶ reported that the change in incidence of MRSA bacteremia was -0.051 after the intervention (95 percent CI: -0.083, -0.020). The change in trend in MRSA bacteremia was -0.006 after the second intervention (95 percent CI: -0.10 to -0.01; p=0.01). In univariate analysis, compared to no screening, both interventions showed a reduction in MRSA bacteremia, though this reduction was not statistically significant. The Ellingson study⁶⁴ simply reported a statistically significant -54 percent reduction in incidence of MRSA bloodstream infection, but did not report confidence intervals. The Wernitz⁷⁰ and Pan⁶⁸ studies also showed a statistically significant reduction in health care-associated MRSA bloodstream infection with screening of high-risk patients compared to no screening. The Chowers study⁶³ showed a statistically significant reduction in health care-associated MRSA bloodstream infection with one component of the intervention (targeted screening with PCR and monitoring) but no statistically significant reduction with two other components of the intervention.

Strength of Evidence

The strength of evidence for the effect of screening for MRSA-carriage in high-risk patients on health care-associated MRSA bacteremia or bloodstream infection was judged to be insufficient based on the high risk of bias and lack of precision. Three CCCS studies addressed this outcome. With segmented regression analysis, the fair quality study⁶⁶ reported nonsignificant univariate analysis reductions after both interventions in the incidence of MRSA bacteremia. One poor quality study⁶⁴ reported a statistically significant reduction in incidence of MRSA bloodstream infection, but did not report confidence intervals. Another poor quality study⁶³ found a statistically significant reduction in health-care associated MRSA bloodstream infection for one component of the intervention (targeted screening with PCR and monitoring); however, for the other two components of the intervention, the results were not statistically significant. The risk of bias was determined to be high, given both study quality and design. The study findings are consistent, because each study showed a reduction in MRSA bacteremia or bloodstream infection with screening. MRSA bacteremia or bloodstream infection is a direct outcome measure. The study findings were judged to be imprecise given the variation in effect size.

Comment, Non-CCS Studies

Two studies that did not use statistical methods to attempt to control for confounders and/or secular trends (non-CCS studies) evaluated this outcome.^{68, 70} Compared to no screening, both studies showed a statistically significant reduction in health care-associated MRSA infection with screening of high-risk patients.^{68, 70}

MRSA Surgical Site Infection

Two studies addressed this outcome. One study⁶⁵ used statistical methods to attempt to control for confounding and/or secular trends (CCS study) and one⁷⁸ did not (non-CCS study). Both the Harbarth⁶⁵ and Keshtgar⁷⁸ studies showed a statistically significant reduction in health care-associated MRSA surgical site infection with screening of high-risk patients compared to no screening.

Strength of Evidence

The strength of evidence for the effect of screening for MRSA-carriage in high-risk patients on MRSA surgical site infection was judged to be insufficient based on the high risk of bias, unknown consistency and lack of precision. One CCS study addressed this outcome.⁶⁵ With screening of high-risk patients for MRSA-carriage, this poor quality study showed a statistically significant reduction in health care-associated MRSA surgical site infection. The risk of bias was determined to be high, given the study quality and design. The consistency of the findings is unknown as only one study addressed this outcome. MRSA bacteremia or bloodstream infection is a direct outcome measure. The findings were imprecise because data were available from only one study.

Comment, Non-CCS Studies

One study⁷⁸ that did not use statistical methods to attempt to control for confounding and/or secular trends (non-CCS study) addressed this outcome. The Keshtgar⁷⁸ study showed a

statistically significant reduction in MRSA surgical site infection with screening of high-risk patients compared to no screening.

Morbidity, Mortality, Harms and Resource Utilization

Results

No studies addressed these outcomes.

Strength of Evidence for Screening of High-Risk Patients for MRSA-Carriage on Morbidity, Mortality, Harms and Resource Utilization

Because no studies addressed these outcomes, the strength of evidence to evaluate the effect of screening of high-risk patients for MRSA-carriage on morbidity, mortality, harms or resource utilization was judged to be insufficient.

Summary Strength of Evidence Across Key Question 3C

A summary of the main syntheses for this question follows in Table 11.

Table 11. Strength of evidence for studies comparing screening of high risk patients versus no screening

Strategies Compared	Outcome	No of Studies [§]	Risk of Bias	Consistency	Directness	Precision	Overall Grade
Screening of High Risk Pts Vs No Screening	MRSA Transmission	2 QEX (N=Unclear) (Rodriguez-Bano 2010 ⁶⁶) (N=Unclear) (Ellingson 2011 ⁶⁴)	High	Inconsistent	Indirect	Imprecise	Insufficient
	MRSA Infection	1 QEX (N=506,012) (Harbarth 2000 ⁶⁵)	High	Unknown	Direct	Imprecise	Insufficient
	MRSA Bacteremia/ Blood Stream Infection	3 QEX (N=Unclear) (Rodriguez-Bano 2010 ⁶⁶) (N=377,945; 1,535,806 [‡]) (Chowers 2009 ⁶³) (N=Unclear) (Ellingson 2011 ⁶⁴)	High	Consistent	Direct	Imprecise	Insufficient
	MRSA Surgical Site Infection	1 QEX (N=506,012) (Harbarth 2000 ⁶⁵)	High	Unknown	Direct	Imprecise	Insufficient

[‡] Patient days; NA: Not applicable; QEX: Quasi-experimental

[§] CCS Studies

Key Question 4

Expanded Screening for MRSA-Carriage Compared to Limited Screening

Overview

This section describes the literature that evaluates expanded screening for MRSA-carriage compared to limited screening. After an overview of the literature, the results are described for each outcome measure: MRSA acquisition, MRSA infection, morbidity, mortality, harms, and resource utilization. Within the category of MRSA infection, we also include results for MRSA bacteremia or bloodstream infection, as some studies present these outcomes rather than the broader outcome of MRSA infection irrespective of site. The emphasis in this chapter is on outcomes describing health care-associated events. Health care-associated outcomes are the primary outcomes of interest because screening for MRSA-carriage in health care facilities is most proximately expected to impact health care-associated MRSA transmission and infection. Strength of evidence syntheses presented here include only studies that attempted to control for confounding and/or secular trends (CCS studies). Because studies that use simple two-group statistical analyses cannot support causal inferences, those studies that did not attempt to control for confounding and/or secular trends (non-CCS studies) were excluded from the strength of evidence analysis. Following the strength of evidence syntheses, we comment on the pattern of results seen in studies that did not attempt to control for confounding and/or secular trends (non-CCS studies). Table 12 summarizes the studies reviewed for Key Question 4.

Table 12. KQ4: Health care-associated MRSA acquisition, infection, or bacteremia

Outcome	Study	Quality	Statistical Result	Synthesis
HCA acquisition	Rodriguez-Bano ⁶⁶	Fair	NS ↓	SOE=insufficient Comment: Causal inference is not possible based on non-CCS studies
	Eveillard ⁷²	Non-CCS	SS ↓	
	Girou ⁷³	Non-CCS	NS ↓	
	Schelenz ⁷⁴	Non-CCS	SS ↓	
	Thompson ⁷⁵	Non-CCS	SS ↓	
	Trautmann ⁷⁶	Non-CCS	SS ↓	
HCA infection	Chaberny ⁷¹	Poor	SS ↓	SOE=insufficient Comment: Causal inference is not possible based on non-CCS studies
	West ⁷⁷	Non-CCS	NS ↓	
HCA bacteremia/ blood stream infection	Rodriguez-Bano ⁶⁶	Fair	NS ↓	SOE=insufficient Comment: Causal inference is not possible based on non-CCS studies
	Thompson ⁷⁵	Non-CCS	SS ↓	
	Trautmann ⁷⁶	Non-CCS	NS ↓	

HCA = Health care associated; KQ = Key Question; NS = nonsignificant; SOE = strength of evidence; SS = statistically significant

Eight studies^{66, 71-77} described limited screening for MRSA-carriage compared to expanded screening. The studies by Chaberny⁷¹ and Rodriguez-Bano⁶⁶ attempted to use statistical methods

to control for confounders or secular trends (CCS studies); the remaining six⁷²⁻⁷⁷ did not (non-CCS studies). All eight studies^{38-44,66} employed a quasi-experimental study design.

