Institute of Health Economics

Effectiveness of Screening for Endemic Antibiotic Resistant Organisms (AROs) in Hospital Settings

Summary of Systematic Reviews, Primary Studies, and Evidence-based Guidelines

Canadian Consensus Development Conference on Surveillance and Screening for AROs

July 2014

IHE INSTITUTE OF HEALTH ECONOMICS ALBERTA CANADA

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EFFECTIVENESS OF SCREENING FOR ENDEMIC ANTIBIOTIC RESISTANT ORGANISMS (AROS) IN HOSPITAL SETTINGS

SUMMARY OF SYSTEMATIC REVIEWS, PRIMARY STUDIES, AND EVIDENCE-BASED GUIDELINES

Canadian Consensus Development Conference on Surveillance and Screening for AROs

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Supported by a financial contribution from Alberta Health. The views expressed herein do not necessarily represent the official policy of Alberta Health.

ACKNOWLEDGEMENTS

The authors wish to thank the following members of the Scientific Committee who acted as an expert advisory group (EAG): John Conly, MD; Mark Joffe, MD; Andrew Simor, MD; Geoff Taylor, MD.

The EAG members provided critical feedback on the project workplan and draft report and provided information to help contextualize the information on ARO screening in Alberta and other provinces.

The authors also thank Bing Guo, Research Associate, Institute of Health Economics, for her assistance summarizing the results of the clinical practice guidelines, and Wendy McIndoo, Institute of Health Economics, for her assistance in formatting and proofreading the report.

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Funding

Production of this document has been made possible by a financial contribution from the Alberta Health.

The views expressed herein do not necessarily represent the official policy of Alberta Health.

Declared Competing Interest of Authors

Competing interest is considered to be financial interest or non-financial interest, either direct or indirect, that would affect the research contained in this report or create a situation in which a person's judgment could be unduly influenced by a secondary interest such as personal advancement.

The authors of this publication claim no competing interests.

Suggested Citation

Bond K, Tjosvold L, Harstall C. *Effectiveness of screening for endemic antibiotic resistant organisms (AROs) in hospital settings. Summary of systematic reviews, primary studies, and evidence-based guidelines.* Canadian Consensus Development Conference on Surveillance and Screening for AROs. Edmonton AB: Institute of Health Economics; 2014 July.

Web Address

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Institute of Health Economics, 2014 www.ihe.ca

ABBREVIATIONS

ARO	antimicrobial resistant organism
CA	community acquired/associated
CPO	Carbapenemase-producing organism
CRO	Carbapenem-resistant organism
ESBL	Extended-Spectrum β-Lactamase
ESBL-E	Extended-Spectrum β-Lactamase Enterobacteriaceae
HCP	healthcare personnel/provider
HA	hospital acquired/associated
HAI	hospital acquired infection
HH	hand hygiene
ICP	infection Control Program
ICU	intensive care unit
IOM	Institute of Medicine
KPC	Klebsiella pneumonia carbapenemase (a subset of CPO)
MIC	minimum inhibitory concentration
MRSA	methicillin-resistant *Staphylococcus aureus*
MRSE	methicillin-resistant *Staphylococcus epidermidis*
NDM	New Delhi Metallobetalactamase (a subset of CPO)
PPE	personal protective equipment
VRE	vancomycin-resistant Enterococci

GLOSSARY

Definitions have been drawn from various sources including Stedman's medical dictionary, the Public Health Agency of Canada and United States' Centers for Disease Control and Prevention websites, and scientific committee members.

Antimicrobial organisms (ARO): A microorganism that has developed resistance to the action of several antimicrobial agents and that is of special clinical or epidemiological significance.

Contact: An individual who is exposed to a person colonized or infected with an antibiotic-resistant organism in a manner that allows transmission to occur (for example, roommate).

Decolonization: Use of antimicrobial or antiseptic agents to eradicate target microorganisms which are present, without causing disease from a human host.

Endemic: The constant presence of a disease or infectious agent (here, ARO) within a certain area.

Epidemic: A newly introduced and transmitted organism (here, ARO) in a clinical environment where it had not previously occurred, or in an endemic setting in which the occurrence of an ARO has increased beyond the frequency it had previously occurred.

Gram test or Gram stain: A Gram stain is a laboratory test that determines whether bacteria are present and determines to which major bacterial group, Gram negative or Gram positive, the bacteria belong. The difference between Gram negative and Gram positive bacteria can be important when determining appropriate treatment for an infection. Gram stains are performed on various types of specimens including blood, tissue, stool, and sputum.

Outbreak: An increase in the number of cases (colonization and/or infection) above the number of normally occurring in a particular health care setting over a defined period of time.

Outpatient: A patient treated in a hospital and released the same day.

Point prevalence screen (or **point prevalence survey**): The collection of specimens on all patients in a specified area at a single point in time, to determine the total number of cases of a particular microorganism and to identify evidence of ongoing transmission.

Screening: A process to identify patients at risk for being colonized with AROs. Screening involves the collection and microbial culture of specimens from specific body sites in asymptomatic patients. Common screening sites include nares (nostrils), rectum, perineum, and wound and surgical incision sites.

Surveillance: The systematic ongoing collection, collation, and analysis of data with timely dissemination of information to those who require it in order to take action.

EXECUTIVE SUMMARY

Background

"Antimicrobial resistant organisms" (AROs) refers to bacteria capable of causing human disease that are resistant to one or more classes of currently available antibiotics. This resistance is associated with treatment failure leading to significant disease, infection complications, prolonged hospital stay, and increased risk of death. In the United States, it is estimated that each year at least 2 million people acquire serious infections caused by AROs, and at least 23,000 people die annually as a direct result of these infections. Of particular concern in Canadian hospitals are AROs such as methicillin-resistant *Staphylococcus aureus* (MRSA), vancomycin-resistant Enterococcus (VRE), and multidrug-resistant Gram-negative bacteria, especially those with extended-spectrum β-lactamase (ESBL), and carbapenem-resistant Enterobacteriaceae (CRE). Active surveillance screening for MRSA, VRE, and ESBL is receiving greater attention for its potential value in identifying carriers of these pathogens to prevent further transmission.

At the request of Alberta Health, the Institute of Health Economics was asked to coordinate a Canadian Consensus Development Conference on Screening and Surveillance for Antimicrobial Resistant Organisms. To help inform the Consensus Development Conference, the IHE produced the following evidence summary describing the state of evidence with respect to screening for AROs.

Objective

The following research questions were addressed in this review:

1. What are the clinical effects of a universal screening strategy for ARO carriage when compared with no screening?
2. What are the clinical effects of a universal screening strategy for ARO carriage when compared with targeted screening (screening of selected patient populations)?
3. What are the clinical effects of targeted screening for ICU patients, surgical patients, and other high-risk patients (for example, patients on hemodialysis, transferred patients) compared with no screening?

Methods

Literature search and selection

An IHE information specialist searched Medline (including in process), EMBASE, CINAHL, Cochrane Database of Systematic Reviews, CRD Databases (DARE, NHS EED, HTA), Web of Science for primary studies published in the English language between 2003 and February 2014, and for systematic reviews and guidelines published up to February 2014. The following sources of grey literature were also searched: Health Technology Assessments (HTAs) or evidence-based reports, clinical trial registries, clinical practice guidelines, position statements, and regulatory and coverage status. Reference lists of published reports were also checked. Non-indexed conference abstracts were not searched.

Titles and abstracts were screened by one reviewer and relevant articles were retrieved. Eligibility of key studies was determined by one reviewer according to the inclusion and exclusion criteria below.

Reviews were included if the methods whereby they were produced indicated the following: a focused clinical question; explicit search strategy; use of explicit, reproducible, and uniformly applied criteria

for article selection; formal critical appraisal of the included studies; qualitative or quantitative data summary or synthesis. Guidelines must have satisfied the Institute of Medicine's (IOM) definition of a clinical practice guideline and indicated that its development used an explicit and transparent process and involved a multidisciplinary panel of experts. In addition to be included, a review or primary study must have met the following criteria (arranged in PICOS format):

Study design	Systematic review or comparative study design (randomized or non-randomized controlled trials, cohort or case-control designs, single group before-and-after designs)
Population	Patients of any age
Condition	Colonization with any of the AROs of interest (Appendix 1)
Intervention	Any ARO screening strategy (that is modality and number of sites screened) that uses a screening modality, for example, PCR, culture and that may or may not include surveillance, isolation and eradication/decolonization for control of endemic (that is not outbreak) AROs
Comparator	No screening or screening of selected (targeted) patient populations.
Outcome	Effectiveness: incidence of ARO infection, morbidity (including complications of ARO infection), mortality, hospital resource utilization, for example, length of stay Safety: allergic and non-allergic toxicity, antimicrobial resistance, reduced quality of care, medical errors, etc.
Setting	Ambulatory or acute care or secondary (community) hospital. Studies included in the review must have been conducted in countries with developed market economies, as defined by the Development Policy and Analysis Division of the United Nations' Department of Economic and Social Affairs.[2] These countries include Australia, Canada, Japan, New Zealand, the United States, and European countries
Language	Limited to English

Quality assessment

The methodological quality of all included systematic reviews and primary studies was assessed by a single reviewer using a quality assessment tool developed for that design; due to time and resource limitations, the quality of guidelines was not assessed. Quality ratings were not used as inclusion or exclusion criteria. Results for all quality assessments were summarized narratively by question or domain.