The study by Rodriguez-Bano and colleagues⁶⁶ utilized a before/after study design (interrupted time series). The seven other studies utilized a before/after study design. The study by Rodriguez-Bano and colleagues was judged to be of fair quality⁶⁶ because it controlled for confounders indirectly, rather than employing statistical adjustment within the segmented regression analysis. The study by Chaberny and colleagues⁷¹ was determined to be of poor quality because it did not report whether its analysis controlled for confounders

All eight studies evaluated hospitalized adult patients. Both of the CCS studies^{66, 71} took place in more than one area of the hospital. Three⁷⁵⁻⁷⁷ of the non-CCS studies took place in the ICU. One of the non-CCS studies took place on a cardiothoracic ward,⁷⁴ one on an internal medicine ward,⁷² and one on a dermatology ward.⁷³

The exact composition of the expanded MRSA screening intervention varied across the studies. Seven studies utilized culture to screen patients for MRSA. The study by Schelenz and colleagues⁷⁴ did not specify whether screening was performed with culture or PCR. For the study by Rodriguez-Bano and colleagues,⁶⁶ the intervention was active surveillance for MRSA and decolonization in patients and health care workers in wards with documented MRSA transmission, and surveillance of all patients admitted from other hospitals or from long-term care facilities and all readmitted patients previously colonized with MRSA. For the study by Chaberny and colleagues,⁷¹ the intervention was screening of readmitted patients as well as roommates of patients with MRSA plus screening of all admitted patients on surgical wards and ICUs. For two of the non-CCS studies, the intervention was screening of all patients admitted to a single ward. The study by Eveillard and colleagues⁷² screened all patients admitted to the internal medicine service. The study by Girou and colleagues⁷³ screened all patients admitted to the dermatology ward within 48-72 hours of admission.

Two of the non-CCS studies included screening of high-risk patients as well as those admitted to the ICU. The study by West and colleagues⁷⁷ defined high risk patients as those transferred from another hospital, admitted from long-term care facilities, readmitted within 30 days after discharge, or admitted to a nephrology service. The study by Trautmann and colleagues⁷⁶ defined high risk patients as 1) patients with chronic open wounds or pressure sores; 2) patients transferred from secondary or tertiary acute care hospitals; 3) bed-bound patients from chronic care facilities; 4) patients with insulin-dependent diabetes mellitus; and 5) patients with chronic renal failure on dialysis. In addition to screening, the Trautmann study⁷⁶ included additional interventions including a written standard detailing hygienic precautions for MRSA, acquisition of long-sleeved isolation gowns, acquisition of carts to facilitate the use of separate supplies for MRSA patients, isolation signs, enhanced documentation of MRSA cases, feedback and staff training, and flagging of electronic charts for patients with MRSA. For the study by Thompson and colleagues,⁷⁵ the intervention was screening all admissions to the ICU, daily antimicrobial washes for all patients regardless of MRSA status, scrubs for medical staff, computer keyboards with a wipeable surface, and standardized care of vascular lines.

For the study by Schelenz and colleagues,⁷⁴ the intervention included multiple components: 1) preadmission, admission, and weekly screening for all admitted ward patients; 2) decolonization (intranasal antimicrobials, topical antimicrobials) for patients found to be MRSA positive; 3) admission of patients from high-risk units (ICUs, other hospitals), only after MRSA status known; 4) audit plus feedback; 5) education and support; 6) closure of operating rooms to facilitate repairs; 7) alcohol hand rub; 8) isolation on admission for patients known to be

colonized with MRSA; 9) decolonization (intranasal antimicrobials, topical antimicrobials) of both MRSA carriers and those with pending screening test results 24 hours before surgery; 9) isolation and barrier precautions for MRSA-positive patients; 10) designated nurses for MRSA-positive patients; 11) a nursing care pathway for MRSA; 12) use of clippers to prepare the skin in the operating room; 13) preoperative skin disinfection with a rapidly drying solution; 14) improvements in environmental cleaning; 15) alternative in IV antibiotic prophylaxis; and 16) recovery in the operating room when possible, rather than admission to the ICU.

An important feature of this group of studies was that targeted screening was already occurring at baseline, so it is important to understand the nature of screening during control periods. For the Rodriguez-Bano study⁶⁶ the control condition consisted of active surveillance for MRSA and decolonization in patients and health care workers in wards with documented MRSA transmission. For five of the lower quality studies, the control condition consisted of screening high-risk patients. The Eveillard study⁷² screened patients with a history of MRSA carriage, hospitalization, or institutionalization within the prior year, intra- or inter-hospital transfers, and patients with chronic skin lesions. The Girou study⁷³ screened patients transferred from other wards, with a history of prior hospitalization in the past 3 years, with chronic wounds, or with a disease with denuded skin. The Trautmann study⁷⁶ screened 1) patients with chronic open wounds or pressure sores; 2) patients transferred from secondary or tertiary acute care hospitals; 3) bed-bound patients from chronic care facilities; 4) patients with insulin-dependent diabetes mellitus; and 5) patients with chronic renal failure on dialysis. The Thompson study⁷⁵ screened high-risk patients, but did not define this population group. The Chaberny study⁷¹ screened readmitted patients as well as roommates of patients with MRSA. For the West study,⁷⁷ the control condition was screening upon admission to the ICU and weekly thereafter. For the Schelenz study,⁷⁴ the control condition was pre-admission, admission and weekly MRSA screening.

While all eight studies evaluated similar MRSA outcomes, the primary outcome of interest varied. For the Chaberny and West studies,^{71, 77} the primary outcome was incidence of nosocomial MRSA infection. For the Rodriguez-Bano study,⁶⁶ the primary outcome was rates of MRSA colonization or infection and rates of bacteremia. For the Eveillard study⁷², the primary outcomes were the prevalence of MRSA carriage on admission, the efficiency of the selective screening program and the effectiveness of the screening program on controlling MRSA transmission. For the Girou study,⁷³ the primary outcomes were the number of patients without risk factors found to screen positive for MRSA, the rate of acquired MRSA, and the rate of imported MRSA. For the Thompson study,⁷⁵ the primary outcome was to detect long-term trends in the prevalence of MRSA in admissions, MRSA acquisition and bacteremia rates within the ICU, and to determine the effect of the three interventions. For the Trautmann study,⁷⁶ the primary outcome was the nosocomial MRSA transmission. For the Schelenz study,⁷⁴ the primary outcomes were rates of MRSA acquisition and infection.

Infection control practices varied in the background of these studies. In terms of actions taken while awaiting test results, the study by Rodriguez-Bano and colleagues,⁶⁶ a fair quality study, recommended actions for patients in the intervention group while awaiting test results. This study⁶⁶ recommended preemptive isolation for readmitted patients previously colonized with MRSA. However, preemptive isolation or decolonization for patients was not recommended for patients in the control group while awaiting test results. The study by Chaberny and colleagues,⁷¹ a poor quality study, recommended no actions while waiting for screening test results. Five of the non-CCS studies utilized the same action for patients in the intervention

group awaiting test results as for patients in the control group awaiting test results. The West study⁷⁷ recommended preemptive isolation and barrier precautions for patients found to have MRSA colonization or infection on a prior admission. The Girou study⁷³ recommended isolation and barrier precautions for patients at high risk of MRSA acquisition. Three studies^{71, 72,75,76} recommended no interventions while awaiting screening test results. The Schelenz study⁷⁴ utilized different actions for patients in the intervention group awaiting tests results as for patients in the control group awaiting test results. No interventions were recommended for patients in the control group while awaiting screening results. In the intervention group, patients were not admitted to the ward until their MRSA status was known. In addition, presumptive decolonization was recommended for patients in the intervention group whose test results were not available 24 hours prior to surgery. Once a patient was found to have a MRSA positive screening test, practices tended to be similar for intervention and control groups. The Rodriguez-Bano study⁶⁶ utilized similar interventions for MRSA-positive patients in the intervention and control groups. For both intervention and control groups, the action consisted of isolation (including barrier precautions), decolonization (intranasal and topical antimicrobials) and follow up nasal swabs. Hand hygiene was recommended for the care of MRSA-positive patients in both groups, but alcohol hand rubs were available only during the intervention period. Similarly, the Chaberny study⁷¹ utilized the same interventions for MRSA-positive patients in the intervention group and in the control group, as did four of the non-CCS studies.^{72, 73, 75, 77} Two^{74, 76} of the non-CCS studies utilized similar interventions for MRSA-positive patients in the intervention group and in the control group. For one of these studies, MRSA-positive patients in the intervention group were isolated, but those in the control group were isolated only if an isolation room was available.

Results by Outcome

Health Care-Associated MRSA Acquisition

Health care-associated MRSA acquisition is measured by MRSA colonization or by MRSA colonization or infection that is health care-associated, rather than imported. Six studies evaluated health care-associated MRSA infection or colonization as an outcome. The study by Rodriguez-Bano and colleagues⁶⁶ used statistical methods to attempt to control for confounders and/or secular trends (CCS studies), while the studies by Eveillard and colleagues,⁷² Trautmann and colleagues,⁷⁶ Thompson and colleagues,⁷⁵ Girou and colleagues,⁷³ and Schelenz and colleagues⁷⁴ did not (non-CCS studies). The Rodriguez-Bano study was determined to be of fair quality⁶⁶ because it controlled for confounders indirectly, rather than employing statistical adjustment within the segmented regression analysis.

The study by Rodriguez-Bano and colleagues, a fair quality study⁶⁶ defined cases as health care-associated if the first sample yielding MRSA was obtained more than 3 calendar days after hospital admission or if the first sample yielding MRSA was obtained from an ambulatory patient with an identified association with recent health care delivery. The Eveillard and Trautmann studies^{72, 76} defined colonization or infection as health care-associated if patients were identified as MRSA positive two or more days after admission. The Thompson study⁷⁵ defined colonization or infection as health care-associated if growth of MRSA was noted five or more days after admission to the ICU in patients who initially screened negative for MRSA. The Girou study⁷³ defined colonization or infection as health care-associated if the first MRSA isolate from

any source was recovered more than 72 hours after admission. The Schelenz study⁷⁴ defined MRSA acquisition as the isolation of MRSA from any site more than 72 hours after admission to the ward in patients who had no previous history of MRSA colonization or infection. MRSA infections were defined as the isolation of MRSA from blood culture or surgical wound sites that had evidence of clinical infection.

The Rodriguez-Bano study⁶⁶ showed reductions in the incidence and trend of health care-associated MRSA infection or colonization with expanded screening compared to limited screening. Though the reduction in trend was statistically significant (change in trend after the third intervention 0.047; 95 percent CI: 0.035-0.059, $p < 0.001$), the reduction in incidence was not (change in incidence after the third intervention 0.077 [NS; 95 percent CI: -0.012 to 0.165]).⁶⁶ Of note, for the calculation of incidences of MRSA colonization or infection, only patients who had MRSA isolated from clinical samples were included because active surveillance was not performed uniformly throughout the study periods. All five of the non-CCS studies showed a reduction in hospital-acquired MRSA infection with expanded targeted screening compared to limited targeted screening. The studies by Eveillard, Thompson, Trautmann, and Schelenz^{72, 74-76} showed a statistically significant reduction and the study by Girou⁷³ did not.

Strength of Evidence

Based on the high risk of bias due to the single quasi-experimental study of fair quality, the unknown consistency and the lack of precision, the strength of evidence to evaluate the effect of expanded targeted screening compared to limited targeted screening on health care-associated MRSA acquisition was judged to be insufficient.⁶⁶ The risk of bias was judged to be high as only one quasi-experimental study of fair quality addressed this outcome.⁶⁶ With segmented regression analysis, the incidence with expanded targeted screening not significantly changed, but there was a significant change in trend.⁶⁶ The consistency is unknown, as only one study addressed this outcome. The study measured MRSA colonization or infection, by definition an indirect outcome measure. The findings were imprecise because data were available from only one study.

Comments, Non-CCS Studies

Five studies that did not use statistical methods to attempt to control for confounders and/or secular trends addressed this outcome.⁷²⁻⁷⁶ With expanded screening compared to limited screening, all five studies showed a reduction in MRSA infection. The reduction was statistically significant for four of the non-CCS studies,^{72, 74-76} though not for one⁷³ of the non-CCS studies.

Health Care-Associated MRSA Infection, Irrespective of Site

Two studies^{71, 77} addressed this outcome. The study by Chaberny and colleagues⁷¹ used statistical methods to attempt to control for confounders and/or secular trends (CCS-study) while the study by West and colleagues⁷⁷ did not (non-CCS) study. The study by Chaberny and colleagues⁷¹ was determined to be of poor quality because it did not report whether its analysis controlled for confounders. Both studies defined hospital-acquired infection as an infection detected at least 72 hours after admission. Chaberny et al.,⁷¹ showed a statistically significant reduction in hospital-acquired MRSA infection (based on the change in level and slope of the incidence density) with expanded screening compared to limited screening. West et al.,⁷⁷ showed

a reduction in hospital-acquired MRSA infection with expanded screening compared to limited screening; however, this reduction was not statistically significant.

Health Care-Associated MRSA Bacteremia or Bloodstream Infection

Three studies addressed this outcome. The study by Rodriguez-Bano and colleagues used statistical methods to attempt to control for confounding and/or secular trends⁶⁶ (CCS study), while the studies by Thompson and colleagues and by Trautmann and colleagues did not^{75,76}. The study by Rodriguez-Bano and colleagues was determined to be of fair quality⁶⁶ because it controlled for confounders indirectly, rather than employing statistical adjustment within the segmented regression analysis. The Rodriguez-Bano study⁶⁶ defined bacteremia as health care-associated if the first sample yielding MRSA had been obtained more than 3 calendar days after hospital admission or if the first sample yielding MRSA had been obtained from an ambulatory patient who had an identified association with recent health care delivery. The Thompson study⁷⁵ defined bacteremia as ICU-acquired if the first positive blood culture occurred on or after the fifth day in the ICU. Patients who grew MRSA from other sites prior to or after the elucidation of MRSA from the blood were included. The Trautmann study⁷⁶ defined septicemia as hospital-acquired if it was identified two or more days after admission. The CDC definition was used to define septicemia.