Data extraction and synthesis

One reviewer abstracted data from the published reports of the selected systematic reviews and primary studies according to predetermined data extraction forms. The following general categories of data were abstracted: publication information, population and setting characteristics, outcomes reported, results, authors' conclusions.

Results of the selected systematic reviews, primary studies, and guidelines were summarized narratively and in tables. Guideline recommendations were summarized in tables.

Results

Systematic Reviews

Seven systematic reviews were identified (Table ES 1 below). The reviews were published between 2006 and 2013. Five of the reviews focused on MRSA screening, one on VRE screening, and one on both MRSA and VRE. The overall quality of the systematic reviews varied widely with AMSTAR scores ranging from 3 to 9. The highest quality reviews (that is, those described in the greatest detail and using the most rigorous methods) were the reviews conducted under the auspices of national HTA agencies, the United States Agency for Healthcare Research and Quality and the Canadian Agency for Drugs and Technologies in Health, respectively. No reviews included more than one RCT and the highly heterogeneous nature of the evidence meant that pooling of results was not conducted in any review.

Many of the studies included in the reviews reported incidence and infection rates, but no evidence was available on the potential harms of screening. Taken together, the reviews indicate that, regardless of comparison, higher quality individual studies (RCTs and reliable quasi-experimental studies) show that screening has little to no effect on ARO-related outcomes. In addition, there was no evidence regarding HA ARO-related morbidities and mortality. Across all systematic reviews, there were many more low-quality studies than high-quality studies. Five of the reviews mentioned explicitly the difficulty in drawing causal conclusions regarding the effects of screening because of the many components included in the interventions and the study designs employed.

Table ES 1: Summary of conclusions from systematic reviews

Review, comparison	Population and setting	Reviewers' Conclusions
Aboelela et al. 2006 United States Universal screening vs. no screening	Adults in tertiary care or long-term care	Studies to date assessing the impact of surveillance cultures and barrier precautions on transmission of multidrug resistant organisms are generally consistent but methodologically flawed and subject to multiple biases. Because the majority of interventions tested have included many components, it is not yet possible to determine whether there is a specific set of interventions that is essential and to identify those minimum components necessary to reduce risk of transmission.
Glick et al. 2012 United States (AHRQ) Universal vs. no screening Universal vs. targeted screening Targeted vs. no screening	Inpatient (hospital wards and ICUs) and ouptient (ambulatory clinics, urgent care centres, and emergency departments)	There is low strength of evidence that universal screening of hospital patients decreases MRSA infection. Insufficient evidence for other outcomes for universal screening. Insufficient evidence to support or refute claims of the effectiveness of MRSA screening for any outcomes in other settings (that is, targeted screening).
Chen et al. 2013 United States Targeted vs. no screening	Orthopedic surgery patients	All studies showed a reduction in SSIs or wound complications by instituting a screening and decolonization protocol in elective orthopedic and trauma patients. Preoperative screening and decolonization in orthopedic patients is an effective and cost-effective means to reduce SSIs.
Loveday et al. 2006 United Kingdom Targeted vs. no screening	Acute care patients (all including high-risk groups, e.g., previous known MRSA/elective orthopedic or cardiac surgery)	No studies reported screening as the primary intervention. In an SR of isolation policy studies, those that included screening as an additional intervention to isolating patients were considered by the reviewers to provide insufficient data to assess the individual effects of the screening of patients as a component of broader

		infection control strategies to prevent and control MRSA transmission.
Halcomb et al. 2008 Australia Targeted vs. no screening	Adult, pediatric or neonatal clients in acute care setting in hospitals in Italy, UK, and Germany	Many included studies had significant limitations. The lack of information in the studies on patient diagnosis and study setting limits the ability to generalize the findings to other settings.
Ho et al. 2012 Canada (CADTH) Targeted vs. no screening	Patients in high-risk units, for example hematology-oncology, transplant, and ICU wards	Evidence from a limited number of observational studies showed that active surveillance with weekly rectal swabs in high-risk units was associated with lower VRE bacteremia rates.
McGinigle et al. 2008 United Kingdom Targeted vs. no screening	Adult medical or surgical ICU patients	Existing evidence may favor the use of active surveillance cultures (screening), but the evidence is of poor quality, and definitive recommendations cannot be made.

Primary Studies

Six primary studies were identified that had not been considered in the included systematic reviews (Table ES 2 below). One study used a cluster randomized controlled designed and five studies used quasi-experimental designs, either interrupted time series or retrospective cohort. Five studies assessed strategies for MRSA screening (universal or targeted) and one study assessed admission screening (universal and risk factor) for extended-spectrum β-lactamase producing Enterobacteriaceae (ESBL-E).

The results of the primary studies provide an unclear picture of the benefits of screening. No studies examined the effectiveness of universal screening vs. no screening. The results of a single, large cluster randomized trial strongly suggest that, in the short term, screening and isolation and screening and targeted decolonization are not as effective as a protocol of no screening and universal decolonization in reducing MRSA colonization and infection in ICU patients. The strengths of the trial include its large size and rigorous design; potential weaknesses of the study include questions about the generalizability of the results, long term impact, and risk of inducing mupirocin resistance. This last potential drawback with universal decolonization may reduce the potential benefits of that approach.

The "bundles" of interventions implemented alongside screening (hand hygiene, barrier or contact precautions, environmental cleaning, and antimicrobial decolonization) limit the strength of the conclusions we can draw that reduction in ARO infection is a result of the effect of screening. Importantly, for infection prevention practice, the results of the three-arm trial conducted by Huang et al. provided evidence of the greater effectiveness of horizontal approaches (not pathogen specific) over vertical strategies (pathogen specific), which are considered to be resource intensive and costly. The remaining studies, though well reported and conducted, are retrospective studies; hence, the results of these should be interpreted in light of the well-known weaknesses of retrospective designs.

Table ES 2: Summary of results for primary screening studies

ARO and Strategy Quality rating	Population and setting	Study authors' conclusions	Support for ARO screening
MRSA			
Universal screening vs. targeted screening			
Lawes et al. 2012 NOS score: 9/9	All admissions to Scottish tertiary referral and teaching hospital	Screening reduced MRSA bacteremia rate	+
		Screening reduced 30-day mortality	+
Sarma et al. 2013 NOS score: 9/9	All adult elective, day case, and emergency admissions in acute and community hospitals	Screening reduced MRSA bacteremia rate	+
Targeted screening vs. no screening			
Huang et al. 2013 Risk of bias: Unclear	Adult ICU patients in 32 HCA hospitals	Universal decolonization (no screening) reduced rate of MRSA positive cultures	-
		Universal decolonization (no screening) reduced rate of bloodstream infection by any pathogen	-
		No strategy reduced rate of MRSA bloodstream infections	Neutral
Kjonegaard et al. 2013 NOS score: 9/9	Adult ICU in single community hospital	Screening did not reduce MRSA infection rate	-
Mehta et al. 2013 NOS score: 8/9	Adults undergoing elective orthopedic surgery in specialty orthopedic hospital	Screening associated with a reduction in MRSA colonization rate	+
ESBL			
Universal screening vs. no screening			
Lowe et al. 2013 NOS score: 8/9	All admissions to 12 academic and community hospitals in Toronto, ON.	Screening associated with reduction in ESBL incidence	+
		Screening associated with reduction in ESBL bacteremia rate	+

HCA = Hospital Corporation of America

Clinical Practice Guidelines

Five clinical practice guidelines (CPGs) (two from Canada and one each from Europe, the United States, and the United Kingdom) were identified that addressed screening for endemic AROs. These CPGs were published between 1997 and 2014. No quality assessment was conducted of the guidelines; however, the inclusion criteria, which were based on the IOM's definition of a practice guideline. acted as a de facto quality filter by excluding those guidelines that were not informed by a systematic review of evidence or did not use an explicit and transparent process involving a multidisciplinary panel of experts. The most recent and comprehensive CPG was produced by Public Health Ontario and published in 2013 and covered four AROs: MRSA, VRE, CPE, and ESBL-E. The remaining four CPGs focused on a specific ARO or class of ARO: MRSA, VRE, CRE, Gram-negative bacteria. Overall, all but one of the CPGs recommended admission screening of high-risk patients in endemic settings. No CPG recommended a universal screening strategy for selected AROs. None of the guidelines recommended routine staff screening for AROs.

Discussion

This review of systematic reviews, primary studies, and guidelines on screening practices for endemic AROs is the most up-to-date summary of the evidence to date. The results indicate that research in this area has focused overwhelmingly on MRSA, with only three studies identified that addressed screening for VRE and ESBL. None have addressed the most recent emerging ARO, CPO. This does not mean, however, that no studies have examined that particular ARO, only that no studies meeting our inclusion criteria did so. There is at least one study that examined interventions for CPO that may provide relevant information, but, because it was conducted in Israel, it did not meet the inclusion criteria. Despite the tremendous effort clinical researchers have put into developing and determining effective components of ARO infection prevention and control protocols, few studies have provided solid ground upon which to base recommendations regarding ARO screening. And several reports have cautioned against the overemphasis of ARO screening at the expense of other important precautions.

Despite the shortcomings in the evidence base for ARO screening, some form of active surveillance for MRSA has become routine in almost all Canadian hospitals. Research on strategies used in Canadian hospitals combined with the research results examined in this review suggest screening may add little, if anything, to the effective control of endemic AROs achieved by infection precautions and control. The difficulty in drawing conclusions because of the "bundling" of measures in all studies has been a recurring theme of this summary. A promising approach for future research would be to employ designs, such as factorial trials, that would disentangle the intervention effects and provide some indication of the relative contribution of and interaction between different prevention and control measures. In addition to the measures used and the study design employed, studies must be adequately reported so that researchers, clinicians, and policy makers can assess the merits and demerits of any single study, including the transferability of the findings. The Outbreak Reports and Intervention Studies Of Nosocomial Infection (ORION) Statement provides guidance on reporting to help researchers ensure that all relevant information needed to assess validity and applicability is provided in their research reports.

Limitations

The expedited process used to prepare this evidence summary has a number of methodological shortcomings that could potentially affect the results. First, a single reviewer only was involved at all stages of the review from literature screening and selection, quality assessment, and data extraction to analysis and summary. Second, the review of reviews did not disaggregate the primary studies included in the reviews in an attempt to resynthesize the evidence (for example, by listing studies common or unique to each review). Third, heterogeneity among the studies with respect to outcome measure, institutional policies, and other potential confounders, precluded statistically combining the results of similar studies. Fourth, because the results were summarized narratively, there was no opportunity to conduct sensitivity or subgroup analyses.

An important topic in successful ARO infection prevention and control, but one unaddressed by this report, is the role of antimicrobial stewardship, which aim to reduce antimicrobial resistance through optimized antibiotic usage. This review has also not identified or considered the potential ethical issues involved in infection prevention and control strategies, though doing so is certainly relevant to the development of robust policy recommendations. Finally, this review has focused on HA AROs; however, as a Canadian prevalence study has shown, although MRSA, VRE, and *C. difficile* are acquired predominantly in healthcare settings, MRSA is more often community associated than is VRE or CDI. Hence, there is a need to better understand the transmission between the community and hospital settings and the contribution community-acquired AROs make to HA ARO colonization, infection, and their sequelae.

Conclusion

ARO infections can have a serious impact on patients and hospital staffing resources and the cost and resources required for effective prevention and control of endemic AROs. Despite much research having been conducted on HA ARO infection prevention and control, there is currently little high-quality evidence that screening of patients (whether universal or targeted, and primarily relating to MRSA) is associated with reduction in HA ARO incidence, infection, mortality or morbidity in endemic settings. Results from a single, large RCT suggest that universal approaches to infection control may be more effective than approaches that aim to target single pathogens. Current clinical practice guidelines recommend that admission screening of high-risk patients be conducted for MRSA, VRE, and CROs. No guidelines currently recommend screening for ESBL-producing organisms. Given the current lack of reliable research evidence with which to guide decisions regarding screening, future research should focus on conducting well-designed, prospective studies that can disentangle the relative contributions of the measures used in the various approaches to HA ARO infection prevention and control.

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BACKGROUND

For the purposes of this report, the term "antimicrobial resistant organisms" (AROs) refers to bacteria capable of causing human disease that are resistant to one or more classes of currently available antibiotics.[1] This resistance is associated with treatment failure leading to significant disease, infection complications, prolonged hospital stay, and increased risk of death. In the United States it is estimated that each year at least 2 million people acquire serious infections caused by AROs and at least 23,000 people die annually as a direct result of these.[3] Of particular concern in Canadian hospitals are AROs such as methicillin-resistant *Staphylococcus aureus* (MRSA), vancomycin-resistant Enterococcus (VRE), and multidrug-resistant Gram-negative bacteria, especially those with extended-spectrum β-lactamase (ESBL), and carbapenem-resistant Enterobacteriaceae (CRE).[4] New AROs are arising on a regular basis. Carbapenemase producing organisms (CPO) are an emerging group of AROs of global concern, currently rarely seen in Canada. Although not an ARO, *Clostridium difficile* is also included since it is often a consequence of antimicrobial use. A recent point-prevalence study[4] involving 176 acute-care hospitals across Canada (68% of eligible facilities) found that approximately 1 in 12 hospitalized adults in Canada are colonized or infected with at least one of MRSA, VRE or *C. difficile*. The incidence of new cases of MRSA colonization or infection in Canadian hospitals is now estimated to be 8.8 per 1000 admissions, and of MRSA infections it is 2.6 per 1000 admissions.[4] MRSA is the single most common healthcare-associated ARO in Canada if both colonized and infected patients are considered. However, *C. difficile* infection (CDI) is now the most common cause of healthcare-associated infection in Canadian and US hospitals. The prevalence of MRSA does not appear to vary substantially in different regions of the country, but CDI rates are higher in central Canada (Quebec and Ontario), and VRE rates are lowest in eastern Canada (the Atlantic provinces). It is also important to note that it is not uncommon for patients to be colonized or infected with more than one of these AROs.[4] AROs can also be present to a greater or lesser extent in community, that is, non-health care, settings either introduced to the community from hospital settings or in the case of MRSA and CDI, arising independently.

Infection prevention and control strategies directed toward AROs in two main scenarios, during outbreaks and for endemic AROs. Endemic AROs refers to the constant presence of an organism (ARO) of epidemiologic significance within a geographical or population group. In contrast, outbreak scenarios refer to an organism (ARO) newly introduced and transmitted in a clinical environment where it had not previously occurred, or in an endemic setting in which the occurrence of an ARO has increased beyond the frequency it had previously occured.[1] It may also refer to the usual prevalence of a given disease within such an area or group.[5]

Infection prevention strategies may be described as being either vertical or horizontal.[6] Vertical strategies are designed to reduce colonization or infection due to a specific pathogen, for example, MRSA (often achieved through the use of a microbiologic screening test), on the assumption that it is more effective to target some pathogens rather than others for control measures.[6] Horizontal strategies are applied universally and use interventions that, if universally applied, can effectively control all pathogens transmitted via the same mechanism, for example, hand hygiene and disinfectant (for example, chlorhexidine) bathing (Table 1).[6]

Routine clinically directed cultures may miss a large portion of patients who are silent carriers of these organisms. As a result, potentially undetected carriers could serve as reservoirs for further transmission and infection. Active surveillance screening for MRSA, VRE, ESBL, and CPO is receiving greater attention for its potential value in identifying carriers of these pathogens to prevent

further transmission.[7] Screening takes place at the earliest point at which the patient has been identified for admission. To identify the population of colonized individuals, microbiological samples are obtained from at-risk patients even in the absence of signs or symptoms of infection. The screening strategy may use a testing modality through which results are made available rapidly (within an hour to 1 day), intermediately (results available next day to 2 days later), or longer (results available great than 2 days later). Because screening on its own is not expected to reduce ARO transmission or affect health outcomes, screening strategies must be implemented in conjunction with prevention strategies such as improving adherence to hand hygiene and use of contact precautions (the use of personal protective equipment [PPE] such as gloves and gowns), isolation of colonized or infected patients, and improved environmental cleaning. By detecting the larger population of colonized individuals, it is hoped that precautions can be implemented in a broader and timelier manner prevent infection and to interrupt horizontal transmission. Detection of colonized patients also permits the use of more aggressive interventions including, in some circumstances, suppressive or decolonization/eradication treatments with antiseptics/disinfectants. These multiple strategies and the ways in which they may be combined in a particular setting makes the assessment of the potential effectiveness of screening complex and difficult.