The Rodriguez-Bano study⁶⁶ reported a reduction in hospital-acquired MRSA bacteremia with expanded targeted screening compared to limited targeted screening, but the confidence intervals included the null (change in incidence after the third intervention -0.022 to 0.026; change in trend after the third intervention 0.000 to 0.006). The Thompson study⁷⁵ showed a statistically significant reduction in hospital-acquired MRSA intravenous catheter-associated septicemia with expanded targeted screening compared to limited targeted screening. The Trautmann study⁷⁶ showed no statistically significant reduction in hospital-acquired MRSA bacteremia with expanded targeted screening compared to limited targeted screening.

Strength of Evidence

Based on the high risk of bias, lack of consistency and lack of precision, the strength of evidence to evaluate the effect of expanded targeted screening compared to limited targeted screening on health care-associated MRSA infection was judged to be insufficient.⁶⁶ Only one CCS study⁷¹ addressed this outcome. With expanded screening compared to limited screening, this poor quality study found a statistically significant reduction in health care-associated MRSA infection based on the change in level of the incidence density. Apart from this one study of health care-associated infection, one quasi-experimental study of fair quality evaluated health care-associated bacteremia, a proxy for health care-associated infection and a direct outcome measure.⁶⁶ This study reported a nonsignificant reduction in the incidence of MRSA bacteremia, and a significant change in trend.⁶⁶ The risk of bias was felt to be high due to the quality of the studies and the before/after designs. The findings are inconsistent due to confidence intervals that included the null for one of the two studies. The findings are imprecise because of the lack of consistency of the findings.

Comment, Non-CCS Studies

Three studies that did not use statistical methods to attempt to control for confounders and/or secular trends (non-CCS studies) addressed this outcome.⁷⁵⁻⁷⁷ One of the studies⁷⁷ evaluated the effect of expanded screening for MRSA-carriage compared to limited screening on health care-

associated MRSA infection, irrespective of site, while two of the studies^{75, 76} evaluated the effect of expanded screening for MRSA-carriage compared to limited screening on health care-associated MRSA bacteremia or bloodstream infection, a proxy for health care-associated MRSA infection.

With expanded screening, all three studies showed a reduction in health care-associated MRSA infection. For one of the studies,⁷⁶ the reduction was statistically significant, while for two of the studies, it was not.^{75, 77}

Morbidity, Mortality, Harms and Resource Utilization

No studies addressed these outcomes.

Strength of Evidence for Expanded Screening for MRSA-Carriage Compared to Limited Screening on Morbidity, Mortality, Harms and Resource Utilization

Because no studies addressed these outcomes, the strength of evidence to evaluate the effect of expanded screening for MRSA-carriage compared to limited screening on morbidity, mortality, harms or resource utilization was judged to be insufficient.

Summary Strength of Evidence Across Key Question 4

A summary of the main syntheses for this question follows in Table 13.

Table 13. Strength of evidence for studies comparing expanded screening versus limited screening

Strategies Compared	Outcome	No of Studies [§]	Risk of Bias	Consistency	Directness	Precision	Overall Grade
Expanded screening vs. Limited Screening	MRSA Transmission	1 QEX (N=Unclear) (Rodriguez-Bano 2010 ⁶⁶)	High	Unknown	Indirect	Imprecise	Insufficient
	MRSA Infection	1 QEX (N=219,124; 1,987,676 [‡]) (Chaberny 2008 ⁷¹)	High	Unknown	Indirect	Imprecise	Insufficient
	MRSA Bacteremia	1 QEX (N=Unclear) (Rodriguez-Bano 2010 ⁶⁶)	High	Unknown	Direct	Imprecise	Insufficient

[‡] Patient days; NA: Not applicable; QEX: Quasi-experimental

[§]CCS Studies

Discussion

Key Findings and Strength of Evidence

Summary of Results

This review addresses the impact of MRSA screening on a variety of outcomes that are interrelated on the path between screening and patient-centered outcomes. Our review found considerable variation in the application of MRSA screening with respect to the specific clinical setting, population screened, microbiologic techniques and infection prevention interventions. Based on the most important and distinctive subgroups of evaluations of MRSA screening strategies, the review is organized to examine the clinical effectiveness of MRSA screening under the following circumstances: 1) universal screening compared to no screening, 2) screening of ICU patients compared to no screening, 3) screening of surgical patients compared to no screening, 4) screening of other high-risk patients compared to no screening, 5) universal versus compared to screening of selected patient populations, and 6) expanded screening compared to limited screening. This discussion specifically addresses the outcomes of MRSA screening strategies in studies appraised to be of fair or good quality. In some cases, comment is also offered with respect to some poor quality studies.

MRSA Transmission

By design, the most immediate effect of MRSA screening strategies should be to interrupt the transmission of MRSA between patients, irrespective of the clinical setting under investigation. The impact of MRSA screening on the frequency of transmission can be estimated through examination of the acquisition of MRSA colonization (often considered in conjunction with the incidence of new infection) among patients not previously affected. Based on all of the fair or good quality studies included in this review, there was insufficient evidence to reach a conclusion on the effect of any screening strategy on this outcome. There were no fair or good quality studies that examined the incidence of MRSA transmission when comparing universal screening to no screening or universal to screening of selected patient populations. Among patients on surgical wards, one study²⁹ compared screening of surgical patients to no screening and failed to show an advantage to screening. Among patients screened in the ICU, one randomized controlled study⁴³ comparing screening of ICU patients to no screening also failed to show an advantage of screening. A single study comparing expanded versus limited screening found an advantage for expanded screening.⁶⁶

Incidence of MRSA Infection

Reduction in the incidence of MRSA infection is the primary anticipated clinical benefit of intensive strategies for MRSA control, and specifically screening. However, in this review, we found that there was insufficient evidence to determine the impact of MRSA screening on the incidence of MRSA infection for any specific comparison. This uncertainty arises from a lack of a consistent pattern of effects and from general differences between fair to good quality studies and poor quality studies. When compared to no screening, universal screening was associated with a decreased risk of MRSA infection in a single high quality study.²⁸ When compared to screening of selected patient populations (targeted screening), universal screening was associated

with a reduction in the incidence of MRSA infection in two studies, but achieved statistical significance in only one.²⁸ Among surgical patients, targeted screening was associated with a reduced incidence of surgical site infections among poor quality studies, although the effect was not demonstrated in the single good quality study that attempted to address confounding.²⁹ Among ICU patients, the only good quality study²⁸ comparing targeted and no screening showed no statistically significant reduction in MRSA. Finally, there were no good or fair quality studies that examined the impact of limited versus expanded screening.

Morbidity and Mortality

Ideally, MRSA screening and other infection prevention strategies will meaningfully impact consequences of infection such as overall patient morbidity and mortality. Unfortunately, comprehensive review of the available literature identified scant studies (and none of fair or good quality) that specifically addressed the issue of whether MRSA screening impacts patient morbidity (including complications of MRSA infection) or mortality. As a result, there is insufficient evidence to reach a conclusion.

Potential Harms

In assessing the comparative effectiveness of any intervention, whether diagnostic, therapeutic or screening, it is essential to assess the potential harms of the intervention. Unfortunately, the harms of MRSA screening were not specifically measured in any of the good or fair quality studies that were included in this review. As a result, there is insufficient evidence to reach a conclusion.