At the request of Alberta Health, the Institute of Health Economics was asked to coordinate a Canadian Consensus Development Conference on Screening and Surveillance for Antimicrobial Resistant Organisms. The main objectives of the conference are as follows: (1) determine the "state of the science" through a literature review and the consensus building process, and (2) transfer of the latest knowledge/evidence on the subject to a broad audience of public sector decision-makers and subsequently impacting public policy, design of services, research priorities, and health system practice. To help inform the Consensus Development Conference, the IHE provide an evidence summary describing the state of evidence with respect to screening for AROs. This evidence summary describes the intended research questions addressed, the approach taken in order to answer the proposed research questions, and the results of the research.

EFFECTIVENESS AND SAFETY OF SCREENING FOR AROS

Objectives

An ARO screening strategy, whether universal or targeted, may be composed of three potentially separate, but closely linked, activities: screening, isolation and associated interventions, and eradication/decolonization. The objective of this review was to summarize the currently available scientific evidence on the potential benefits and harms of screening (universal or targeted) for carriage of AROs (Appendix 1) in inpatient or outpatient settings and to include any primary studies on screening that were not included in the systematic reviews. The summary examines ARO screening strategies applied to all hospitalized or ambulatory patients (universal screening) and strategies applied to selected inpatient populations (for example, patients admitted to the ICU, for surgical procedure, or patients at high risk of ARO colonization or infection) and compare them with no screening or with screening of selected populations.

Research questions

1. What are the clinical effects of a universal screening strategy for ARO carriage when compared with no screening?
2. What are the clinical effects of a universal screening strategy for ARO carriage when compared with targeted screening (screening of selected patient populations)?

3. What are the clinical effects of targeted screening for ICU patients, surgical patients, and other high-risk patients (for example, patients on hemodialysis, transferred patients) compared with no screening?

Methodology

The review sought to identify and summarize the results of systematic reviews that address the research questions. In addition, literature searches were conducted to identify primary studies that would answer the research question posed for this review, but that were not included in the published reviews (because they examined screening for a different ARO than has been the subject of an existing systematic review or because the study was published subsequent to published reviews). The review also sought to identify existing evidence-based guidelines on screening for AROs.

Literature search

Detailed descriptions of the electronic searches (including inception years) are provided in Appendix 1.

Publication period:

Primary studies: 2003–February 2014 (IHE typically truncates expedited reviews of primary studies at 10 years)

Systematic reviews and guidelines: database inception to February 2014

Sources:

- **Electronic databases:** Medline (including in process), EMBASE, CINAHL, Cochrane Database of Systematic Reviews, CRD Databases (DARE, NHS EED, HTA), Web of Science
- **Grey literature** search for Health Technology Assessments (HTAs) or Evidence Based reports, clinical trial registries, clinical practice guidelines, position statements, and regulatory and coverage status. Meeting abstracts were identified through the electronic search and no additional searches were conducted for that type of report, for example, hand searches.
- **Reference lists** of the retrieved articles

Search terms: See Appendix 2 for the list of search terms.

Search limitation: limited to human studies; language limited to English

Selection of key studies

Titles and abstracts were screened by one reviewer and relevant articles were retrieved. Eligibility of key studies was determined by one reviewer according to the inclusion and exclusion criteria below.

Screening

References were screened by a single reviewer and screened out if, based on the title and abstract, it could be determined that a report was clearly not

- an organism or organism produced condition of interest (for example, *C. difficile*, *H. pylori,* tuberculosis, gonorrhea)
- on screening for AROs (for example, on prevalence, treatment)
- on screening in endemic setting (for example, screening in an outbreak)

- in a country with a developed market economy
- a primary study, systematic review, or guideline

Inclusion criteria

The full-text of studies screened in was retrieved and eligibility assessed by a single reviewer based upon the following criteria:

Reviews were included if the methods whereby they were produced were judged to be systematic. A literature review was considered systematic if it met all of the following criteria:

- focused clinical question
- explicit search strategy
- use of explicit, reproducible, and uniformly applied criteria for article selection
- formal critical appraisal of the included studies
- qualitative or quantitative data summary or synthesis (that is, a meta-analysis)

Guidelines must have satisfied the Institute of Medicine's (IOM) definition of a clinical practice guideline, which is used by the National Guideline Clearinghouse: "statements that include recommendations intended to optimize patient care that are informed by a systematic review of evidence and an assessment of the benefits and harms of alternative care options."[8] In addition, the guideline must have indicated that its development satisfied the standards articulated by the IOM with respect to an explicit and transparent process and the use of a multidisciplinary panel of experts. The definition distinguishes evidence-based guidelines from other forms of guideline development such as consensus statements, expert advice, and appropriate use criteria.

In addition, to be included, a review, primary study, or guideline must have met the following criteria (arranged in PICOS format):

Study design	Systematic review or comparative study design (randomized or non-randomized controlled trials, cohort or case-control designs, single group before-and-after designs)
Population	Patients of any age
Condition	Colonization with any of the AROs of interest (Appendix 1)
Intervention	Any ARO screening strategy (that is modality and number of sites screened) that uses a screening modality, for example, PCR, culture and that may or may not include surveillance, isolation and eradication/decolonization for control of endemic (that is not outbreak) AROs
Comparator	No screening or screening of selected (targeted) patient populations
Outcome	Effectiveness: incidence of ARO infection, morbidity (including complications of ARO infection), mortality, hospital resource utilization, for example, length of stay Safety: allergic and non-allergic toxicity, antimicrobial resistance, reduced quality of care, medical errors, etc.
Setting	Ambulatory or acute care or secondary (community) hospital. Studies included in the review must have been conducted in countries with developed market

	economies, as defined by the Development Policy and Analysis Division of the United Nations' Department of Economic and Social Affairs.[2] These countries include Australia, Canada, Japan, New Zealand, the United States, and European countries
Language	English

In the case of duplicate publications, the most recent, that is, most comprehensive, version of the study was included.

Exclusion criteria

Studies were excluded if they met any one of the following criteria:

Study design	Conference abstracts, letters, news, editorial comments, reports of single cases, or guideline that is not evidence-based
Population	People not in outpatient or inpatient (hospital) setting. Outpatient settings include patients going to the ER but then released and not admitted to hospital and patients attending day clinics or day surgeries which are located in hospitals and in which the patients are not admitted overnight
Condition	ARO other than those of interest (Appendix 1)
Intervention	Practices that do not include screening for carriage (for example, surveillance, isolation or decolonization only) or screening practices during ARO outbreaks
Comparator	Comparators other than no screening or screening of selected (targeted) patient populations
Outcomes	Studies that did not report quantitative data on any of the pre-defined outcomes
Setting	Long-term care or non-hospital setting
Language	Language other than English

Quality assessment

The methodological quality of all included systematic reviews and primary studies was assessed by a single reviewer using the following assessment tools:

Systematic reviews: Assessing the Methodological Quality of Systematic Reviews (AMSTAR) checklist.[9]

Randomized studies: Cochrane Collaboration risk of bias tool.[10]

Non-randomized studies: Ottawa-Newcastle Checklist[11] for cohort, time series, and case-control studies.

Due to time and resource limitations, the quality of guidelines was not assessed. Quality assessment results were not be used as inclusion or exclusion criteria. Results for all quality assessments were summarized narratively by question or domain.

Data extraction

One reviewer (KB or BG) abstracted data from the published reports of the selected systematic reviews, primary studies, and guidelines according to predetermined data extraction forms. The following general categories of data were abstracted: publication information, population and setting characteristics, outcomes reported, results, and authors' conclusions.

Data synthesis

Results of the selected systematic reviews, primary studies, and guidelines were summarized narratively and in tables. Guideline recommendations were summarized in tables.

RESULTS

Literature Search

From 8847 citations identified through the electronic and grey literature searches, 18 reports were included: seven systematic reviews,[5,12-17] six primary studies,[18-23] and five guidelines.[1,24-27] A flow diagram illustrating the selection process and a complete list of the excluded studies and reasons for exclusion can be found in Appendices 3 and 4.

Summary of Included Systematic Reviews

The seven systematic reviews[5,12-17] were published between 2006 and 2013. Five of the reviews focused on MRSA screening,[5,13,14,16,17] one on VRE screening[15] and one on both MRSA and VRE.[12]

Quality assessment

The overall quality of the systematic reviews varied widely with AMSTAR scores ranging from 3 to 9 (Appendix 4). The highest quality reviews (that is, those described in the greatest detail and using the most rigorous methods) were the reviews by Glick et al.[14] and Ho et al.[15] The reviews were conducted under the auspices of national HTA agencies, the United States Agency for Healthcare Research and Quality[14] and the Canadian Agency for Drugs and Technologies in Health,[15] respectively. In general, the lower scoring reviews[12,13,16,17]did not indicate explicitly that an a priori protocol had been developed; did not use two reviewers for study selection, quality assessment, and data extraction; did not describe searching for "grey" or unpublished literature; and did not report a complete list of included and excluded studies. The latter omission, no report of excluded studies, was in all four cases a likely result of editorial restrictions. No studies included more than one RCT and the highly heterogeneous nature of the evidence was frequently commented on and described by the reviewers, so pooling of results was considered "not applicable" for all reviews. No reviews described or commented on the need for an assessment of potential publication bias or described the potential conflicts of interest for individual studies included in the reviews.

Individual systematic reviews

The individual components (objective, literature search, quality assessment, studies included, outcomes, strength of evidence, and conclusions) of each of the included systematic reviews is described below and summarized in tables in Appendix 5. A discussion of the systematic review evidence follows the individual review summaries.

Aboelela et al. 2006[12]

Background: Aboelela et al. conducted a review of guidelines and the clinical scientific literature to describe the current recommendations for and the effectiveness of barrier precautions and surveillance cultures to control transmission of multidrug resistant organisms (MRSA and VRE).

Search: Literature searches for guidelines, randomized controlled trials, and non-randomized studies were conducted in PubMed, Cochrane CENTRAL, and the Cochrane database of systematic reviews from January 2004 to June 30, 2005. Searches were restricted to peer-reviewed English language publications.

Quality assessment: The methodological quality of included studies was assessed using a tool developed from quality assessment instruments used in previous reviews. Quality assessment examined five domains: representativeness, bias, confounding, description of intervention, outcomes assessment, and statistical analysis. The quality of each domain was rated as "completely adequate," "partially adequate," "inadequate," or "not specified," and "not applicable." Ratings were given numerical scores and summary scores provided for each study. The average overall study score was 75% (range 41 to 100). Studies scored lowest on average in the domain of intervention description (66% SD ±19). Of seven studies that had quality scores ≥90%, three assessed the use of surveillance cultures.

Included studies: Thirty published articles were included in the review, 21 of which assessed the effectiveness of interventions that included surveillance cultures among other interventions (for example, isolation, gowns and gloves, environmental cleaning), seven of which employed surveillance cultures as one of the main interventions under study. All studies used a quasi-experimental design without a control group and with a single pretest and posttest measure. Almost all of the studies examined patients in acute care/ICU settings.

Outcomes: Among the seven studies that specifically examined the effectiveness of surveillance cultures, five studies found a statistically significant decrease in colonization or infection rates. The remaining two studies found no difference.

The review provides outcome data for the three before-and-after studies on surveillance cultures that had quality scores of ≥90%. A study in a medical ICU in a teaching hospital found no difference in VRE colonization rates. A study in an ICU in a university teaching hospital found that VRE acquisition rates decreased from 3.78 cases/100 days to 1.8 cases/100 days. A study in a German acute care hospital that cultured all high-risk patients upon admission found a 48% reduction in the frequency of hospital acquired MRSA.

Rating of strength of evidence: No assessment was made of the strength of evidence.

Reviewer conclusions: The reviewers concluded that studies to date assessing the impact of surveillance cultures and barrier precautions on transmission of multidrug resistant organisms are generally consistent but methodologically flawed and subject to multiple biases. Because the majority of interventions tested have included many components, it is not yet possible to determine whether there is a specific set of interventions that is essential and to identify those minimum components necessary to reduce risk of transmission.

Chen et al. 2013[13]

Background: Chen et al. conducted a systematic review of the clinical scientific literature to determine whether MRSA screening and decolonization reduce surgical site infections (SSI) in orthopaedic patients and if this protocol is cost-effective.

Search: Literature searches for randomized controlled trials and non-randomized studies were conducted in PubMed, Cochrane CENTRAL, and the Cochrane database of systematic reviews, DARE, Health Technology Assessment Database, and NHS Economic Evaluation Database from inception to December 2012.

Quality assessment: The methodological quality of included studies was assessed by the type of study, the year the study was conducted, and the sample size (studies more than 1000 participants were considered more favorably). Studies were categorized into good, fair, and low. Most studies were judged "fair" as a result of the use of a retrospective design, small sample sizes, or being published before 2007 (the authors do not indicate why this date was significant for study validity).

Included studies: Nineteen studies evaluated the ability of MRSA screening and decolonization to reduce SSIs in orthopaedic patients. Nine of the studies were prospective (including three RCTs) and ten were retrospective. Most studies evaluated screening and decolonization on patients undergoing elective joint arthroplasty. The majority of studies screened using cultures and defined SSIs according to CDC criteria. Five studies reswabbed patients after decolonization to ensure they were negative and before proceeding to surgery. In all studies, contact precautions were instituted for patients who were MRSA colonized.

Outcomes: All 19 studies indicated a reduction in SSIs when an MRSA screening and decolonization protocol was used; however, statistically significant reductions were reported in 14 studies. The reduction in overall SSIs ranged from 13 to 200%, the reduction of S. aureus SSIs ranged from 40 to 200%, the reduction of MRSA SSIs range from 29 to 149%.

Rating of strength of evidence: No assessment was made of the strength of evidence.

Reviewer conclusions: All 19 studies showed a reduction in SSIs or wound complications by instituting a screening and decolonization protocol in elective orthopaedic and trauma patients. Preoperative screening and decolonization in orthopaedic patients is an effective and cost-effective means to reduce SSIs.

Glick et al. 2013[14]

Background: Glick et al. conducted a systematic review for the U.S. AHRQ to synthesize comparative studies that examined the benefits or harms of screening for MRSA carriage in inpatient or outpatient settings. The review examined MRSA-screening strategies applied to all hospital or ambulatory patients (universal screening) as well as screening strategies applied to selected inpatient or outpatient populations (patients admitted to ICU, to surgical procedure or patients at high risk of MRSA colonization or infection) and compared them to no screening or with screening of selected populations. The review included strategies that included screening with or without isolation or attempted eradication/decolonization.

Search: Literature searches for comparative studies and systematic reviews were conducted in MEDLINE, Embase, Cochrane CENTRAL and database of systematic reviews from 1990 to March 30, 2012. Websites of NICE, National Guideline Clearinghouse, and the UK NHS HTA Programme were also searched and grey literature was also searched. The search and selection identified 48 studies.

Quality assessment: Quality of the studies was assessed using the United States Preventive Services Task Force framework that assesses studies according to the following criteria: assembly and maintenance of comparable groups; loss to follow-up; measurements (equal, reliable, and valid); clear definition of interventions; consideration of all important outcomes; and analysis (adjustment for potential confounders and intention-to-treat analysis). Overall quality of individual studies was rated as "good," "fair," or "poor." Of the 16 studies providing evidence on the effectiveness of screening, nine studies were rated "poor", one "fair", and six "good".

Included studies: Of 48 studies that met the inclusion criteria, only 16 quasi-experimental studies were considered to have controlled for potential confounding or secular trends and sufficiently trustworthy for drawing causal inferences. This summary describes only the results of those studies that were judged adequate to supporting causal inferences regarding screening. Three studies (two "poor," one "good") compared universal screening with no screening; two studies (both "good") compared universal screening with targeted screening (ICU patients); seven studies (two "good," one "fair," four "poor") compared screening of ICU patients with no screening; three studies (one

"good," two "poor") compared screening of surgical patients (orthopaedic, cardiothoracic, head and neck cancer, percutaneous endoscopic gastronomy replacement) with no screening; three studies (all "poor") compared screening of high-risk patients with no screening.

The reviewers reported that no meta-analyses were conducted for any comparison because of the heterogeneity of the studies.

Outcomes:

Universal screening vs. no screening: One study showed a 17% reduction in health-care associated MRSA acquisition in the ICU and 21% reduction in non-ICU settings. Two studies reported reductions in MRSA infection: one reported a reduction of 69.6% (95% CI 19.6--89.2), the other a reduction of 62% in ICU settings and 45% in non-ICU settings.

Universal screening vs. targeted screening: One study showed a 52.4% (95% CI 9.3--78.3) reduction in hospital acquired MRSA infection with universal screening compared with targeted screening. One study found a 0.12% reduction, but the difference was not statistically significant (p = 0.23).

Screening of ICU patients vs. no screening: One good quality cluster RCT found no difference in MRSA acquisition rates between no screening and screening of ICU patients. Three poor quality studies found statistically significant reductions between no screening and screening of ICU patients.