Hospital Resource Utilization

Hospital resource utilization is an increasingly important element of any intervention that is considered for widespread adoption. MRSA screening programs could offer both the anticipated benefit of reduced consumption of some resources (generally accounted for through a reduced length of hospital stay). However, these potential benefits must be weighed against the possibility that screening and subsequent infection prevention interventions could also be associated with additional costs. In this review, no study of good or fair quality was identified that systematically examined the impact of screening on resource utilization. As a result, evidence is insufficient to support a conclusion regarding the impact of screening on resource utilization.

Strength of Evidence

Overall, this review revealed that for all of the comparisons and outcomes of interest, regarding MRSA screening, insufficient evidence is available to reach a conclusion regarding the effectiveness of this infection control technique. In large measure, the studies included in this review were determined to offer insufficient evidence owing to shortcomings in methodological design and execution that are summarized at length later in this discussion. More generally, the strength of evidence of the various studies was examined in the context of several critical domains: 1) risk of bias, 2) consistency, 3) directness, and 4) precision. The risk of bias in many of the studies was assessed as moderate to high owing to the reliance on observational and before/after designs. The one cluster randomized trial⁴³ (a design that minimizes the risk of bias) to examine the impact of MRSA surveillance actually failed to show a favorable impact of screening. Taken together, the studies reviewed were additionally hampered by the indirect

nature of some of the outcomes reported. Notably, there were no fair or good quality studies that specifically measured and reported the impact of screening on mortality and morbidity (complications of MRSA infection). While poor quality studies tended to report favorable results for screening, these results were not consistently replicated in the fair to good quality studies that were the focus of our synthesis.

Given the observational nature of many of the studies included in this review, a higher strength of evidence was assigned to those reports that endeavored to control for the risk of bias and confounding through the use of advanced statistical measures. As a result, those reports that did not employ regression analysis or interrupted time series analysis to determine the effect estimate associated with MRSA screening were determined to be of poor quality. Unfortunately, these poor quality studies comprised the bulk of the available literature on screening for MRSA-carriage.

Publication bias is a consideration in weighing the potential impact of a new strategy or technique in infection prevention and clinical quality improvement. To the extent that these methods are applied widely (both as a part of clinical trials and experimental designs as well as through more routine and common efforts at hospital based performance improvement), considerable experience with both the potential benefits and harms is accumulated in the clinical community. As a result, the evidence available for assessment in even a comprehensive review will only reflect a fraction of the actual experience. However, examination of meeting abstracts and other grey literature did not confirm publication bias.

As was acknowledged by the authors of many of the reports assessed as part of this review, substantial limitations exist that preclude the opportunity to reach important conclusions about the overall effect and utility of MRSA screening. Many of these limitations are detailed specifically later in this discussion. Foremost among these considerations is the ability to adequately control for bias and confounding owing to omissions in design features and statistical analysis of observational studies. As to specific key questions included in this review, nearly all of the studies examined were limited in the extent to which critical outcomes such as morbidity and mortality were assessed. In addition, few if any studies assessed the outcomes proposed for a number of key questions, including the potential harms and resource utilization associated with MRSA screening.

Findings in Relationship to What is Already Known

Systematic Reviews

At least two previous systematic reviews have been undertaken in order to assess the impact of MRSA screening in a variety of settings.⁸⁰ A 2008 systematic review identified 16 observational studies and four economic analyses. The authors reported that none of the assessed studies was graded as good quality. The authors concluded that there were significant gaps in the evidence that precluded definitive recommendations about the effectiveness of MRSA screening.

Tacconelli et al.⁸¹ reviewed nine intervention studies and one cluster randomized crossover trial. This meta-analysis of studies reporting the same outcome measures revealed a statistically significant reduction in the risk of MRSA bloodstream infections but not surgical site infections.

In essence, the conclusions of the present report are not substantially different than those reached in the previous systematic reviews, although there are some differences in the interpretation of the findings. In all three reports, the paucity of rigorous, well-controlled studies employing standardized microbiological and infection control techniques serves as a critical

limitation. In the present review, a much larger set of published studies is included for assessment. This is largely a function of the large number of studies and reports that have been published since the time that the previous two reports were completed. This is also an indicator of the intense activity in this field over the past several years, itself indicative of the proliferation of MRSA screening in the U.S. and elsewhere. Also distinguishing the present study is the more rigorous standard for grade of evidence that has been applied.

Guidelines and Public Policy

In contrast to the alignment of the conclusions across the range of evidence-based reviews is the diversity of opinions and recommendations offered by authoritative bodies in recent practice guidelines and position papers. The 2006 Guidelines for the Management of Multidrug-Resistant Organisms in Healthcare Settings published by the CDC Healthcare Infection Control Practices Advisory Committee (HICPAC)⁸² include active surveillance screening as a recommended intensified control strategy for multidrug resistant organisms (MDRO), including MRSA. The document recommends that such interventions should be implemented when the frequency of MDRO infections are not decreasing despite the use of more routine control measures.

The 2003 Society for Healthcare Epidemiology of America Guidelines for Preventing Nosocomial Transmission of Multidrug-Resistant Strains of *Staphylococcus aureus* and *Enterococcus*⁸³ take a more affirmative stand regarding the deployment of MRSA screening. The authors recommend that active surveillance cultures and contact precautions be implemented to prevent the spread of epidemiologically significant antibiotic-resistant pathogens. The guidelines further advise that these measures “should be implemented in all types of healthcare facilities throughout the system.”

On the basis of such strong conclusions articulated by authoritative bodies, MRSA screening has been accepted by many key stakeholders as an established standard of care. In a number of U.S. jurisdictions, the practice has been mandated through legislative and regulatory rules, beginning in 2008. A subsequent SHEA position paper,⁸⁴ stepped back from advocating for mandatory screening, citing concerns about the importance of institutional risk assessment and possible unintended consequences of mandatory and widespread screening.

Based on the conclusions reached in the current review of specific key questions regarding MRSA screening, the applicability of these findings and the strength of the available evidence do not appear to readily support the recommendations adopted by the CDC HICPAC⁸² or in the earlier SHEA Guidelines. As was true when comparing the present findings against those of earlier systematic reviews, the availability of additional studies published over the past several years likely contributes to this inconsistency. However, it is also likely that a more stringent grading of the available evidence paired with a higher expectation regarding the directness of the outcomes measured also contributed to the different conclusions reached in the various reports and guidelines. That MRSA screening has been adopted as a mandatory practice through legislative action in some jurisdictions is also not easily supported by the findings of the present review.

Applicability

Applicability assessment depends on a body of evidence sufficient to permit conclusions about the comparative outcomes of MRSA screening strategies. This body of evidence does not reach a level of sufficiency; therefore, comments will be limited to relevance to the PICOTS (population, intervention, comparator, outcomes, timing, setting) elements rather than

applicability.³⁸ Ultimately, the value of published evidence regarding MRSA screening or indeed any clinical intervention is largely determined by the applicability of these data to a wider range of populations in diverse settings once the intervention becomes more widespread. To this end, it is useful to assess the applicability of the findings regarding MRSA screening as assessed in this review in a systematic manner, reflecting on the design and execution of the studies examined. The PICOTS format provides a practical and useful structure to this exercise and is employed in the subsections that follow.³⁸

Population and Settings

The question of which patient populations may benefit most from MRSA screening remains controversial and is reflected in the diversity of clinical contexts in which screening has been evaluated to date. In a number of studies, the impact of screening when applied to groups of clinically or geographically well-defined populations has been examined. Prominent among these are the ICU and surgery inpatient populations. That the findings from the experience with these patients can be applied to other patient populations may be questioned. Specifically, ICU and surgery patients are at especially high risk for health care-associated infection as a result of distinctive aspects of their condition and management. For example, patients in both groups frequently undergo compromise of the integument barrier (e.g., insertion of vascular access devices, other invasive procedures) that unquestionably increase the likelihood of clinical significant infection caused by colonizing strains of bacteria. Therefore, these groups may be especially likely to derive benefit from interventions that reduce the risk of acquisition or colonization with virulent pathogens such as MRSA.