One good quality quasi-experimental study did not find a statistically significance in rates of MRSA infection, rate difference -1.46 (95% CI, -3.43–0.51). One poor quality study found a 75% reduction in infection rates: 5.45/1000 patient-days before intervention, 1.35/1000 patient-days after intervention, (p = 0.001).

One good quality quasi-experimental study found no statistically significant reduction in MRSA bloodstream infections between screening ICU patients and no screening: absolute change in prevalence density -0.18 (95% CI, -0.99–0.62). One poor quality study found a statistically significant reduction in infections.

One good quality study did not find a statistically significant reduction in surgical site infection between screening ICU patients and no screening.

Screening of surgical patients vs. no screening: One good quality cohort study including a range of surgical procedures did not find a statistically significant difference in MRSA acquisition rates between screening and no screening: rate ratio 1.1 (95% CI, 0.8–1.4). One poor quality time-series study did not find a statistically significant difference in the incidence of MRSA acquisition between screening and no screening: rate ratio 0.775 (95% CI, 0.371–1.617) or in incidence of MRSA infection: rate ratio: 0.958 (95% CI, 0.909–1.009).

One good quality cohort study including a range of surgical procedures did not find a statistically significant difference in MRSA infection between screening and no screening: 1.11/1000 patient-days vs. 0.91/1000 patient-days. One poor quality before-and-after design found a statistically significant reduction in MRSA infection favouring screening: 0.63/1000 patient-days vs. 1.56/1000 patient-days (p = 0.003).

One good quality cohort study including a range of surgical procedures did not find a statistically significant difference in surgical site infection between screening and no screening: rate ratio 1.2 (95% CI, 0.8–1.7).

Screening of high-risk patients vs. no screening: "Screening of high-risk patients" was defined variously in the studies and referred to the patient population (for example transferred from a nursing home or other health care facility) or ward (for example high prevalence of MRSA transmission or infection). One poor quality interrupted time-series study found a statistically significant reduction in MRSA acquisition between screening of both high-risk patients and patients on high-risk wards and no screening: change in acquisition rate -0.045 (95% CI, -0.029– -0.062).

One poor quality before-and-after study found a statistically significant reduction in the rate of MRSA infection favouring screening over no screening: 0.87/10,000 patient-days vs. 2.25/10,000 patient-days ($p<0.001$).

One poor quality interrupted time-series study found a statistically significant reduction in incidence of MRSA bacteremia favouring screening over no screening: -0.051 (95% CI, -0.02– -0.083, $p = 0.002$) and -0.006 (95% CI, -0.01– -0.10, $p = 0.01$). A second poor quality interrupted time-series study found a statistically significant reduction in the incidence of MRSA bacteremia favouring screening over no screening: 0.55/1000 patient-days (95% CI, 0.36–0.83) and 0.27 (95% CI, 0.14–0.58).

One poor quality before-and-after study found a statistically significant difference in rates of surgical site infection favouring screening high-risk patients over no screening: 0.27/10,000 patient-days vs. 0.75/10,000 patient-days ($p<0.001$).

Rating of strength of evidence: The system for rating the strength of the overall body of evidence was developed by the AHRQ and is a modified version of the GRADE system. Strength of evidence is determined for each outcome according to four domains: risk of bias, consistency, directness, and precision, and is given one of four ratings: "high," "moderate," "low," or "insufficient." Observational studies that did not control for confounding (32 of the 48 studies) were considered "fatally flawed' and not sufficiently trustworthy to support casual inference. Hence, these studies were not included in the strength of evidence assessment. Evidence for reduction of MRSA acquisition using universal screening was considered low. Evidence for all other comparisons and outcomes was considered insufficient to draw conclusions regarding MRSA screening.

Reviewer conclusions: The reviewers found low strength of evidence that, compared with no screening, universal screening for MRSA carriage reduces healthcare-associated MRSA. There was insufficient evidence to determine the effectiveness of the other screening strategies (targeted screening) in reducing MRSA acquisition or infection.

Halcomb et al.[5]

Background: Halcomb et al. conducted an update of a 2002 systematic review to identify and synthesize the results of research on the efficacy of infection control practices in controlling endemic MRSA or MRSA outbreaks in acute hospital settings.

Search and results: Searches were conducted MEDLINE, Embase, CINAHL for studies published in English between 1990 and August 2005. Searches were also conducted in the Cochrane Library (to Issue 3, 2005) and the Joanna Briggs Institute Evidence Library (to August 2005) to identify primary studies that examined the efficacy of MRSA outbreak or endemic MRSA infection control strategies for adult, pediatric or neonatal populations in acute care settings. Reference lists of studies and bibliographies of expert committee reports and guidelines were also searched to identify primary literature. In addition, hand searching was conducted in 15 journals.

Quality assessment: Methodological quality of the included studies was assessed using an instrument developed by the reviewers. The instrument assessed the reporting quality of the study sample,

setting, method of sampling, history of MRSA, type of study, method of data collection, cleaning regime, research design, blinding, type of analysis, clinical significance and consistency of the conclusions with results. The maximum score attainable was 36. A quality threshold was established as an inclusion criterion based on the mean quality score of all studies, a score of 29.

Included studies: The reviewers identified five studies that describe the management of endemic MRSA either prior to hospital admission for elective surgical patients (one study) or following admission (four studies).The screening cultures varied from single nasal cultures to nasal passages and a combination of rectal, axilla and groin swabs; throat, skin, lesions, and invasive devices. Studies also varied in the frequency of taking cultures: some reported regular weekly cultures, others did not report the frequency of follow-up cultures.

Outcomes: One study in a community hospital in Italy employed active nasal surveillance cultures from high-risk patients (for example nursing home residents, those transferred from ICU, cardiac, or neurosurgery) or those admitted to high risk wards (for example, ICU, bone marrow transplant unit).The incidence of MRSA bloodstream infections was reduced from o.64 to 0.30 per 10,000 admissions (RR 0.46; 95% CI 0.25-0.87).

A study conducted in an elective orthopedic ward in the United Kingdom employed nose, axilla, and groin swabs taken 7 days prior to admission. The study reported a reduction in hospital acquired infections from 8.5% to 3.5%, $p<0.05$, which the study authors attributed to preadmission MRSA screening.

A study conducted in an adult cardio-thoracic unit in the United Kingdom pre-admission, admission, and weekly MRSA screening. No significant change was found in proportion of patients admitted with MRSA. There was a 62.5% reduction in the proportion of patients acquiring MRSA on the ward, RR 2.4, 95% CI 1.32-4.42. There was an 82% reduction in the rate of bloodstream MRSA infections RR 5.34, 95% CI 1.20, 23.78.

A study in a medical/surgical ICU in France instituted nasal and rectal swabs on admission, weekly, and at discharge. There number of patients infected or colonized with MRSA was reduced from 7.7% to 2.6%, $p = 0.004$.The rate of patients infected or colonized with MRSA per 1000 patient days was reduced from 4.4 to 2.2.

A study in a university hospital in Germany screened all potential MRSA patients (known history of MRSA, admitted from hospitals with endemic MRSA, nursing homes, pressure sores, invasive devices). Based on the control period, a predicted total of 73.2% hospital acquired MRSA was expected; however, only 52% were observed.

Rating of strength of evidence: The strength of the evidence was graded using National Health and Medical Research Council Levels of Evidence. Included studies were classified as either level III (comparative studies with historical control, two or more single arm studies or interrupted time series without parallel control group) or IV (case series, posttest or pretest/posttest).The reviewers described the overall quality of evidence as poor.

Reviewer conclusions: The heterogeneity among studies in setting, suites of interventions, and outcome measures made evaluating the relative effectiveness of infection control strategies (including screening) impossible. The overall poor quality of evidence further impairs the ability to draw conclusions regarding the contribution any single component makes in reducing MRSA transmission. The review authors recommend that, among other issues, future research ought to evaluate the available literature on optimal prospective surveillance strategies, in terms of optimal

screening sites, frequency of screening, and the number of negative cultures to ensure clearance of MRSA.

Ho et al. 2012[15]

Background: Ho et al. conducted a review of the clinical literature for the Canadian Agency for Drugs and Technologies in Health (CADTH) to assess the relative effectiveness of universal versus selective screening for adult and pediatric populations colonized or infected with VRE and ESBL-producing organisms in acute and long-term care facilities

Search and results: Literature searches for HTAs, systematic reviews, meta-analyses, randomized controlled trials, and non-randomized studies were conducted in MEDLINE, Embase, Cochrane library and PubMed from 2002 to March 25, 2012. Grey literature and Google searches were also conducted to search for web-based materials. Searches were restricted to English language publications. One observational study was identified.

Quality assessment: The methodological quality of included studies as assessed using the Downs and Black checklist. Quality assessment results were reported narratively.

Included studies: One retrospective cohort studies conducted provided data on the effectiveness of screening for endemic VRE. The study compared the effects of active surveillance (screening) versus no active surveillance of patients at risk for VRE infection in two tertiary care hospitals in the United States during a 6-year period. Active surveillance included rectal swabs from all patients for 3 consecutive weeks in high-risk units such as the hematology-oncology, transplant, and ICU wards.

Outcomes: The hospital without active surveillance (screening) had 2.1 fold more cases of VRE bacteremia than did the hospital with the screening program (17.1 versus 8.2 patients per 100,000 patient days).

Rating of strength of evidence: No assessment was made of the strength of evidence.

Reviewer conclusions: The reviewers concluded that the findings on the effectiveness of infection prevention strategies for VRE and ESBL-producing organisms should be interpreted with caution given the scarcity of evidence and the noted limitations of the included studies.

Loveday et al. 2006[16]

Background: Loveday et al. conducted a systematic review of the literature to inform guideline development by the Joint Meticillin Working Party Subgroup A, Prevention and Control of MRSA. As part of the review, which focused on interventions to prevent and control the transmission of MRSA in hospital settings, the reviewers sought to identify any systematic reviews or primary studies that examined the effectiveness of pre-admission or on-admission screening of all or high-risk patients (previous known MRSA, elective orthopedic/cardiac surgery) in reducing the incidence of MRSA transmission.

Literature search: Searches were conducted in six electronic bibliographic databases: MEDLINE, Embase, CINAHL, Cochrane Clinical Trials Register, DARE, Health Management Information Consortium Database, and the National Research Register. Searches were limited to studies published in English from 1996–2006. The reviewers sought primary studies, systematic reviews and guidelines that addressed the research question.

Quality assessment: The methodological quality of included studies was assessed by a single reviewer using a process developed by the Scottish Intercollegiate Guideline Network.

Included studies: The search did not identify any studies that reported screening as a primary intervention. Studies of isolation policies that included screening strategies did not contain sufficient data to assess individual effects of screening.

Outcomes: The primary outcome of interest was reduction in colonization or infections. Secondary outcomes were length of stay and antimicrobial prescribing. A single time series study conducted in an ICU setting indicated that the combination of controlling antimicrobial prescribing, screening patients on admission, and isolation of colonized patients resulted in a reduction of MRSA infection attributed to nosocomial acquisition from 8.6% to 0% ($p = 0.0001$).

Rating of strength of evidence: The evidence was graded using a system developed by Eccles and Mason. The reviewers graded the evidence for the effectiveness of screening as Grade III (evidence from non-experimental descriptive studies, for example correlation studies and case-control studies).

Reviewer conclusions: The reviewers conclude that the baseline data for the single study described may have overestimated MRSA incidence and that the number of interventions precluded attributing the reduction in infection to any single component of the intervention. No conclusions were drawn regarding the effectiveness of screening.

McGinigle et al. 2008[17]

Background: McGinigle et al. conducted a systematic review of studies that examined the use of active surveillance cultures (admission screening and at least weekly screening thereafter) in ICU patients to assess its ability to reduce MRSA transmission rates, infection rates, MRSA-related mortality or all-cause mortality.

Literature search: Searches to identify any experimental, observational, uncontrolled or ecological studies published in English were conducted in four electronic bibliographic databases: MEDLINE, Web of Science, CINAHL, and the Cochrane library (database inception to September 2007). The reference lists of all included articles were searched and hand searches were conducted in five major journals (2000–2007). Searches were also conducted of the websites of the Centers for Disease Control and Prevention and the Institute for Healthcare Improvement.

Quality assessment: Methodological quality of the included studies was assessed using the UK National Health Service Centre of Reviews and Dissemination guidelines. Overall study quality was rated as "good," "fair," or "poor." None of the included studies were of rated "good." Five studies (one retrospective cohort, one case-control, and three interrupted time-series) were rated as "fair" quality; the remaining studies were rated "poor".

Included studies: Sixteen observational studies (retrospective cohort, case-control, interrupted time series, before-and-after, and ecological studies) were included in the review. Two of the studies contained a control group. The studies were conducted in Europe (nine studies), United States (five studies), Brazil, and Israel (one study each). All studies took nasal samples as part of screening, but half of the studies also took samples from other sites, including the throat, groin, rectum, and open wounds.

Outcomes: Thirteen of the 16 studies (including both controlled studies) reported a decrease in the incidence of hospital acquired MRSA infections in association with the use of screening. The most dramatic result was a study that reported a 75% decrease in MRSA infections in the ICU where screening was used and a 40% reduction in the remainder of the hospital where no intervention was in place. The majority of the other studies showed a 40–60% decrease in hospital acquired MRSA incidence. Three studies reported negative findings and did not find an association between screening and MRSA incidence.

Rating of strength of evidence: No assessment was made of the strength of the evidence.

Reviewer conclusions: Evidence from multiple observation-based studies suggests that the use of active surveillance cultures reduces the incidence of MRSA infection, but the overall quality of the evidence is poor; thus, definitive, evidence-based clinical recommendations cannot be made. An unambiguous definition of "active surveillance culture," a clear implementation protocol including defined screening groups and laboratory methods, and rigorous economic evaluations are all lacking.

Summary of systematic review evidence

This overview identified seven moderate to high-quality systematic reviews examining the effectiveness of universal and targeted screening for HA MRSA and VRE. No reviews addressed ESBL or CPO. The reviews varied in the study designs considered for review, in the rigor of the literature search and selection process used to identify relevant studies, as well as in the methods used to appraise the potential risk of bias of the included studies. Despite these differences, there are some common patterns in the results. While many studies reported incidence and infection rates, no evidence was available on the potential harms of screening. Though still little investigated, some research has investigated the impact of control measures such as isolation on psychosocial outcomes.[15] Taken together, the reviews indicate that, regardless of comparison, higher quality individual studies (RCTs and reliable quality quasi-experimental studies) show that screening has little to no effect on ARO-related outcomes. In addition, there is no evidence regarding what may arguably be the most important measures of the effectiveness of infection prevention strategies, namely, HA-ARO related morbidities and mortality.

Retrospective studies (both cohort and time series analysis) found screening to significantly reduce ARO acquisition and infection. This difference between study results and study design is noted explicitly in the category of "consistency' in the rating of the strength of evidence by Glick et al.[14] Across all systematic reviews, there were many more low-quality studies than high-quality studies. Five of the reviews[5,12,14,16,17]mentioned explicitly the difficulty in drawing causal conclusions regarding the effects of screening because of the many components included in the interventions and the study designs employed (Table 1 below).

The largest and one of the most recent reviews on MRSA, that by Glick et al.,[14] excluded half of the studies that met inclusion criteria because the studies used simple two-group statistical analyses. The reviewers believed this form of analysis prohibited making causal inferences because the confounding was considered too great. For example, because the incidence of MRSA infection is decreasing, studies that employ a before-and-after design without controlling for secular trends are unable to distinguish between an effect due to the intervention and an effect due to the persistence of the secular trend itself. Potential confounders include compliance with taking swabs for culture; compliance with isolation precautions, including hand hygiene and glove and gown use; length of time before reported culture results and whether interventions have been initiated during this period; patient length of stay; patient case mix; staffing levels; use of prophylactic antibiotics; type and endemnicity of MRSA and the endemic level of community-acquired MRSA.[17]

Nevertheless, though the authors excluded these weaker study designs (so-called non-CCS studies) in judging the overall strength of evidence, they believed it was of value to comment on the pattern of results seen in these very low-quality studies. However, the review authors give no reason as to why the "pattern of results" may be of interest given the inability to draw causal inferences from them (for example they do not describe *other* inferences that might be made based on these results) nor do the authors appear to draw conclusions of any kind from the results. Hence, this overview has not considered this additional information. No other review authors considered categorizing and

rating the evidence based on the approach used in statistical analysis to help adjust for potential confounders and secular trends and, as a result, many non-CCS studies are included in the bodies of evidence assembled in the other reviews. The results of the reviews should be interpreted and compared with these facts in mind.