Perhaps in recognition of this potential bias, a number of studies reviewed here examined the impact of MRSA screening in more clinically heterogeneous patient populations, encompassing a broader range of risk for subsequent deep infection. When high risk patients are identified among this more diverse pool, the same questions arise regarding the applicability to less vulnerable patients. Ultimately, some of the most compelling evidence arises from the examination of the impact of MRSA screening on the widest range of patients (universal screening). However, even when applied most broadly, it is likely that there is sufficient variation between geographic regions and individual institutions to call into question whether similar impact will be seen when the method is applied more broadly. Examination of the experience when MRSA screening is applied most broadly, such as in response to legislative mandates over wide geographic areas, may be most informative.

The potential benefit and harms of MRSA screening has not yet been systematically evaluated in a number of special populations. Specifically, this review did not identify published studies examining the utility of MRSA screening among children, pregnant women and elderly individuals (except in those cases where advanced age was identified as a specific indicator of high risk). An evaluation of the favorable and unfavorable experience with MRSA screening in such groups is essential.

Interventions

The first fundamental barrier to widespread applicability of the findings of any MRSA screening program relates to technical variation in the screening methodology itself. Given the limited evidence base, the present review did not allow for a more rigorous and systematic comparison of the relative performance of various laboratory methods or reporting standards. That said, these differences have been widely identified as important potential confounders

affecting the evaluation of the performance of an MRSA screening program. One key element relates to the timing with which microbiologic assay results are returned and made available to treating clinicians. Presumably, a delay in reporting such results (such as might be associated with a culture-based lab approach) could limit the potential impact of screening in that the benefit in reduced transmission derived from the implementation of barrier precautions would itself be delayed. The extent to which such a delay, or for that matter variability in the performance sensitivity of one laboratory method versus another, could impact the effectiveness of a screening program and the resultant applicability.

Another important limitation to the applicability of the available evidence regarding MRSA screening relates to heterogeneity in the nature of the interventions performed. By its nature, MRSA screening itself (that is to say, the act of detecting MRSA through microbiologic techniques) would not be expected to impact the frequency of subsequent transmission or infection. Rather, it is the application of additional infection control interventions in response to the detection of colonization, including more rigorous hand hygiene and strict barrier precautions, environmental cleaning and even antimicrobial decolonization, that will influence clinical outcomes. That these interventions are often deployed as part of a “bundle” can further limit the conclusions that can be drawn about the attributable benefit of screening versus any of the other interventions.

A number of the studies examined as part of this review offered insufficient information to the reader regarding the full scope of interventions deployed in conjunction with MRSA screening, and specifically those measures implemented in response to the new detection of MRSA colonization. While the application of barrier precautions (the donning of gowns and gloves when caring for MRSA-positive patients) was frequently cited, most reports did not completely control for other practice standards that may have changed in light of new positive screening tests. For example, while decolonizing may not have been recommended as part of an MRSA screening intervention, available studies do not, for the most part, address whether or not the use of products such as intranasal mupirocin was specifically prohibited. As a result, the reader cannot be certain that the measured effect was not influenced by the application of such uncontrolled and unmeasured interventions targeting MRSA. In addition, the studies examined as part of this review frequently excluded mention of the assessment of compliance to the specified interventions, leaving readers uncertain as to whether the failure to impact clinical outcomes can be attributed to a lack of effect or poor execution on the part of practitioners.

The heterogeneity in describing interventions was further compounded by a failure in the majority of reviewed reports to explicitly examine the potential impact of other concurrent interventions targeting different outcomes apart from MRSA that could have affected the measured impact of MRSA screening itself. These include but are not limited to campaigns to reduce the frequency of vascular device infections, hand hygiene improvement initiatives and even interventions meant to promote an institutional culture of safety. In that such measures have been shown to potentially influence the frequency of a diversity of health care-associated infections (including those caused by MRSA), their omission may be important.

Comparisons

The majority of studies included in this review are of an observational nature and employ a relatively straightforward before/after design. While this approach is generally appreciated to be of limited rigor, the application of historical controls (pre-intervention) may be especially problematic in the assessment of interventions to prevent the dissemination of infectious

pathogens in closed populations (such as hospital inpatients). More specifically, studies conducted in this environment and in this manner are subject to confounding owing to epidemiological trends and phenomena that contribute to typical variations in the incidence of infectious diseases over time. In this context, the smaller the population, the greater the variability that may be encountered. While such changes over time may reflect statistical variation alone, changes in disease incidence may also be due to clusters of infection (which in turn might be attributable to new and more aggressive strains of pathogens such as MRSA), deviations and departures from best practice or even the application of other interventions that might influence transmission or infection.

Larger before/after studies, even when conducted across multiple geographic sites and clinical settings, could also be influenced by larger secular trends in the incidence of contagious diseases.³⁹ These broader changes in infectious diseases epidemiology may be attributed to diverse influences including the more widespread dissemination of new prevention practices, changes in antibiotic prescribing, seasonal influences or other unknown factors. That there have been changes in the incidence of some specific MRSA infections over the past decade has been well documented. Unless these macro-trends in epidemiology are identified and accounted for, it is possible that such phenomena could be attributed to the influence of interventions such as MRSA screening.

Where specific populations have been screened (e.g., high risk, expanded targeted, etc) also introduces a challenge to applicability. This is especially the case when decision rules are applied in order to identify individuals at high risk for MRSA carriage and/or infection. While some risk factors for MRSA disease have been well characterized across diverse populations (e.g., prior antibiotic receipt or frequent contact with the health care system), other factors may be more institution- or population-specific, again limiting the applicability of some of these studies.

Outcomes

The challenge of identifying specific direct health outcomes (such as morbidity and mortality) affected by MRSA screening again limits the applicability of the available evidence and is discussed in greater detail later in the discussion. In general however, it can be noted that the value of transmission or new acquisition as a surrogate for more meaningful clinical outcomes is limited. Acquisition of new colonization represents just one step in the continuum of a patient progressing through the following states: 1) uncolonized to 2) colonized to 3) infected to 4) complications and even death. To the extent that there is variation between individual patients, patient types, clinical settings and institutions in terms of the risk of progressing from colonized to overtly infected and from infected to morbidity and mortality will impact the applicability of the results based on just consideration of acquisition. Similarly, one must anticipate that even in the rare studies in which more meaningful outcomes are reported (including mortality), variation in clinical practices and management between patients, providers and organizations could serve to blunt or exaggerate the benefit attributed to MRSA screening itself.

More detailed analysis of the effect of MRSA screening on specific types of infection (such as vascular access device related bloodstream infections and surgical site infection), whether considered as a primary outcome or examined on a post hoc basis, offers at least the opportunity to more clearly estimate the applicability of study findings. However, this opportunity is contingent on an examination and quantification of the impact of other variables related to both

the risk of and interventions to prevent such infections in the study population. Unfortunately, such analysis was not available among the studies included in the present review.

Implications for Clinical and Policy Decision-making

Based on the insufficiency of the evidence base and its uncertain applicability, the evidence gaps research needs will need to be addressed before implications can be drawn for clinical practice and policy decision-making. That a more conservative and circumspect approach is warranted is further supported by the complex context in which decisions about the deployment of a resource intensive strategy such as MRSA screening must be made. A number of factors that contribute to this complexity are outlined in the following sections which consider the circumstances surrounding decision-making at the level of an individual hospital and the wider community.

Clinical (Hospital-Based) Decision-making

Clinical and administrative leaders make decisions about the deployment of hospital-based infection prevention strategies based on a number of factors. First among these is the clinical impact of the particular infection or pathogen that is to be targeted (as determined by the size of the population affected and the severity of associated disease). In this context, infections that occur frequently and that are associated with substantial morbidity and mortality are generally targeted as a high priority for intervention. Ideally, an important next step is to critically examine the performance of those prevention strategies that have already been deployed. In addition to pursuing rigorous surveillance data to accurately measure the impact on outcomes, hospital decision makers strive to determine whether the effectiveness of these strategies is in any way limited, such as by poor compliance with best practices or inadequate resource allocation. The next step is to determine the likely impact of the strategy under consideration. This assessment, which is aligned most closely with the type of systematic examination of the available evidence included in this review, compels hospital leadership to identify best practices that are most applicable to the problem and the local environment. A critical element of this review is to ascertain the potential unintended consequences and harms of the intervention so as to best assess the impact and to try to mitigate risk. Finally, economic considerations must be evaluated. In general, resources applied to infection prevention are limited and must be allocated so as to minimize risk of infection to the greatest number of patients.

According to accreditation standards adopted at most U.S. hospitals, the process described in the preceding paragraph should be undertaken on a periodic basis by a multidisciplinary group as part of formal infection control risk assessment. This exercise, which may be undertaken in a semi-quantitative fashion employing standardized tools, is intended to ensure that infection prevention resources are allocated in the most rational manner.

Based on examination of the available evidence as summarized in this review, it appears that insufficient information is currently available to support local infection prevention experts and hospital leaders in routinely implementing MRSA screening as part of organizational infection control risk assessment in all settings. Fundamental limitations (discussed in the following section) regarding the impact of MRSA screening on diverse populations and a variety of outcomes are most critical. Decision-making is further hindered by a near complete absence of systematic evidence regarding the potential harms of MRSA screening. However, even in the absence of these data, hospital leaders may be compelled to make a determination regarding the appropriateness of MRSA screening based on the other factors described at the beginning of this

section. More specifically, if MRSA infection is affecting a large number of patients and the resultant infections are severe and even life threatening, it may be sensible even in light of the limited available evidence to deploy a screening program. This may especially be the case if other interventions, when maximally deployed and supported, have been unable to check the spread of infection. In essence, this advice mirrors that offered in the CDC HICPAC guidelines previously cited.

Policy Decision-making

The challenges of applying the available evidence base are further compounded when decision making about MRSA screening is considered as a matter of public policy (such as in accreditation standards or legislative mandates). In this context, limitations of the applicability of the available evidence (see previous section) are especially important. One of the key arguments that has been raised against the application of broad policy mandates compelling the implementation of MRSA screening relates to the value of institutional risk assessment in determining the most appropriate control strategies for MRSA and indeed all infectious threats. In this setting, understanding the precise needs and values of the institution and then reviewing the available evidence to determine the extent to which the experience reported in the literature can be applied is essential.

Limitations of the Clinical Effectiveness Review Process

There were a number of questions and potential limitations that arose during the clinical effectiveness review process. One unexpected challenge related to intense research and policy activity surrounding MRSA screening in the time during which the review was conducted. Ongoing surveillance of the available literature as well as close scrutiny of meeting abstracts and the grey literature was undertaken to mitigate the risk that important new studies would be omitted.

Another important challenge came when determining the scope of the review. In general, the decision was made to be inclusive in considering the available literature, in which observational studies are overrepresented. One important methodological consideration related to the inclusion of reports emanating from the experience with outbreaks and clusters of infection. In this case, the decision was made to exclude such studies with the rationale that because such phenomena are so often driven by unique and sometimes undetected epidemiological factors that the applicability of findings would be severely limited.

In the same vein, contributors to this review were challenged to negotiate a rational and justifiable framework for grading the strength of evidence of the many observational reports included in the assessment. To this end, the decision was made to recognize the importance of more advanced statistical methods in attempting to control for confounding inherent in this study approach.⁸⁵⁻⁸⁷ As a result, those reports that employed regression analysis or time series analysis were graded at a higher level than other reports. A more detailed discussion of the review of the strength of evidence is provided elsewhere in this report.

Limitations of the Evidence Base, Research Gaps and Future Research Opportunities

As has been noted, there are numerous limitations to the available evidence base that ultimately compromise the applicability of these findings to clinical and policy decision-making.

In this section, these limitations are more clearly articulated and then important gaps in the available evidence are identified as targets for future research. In undertaking the comprehensive needs assessment, the PICOTS structure is once again adapted. Finally, specific concerns related to study design and analytical methods are outlined, again in the hopes of encouraging improved standards in future research.

Populations and Settings

There is an inherent tension when selecting patient populations and clinical settings for the application of MRSA screening. Larger and more diverse patient groups (such as those that might be captured in a universal screening algorithm) offer through scale alone the greatest opportunity to detect benefits and harms as measured by meaningful clinical outcomes (including morbidity and mortality). At the same time, the impact of screening on such heterogeneous groups may be biased by uncontrolled confounders or diluted by the inclusion of patients at varying degree of risk for MRSA acquisition or subsequent infection.

Ideally, future studies could target larger more homogeneous patient populations. This approach will permit the detection of even rare outcomes while simultaneously extending the applicability of the findings to similar large populations and patient groups. Moreover, by restricting inclusion so as to control for confounding that arises in heterogeneous patient populations, the opportunity to detect true biological predictors of benefit or harm are maximized. Realistically, this degree of scale will only be achieved through large multicenter trials, as is noted at the end of this section. In the future, widespread use of electronic medical records may provide predictors of benefits or harms.

Another concern regarding the patient populations included in the available evidence base relates to the study of special populations. While the risk of MRSA infection varies in some of these groups, it is essential that the potential positive and negative impact of MRSA screening on unique groups such as children and pregnant women be explored.

Interventions

As has been noted, there are severe limitations in the available evidence that can be attributed to pronounced inconsistency in defining, applying and measuring the various interventions that are bundled as part of MRSA screening. A more uniform approach to the application of specific lab measures (e.g., PCR versus culture), lab turnaround time, the handling of patients while awaiting lab results, transmission prevention strategies (e.g., contact precautions), and the use of decolonization therapy and environmental control. In addition, more precise accounting is required in order to best understand and quantify the potential bias introduced by secular and local epidemiologic trends and the influence of concomitant infection prevention strategies and interventions. This last point is especially important as infection prevention strategies (including MRSA screening) are typically deployed in sequence or concurrently. In this manner, it is essential to document the context in which screening was implemented so as to best understand the impact of the intervention. Important considerations could include prior MDRO control programs and an assessment of the culture of safety at the study sites.

In terms of addressing these shortcomings, it is unrealistic to believe that a standardized and uniform approach can be recommended and applied to all future studies or MRSA screening. Lacking such a standard, a maximally transparent approach to reporting such details is absolutely critical. During study design and budgeting, extreme caution should be applied to ensure that early methodological decisions (such as the selection of an inefficient or otherwise substandard

laboratory method) do not undermine the applicability and strength of the findings that might ultimately be generated.

Ideally, additional studies can be undertaken that will effectively compare the impact of screening strategies employing a variety of specific interventions and approaches. In essence, this work will entail examining each element of an intervention bundle in order to accurately determine the attributable benefit or harm for each component of the bundle. It may be the case, for example, that a component such as decolonization for incidentally discovered cases of MRSA may independently produce a significant clinical benefit.

Comparisons

Clinically meaningful and methodologically sound comparisons serve as the cornerstones that support the strength of evidence and applicability of applied clinical research. This is especially true when reporting the findings of observational studies. If there is one key shortcoming in the available evidence for MRSA screening it relates to fundamental issues of study design and specifically the overreliance on before/after studies.

As has been noted elsewhere in this discussion, the before/after design allows for the introduction of considerable unmeasured bias into even large observational epidemiologic studies. In this regard, even the large multicenter examinations of the impact of MRSA screening, when executed as a simple before/after design, may be seen as severely flawed.

Increasingly, it is recognized that the optimal design for testing and evaluating the impact of a novel infection prevention strategy is the cluster-randomized trial. With this approach, individual units (such as a single ICU) is randomized to either an intervention or control arm. This approach, used sparingly to date,⁴³ offers the highest standard in study design and execution and should be adopted as an expected standard on the part of grant committees, journal editors and reviewers.

Outcomes

Deficiencies in the evidence base regarding specific outcomes can be addressed in alignment with the outcomes of interest that served as the original basis for much of this review. For any future research comparing MRSA screening strategies, it is critical that these clinically significant outcomes be precisely defined and collected.

In terms of the incidence of MRSA infection, we did find that many MRSA screening studies routinely reported on MRSA infection. However, the exact definition of MRSA infection was highly variable from study to study. For future research in this field, it is imperative that case definitions are precise and specific. Ideally these will be adjusted to harmonize with existing case definitions from the CDC and elsewhere.

Precise estimates of the impact of MRSA screening on morbidity and mortality remain lacking in the extant MRSA screening literature. To allow more meaningful assessment of these crucial health outcomes, future studies will need to enroll sufficient numbers of patients to be adequately powered to detect any effect. Once again, this purpose will be best served in all likelihood through the establishment of multicenter studies.

So long as more comprehensive studies of morbidity and mortality remain elusive, the use of MRSA acquisition and transmission as a surrogate to measure the impact of screening will persist. That said, the rigor with which this outcome is tested should be enhanced. Specifically, there is the opportunity to apply more standardized approaches to the collection of surveillance specimens to detect new colonization events. Moreover, the confounding that could be

introduced by failing to examine the frequency with which various patient population proceed from colonization to infection can be mitigated through more careful analysis.

If there is a singular deficiency in determine the applicability of the results of MRSA screening studies it is directly linked to the failure to measure the unintended harm that can come with even a well-intentioned screening program. Among the numerous potential harms that have been associated with MRSA screening and related interventions are: social isolation and increased risk of safety events associated with contact precautions, inappropriate use of mupirocin, increased risk of inappropriate systemic antibiotic use, delays in patient flow and hospital discharge, stigma associated with colonization or infection. To attempt to measure the favorable impact of MRSA screening while ignoring the potential risks is to present incomplete and potentially misleading data.

Conclusions

Overall, there is insufficient evidence from good or even fair quality studies to make a conclusion regarding the effectiveness of MRSA screening in any specific setting. Even when lower quality studies are considered, considerable gaps in the evidence base remain that preclude a definitive conclusion. Compounding matters, there have been no studies that have adequately assessed the potential harms of MRSA screening, further limiting our understanding of the effectiveness of this approach.

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Abbreviations

↓:	decrease
↑:	increase
Abd:	abdominal
ACP:	American College of Physicians
AHRQ:	Agency for Healthcare Research and Policy
ANOVA:	analysis of variance
APIC:	Association of Professionals in Infection Control and Epidemiology
BA:	before/after
BICP:	background infection control practices
BP:	barrier precautions
BPCC:	barrier precautions compliance checks
BSI:	bloodstream infections
C:	control
CADTH:	Canadian Agency for Drugs and Technologies in Health
CA-MRSA:	community-acquired MRSA
CCS:	studies attempted to control for confounding/secular trends
CDC:	Centers for Disease Control and Prevention
CG:	control group
CHKGL:	checklist/guidelines
CI:	confidence interval
Coh:	cohorting
EPC:	Evidence-based Practice Center
EPICOT:	Evidence, Population, Intervention, Comparison, Outcome, Timestamp
ESCMID:	European Society of Clinical Microbiology and Infectious Diseases
ESICM:	European Society of Intensive Care Medicine
FDA:	U.S. Food and Drug Administration
GRADE:	Grading of Recommendations Assessment, Development and Evaluation
HICPAC:	Healthcare Infection Control Practices Advisory Committee
HCA:	health care-associated
HCW:	health care worker
HH:	hand hygiene
HW:	handwashing
ICAAC:	Interscience Conference on Antimicrobial Agents and Chemotherapy
ICP:	infection control practices
ICPW:	infection control practices while waiting for MRSA test results
ICU:	intensive care unit
INAM:	intranasal antimicrobial
Int:	intervention
IRR:	incidence rate ratio
ISDA:	Infectious Disease Society of America
ISF:	International Sepsis Forum
ISID:	International Society of Infectious Diseases
Iso:	isolation
ITS:	interrupted time series
IV:	intravenous
IVAB:	intravenous antibiotics
KI:	Key Informants
KQ:	Key Question
MDRO:	multi-drug resistant organism
MeSH®:	Medical Subject Headings®
MICU:	medical intensive care unit
MRSA:	methicillin-resistant <i>Staphylococcus aureus</i>

MSSA:	methicillin-sensitive <i>Staphylococcus aureus</i>
NA:	not applicable
N/n:	no; number
NG:	nasogastric
NHS:	National Health Service
NHSN:	National Healthcare Safety Network
non-CCS:	studies did not attempt to control for confounding/secular trends
NR:	not reported
NS:	not significant
PCR:	polymerase chain reaction
PEG:	percutaneous endoscopic gastrostomy
PICU:	pediatric intensive care unit
PICOTS:	patient(s), intervention(s), comparator(s), outcome(s), timing, setting(s)
PIDS:	Pediatric Infectious Diseases Society
PO:	oral/by mouth
POAB:	oral antibiotics
PRISMA:	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
QEX:	quasi-experimental
RCT:	randomized, controlled trial
RR:	relative risk
SHEA:	Society for Healthcare Epidemiology of America
SICU:	surgical intensive care unit
SIR:	standardized infection ratio
SOE:	strength of evidence
SS:	statistically significant
SSI	surgical site infection
TAMW:	topical antimicrobial washes
TEP:	Technical Expert Panel
Test +:	positive MRSA screening test result
Test -:	negative MRSA screening test result
TOO:	Task Order Officer
U.S.:	United States
U:	unclear/unknown
UK:	United Kingdom
Unspec:	unspecified
USPSTF:	U.S. Preventive Services Task Force
VRE:	vancomycin-resistant <i>Enterococcus</i>
WHO:	World Health Organization
X-over:	crossover
Y:	yes