Further related to issues of the interpretation of evidence, only three reviews[5,14,16] employed a framework for grading the strength of the evidence (what is termed the "quality of the evidence" by GRADE,[28]") summarized by systematic review. Glick et al.[14] commented that their use of a more rigorous evidence grading system, one that forces researchers to explicitly examine and state the components thought most important to drawing inferences regarding clinical effectiveness, may have contributed to any differences in conclusions. The use of a grading scheme such as that used by Glick et al. makes clear that the main difficulty confronting the reviewers was making judgements that took account of the varying degrees of risk of bias across the studies. The other components of the grading scheme (consistency of results, directness in outcome and comparison, and precision of result) were relatively stable (outcomes and comparisons were direct, precision did not apply as no meta-analyses were conducted, and consistency was often unknown). Though only a few reviews employed a grading scheme, Glick et al.[14] noted that, though their review included a much larger evidence base (and arguably the most explicit and rigorous grading of the body of evidence), the results of their review were not substantially different from previous reviews.

The conclusions of all three of these reviews highlight the difficulties the evidence creates when formulating causal conclusions regarding the effectiveness of ARO screening and in generalizing beyond the individual study settings. The review by Chen et al.[13] drew an overall positive conclusion regarding the effectiveness of screening (in orthopedic surgery patients), but did not systematically grade the body of evidence; the reviewers' conclusions have not gone unchallenged. Verhoeven et al.[29] argued that, despite the inclusion of some well-conducted studies in the review,[13] many studies had questionable methodology. They argue also that the positive conclusion regarding screening and decolonization for the orthopedic population seems to have been based primarily on the results of one well conducted study, only a small proportion of the population of which was orthopedic surgery patients. Using the results of a sub-group meta-analysis of randomized trials, Verhoeven et al. argue that, if the results are restricted to the orthopedic populations in the trials they examined, the potential benefit of the strategy is no longer statistically significant. Hence, no clear conclusions can be drawn regarding the effectiveness of screening and decolonization for this population. The response by Chen et al.[30] underlines the difficulty in synthesizing the results of studies that employed different methodologies, even if they are well conducted, and in drawing conclusions from this body of evidence.

Drawing conclusions regarding the effect of screening itself was also made difficult by the substantial heterogeneity among the studies with respect to the definitions of outcomes (e.g. being "hospital acquired") and in the additional components of the prevention and decolonization protocols that were employed along with screening (for example, contact precautions, isolation, decolonization protocols). Clinical outcomes are influenced by the application of additional infection control interventions that come in the wake of screening, including hand hygiene, barrier or contact precautions, environmental cleaning, and antimicrobial decolonization. Studies also varied in the different methods used for testing swabs and the variation in turn-around time may also have affected efficient communication among staff. This is important because direct and efficient communication between different teams regarding new infections may be an important factor in the effectiveness of infection prevention and control.[31]

Table 1: Summary of conclusions from systematic reviews

Review, comparison	Population and setting	Reviewers' Conclusions
Aboelela et al. 2006[12] United States Universal screening vs. no screening	Adults in tertiary care or long-term care	Studies to date assessing the impact of surveillance cultures and barrier precautions on transmission of multidrug resistant organisms are generally consistent but methodologically flawed and subject to multiple biases. Because the majority of interventions tested have included many components, it is not yet possible to determine whether there is a specific set of interventions that is essential and to identify those minimum components necessary to reduce risk of transmission.
Glick et al. 2012[14] United States (AHRQ) Universal vs. no screening Universal vs. targeted screening Targeted vs. no screening	Inpatient (hospital wards and ICUs) and ouptient (ambulatory clinics, urgent care centres, and emergency departments)	There is low strength of evidence that universal screening of hospital patients decreases MRSA infection. Insufficient evidence for other outcomes for universal screening. Insufficient evidence to support or refute claims of the effectiveness of MRSA screening for any outcomes in other settings (that is, targeted screening).
Chen et al. 2013[13] United States Targeted vs. no screening	Orthopedic surgery patients	All studies showed a reduction in SSIs or wound complications by instituting a screening and decolonization protocol in elective orthopedic and trauma patients. Preoperative screening and decolonization in orthopedic patients is an effective and cost-effective means to reduce SSIs.
Loveday et al. 2006[16] United Kingdom Targeted vs. no screening	Acute care patients (all including high-risk groups, e.g., previous known MRSA/elective orthopedic or cardiac surgery)	No studies reported screening as the primary intervention. In an SR of isolation policy studies, those that included screening as an additional intervention to isolating patients were considered by the reviewers to provide insufficient data to assess the individual effects of the screening of patients as a component of broader infection control strategies to prevent and control MRSA transmission.
Halcomb et al. 2008[5] Australia Targeted vs. no screening	Adult, pediatric or neonatal clients in acute care setting in hospitals in Italy, UK, and Germany	Many included studies had significant limitations. The lack of information in the studies on patient diagnosis and study setting limits the ability to generalize the findings to other settings.
Ho et al. 2012[15] Canada (CADTH) Targeted vs. no screening	Patients in high-risk units, for example hematology-oncology, transplant, and ICU wards	Evidence from a limited number of observational studies showed that active surveillance with weekly rectal swabs in high-risk units was associated with lower VRE bacteremia rates.
McGinigle et al. 2008[17] United Kingdom Targeted vs. no screening	Adult medical or surgical ICU patients	Existing evidence may favor the use of active surveillance cultures (screening), but the evidence is of poor quality, and definitive recommendations cannot be made.

Summary of Recently Published Primary Studies

Six primary studies[18-23] were identified that had not been considered in the included systematic reviews because they were published subsequent to the literature searches. Five of the primary studies[18,19,21-23] identified were published in 2013 and one[20] in 2012. Five studies[18-20,22,23] assessed strategies for MRSA screening (universal or targeted); one study[21] assessed admission screening (universal and risk factor) for extended-spectrum β-lactamase producing Enterobacteriaceae (ESBL-E). The studies were conducted in Canada,[21] the United States,[18,19,22] and the United Kingdom.[20,23]

One study[18] used a cluster randomized controlled designed, and five studies used a quasi-experimental design, either interrupted time series[23] or retrospective cohort.[19-22] The characteristics of the individual studies are summarized in Appendix 7.

Quality assessment

The single cluster randomized RCT on screening for MRSA was judged overall to be at unclear risk of bias overall. The study authors did not report explicitly the method of randomization sequence generation (for example, computer generated or random number table) or allocation concealment (for example, telephone or web-based allocation or unconcealed procedure), so these two domains were rated "unclear" risk of bias.

Overall, the five quasi-experimental studies (four screening for MRSA,[19,20,22,23] one screening for ESBL[21]) were considered well conducted (Newcastle Ottawa Scale score range 8 to 9). Assessment of comparability (by design or analysis) was based on the adjustment for secular trends or confounders through statistical analysis, similar as was done in the review by Glick et al.[14] Two studies, one on MRSA screening[22] and one on ESBL screening,[21] were judged to be of poor quality because there was no report of statistical adjustment for secular trends or potential confounders. Results for individual study quality assessments are provided in Appendix 6.

MRSA screening studies

Universal screening vs. no screening

The literature search of electronic databases (current to November 4, 2013) did not identify any primary studies evaluating universal screening compared with no screening additional to those identified in the included systematic reviews.

Universal screening vs. targeted screening

Two studies (one retrospective cohort[20] and one interrupted time series[23] compared the impact of universal screening compared with targeted screening.

Lawes et al.[20] conducted a retrospective cohort study to assess the impact of targeted screening for MRSA vs. no screening in the Royal Aberdeen Infirmary, a tertiary care and teaching hospital in north-east Scotland, between 2006 and 2010. The study included all patients admitted to medical, surgical, pediatric, and maternity services between January 1, 2006 and December 31, 2010. As part of an NHS project, the hospital had implemented universal admission screening in August 2008 until March 2011.

In the pre-intervention period (2006–2008), MRSA screening was performed on selected high-risk patients only, including intensive care and elective surgical admissions with the same strategy of isolation and decolonization as was used in the intervention period. High-risk patients were those hospitalized from at least 48 hours without previously documented *S. aureus* bacteremia. In the intervention period, universal admission screening was implemented that involved screening all overnight admissions to acute specialties by nasal swab, and isolation or cohorting of all patients with known or new colonization or infection with MRSA and decolonizing of all MRSA positive patients admitted to any specialty. Decolonization therapy included 5 days of daily body wash with chlorhexidine gluconate and mupirocin nasal ointment applied three times daily. Elective patients were screened at preadmission assessment or on admission.

Swabs were tested by latex slide test followed by confirmatory coagulase test and antibiotic sensitivity by disc-diffusion test; turnaround for testing was typically less than 24 hours. Hospital-associated bacteremia was defined as isolation of *S. aureus* from blood cultures >48 hours after

admission or within 14 days of discharge, without history or bacteremia or MRSA colonization or infection.

The primary outcome was prevalence density of MRSA and methicillin-sensitive *S. aureus* (MSSA) bacteremia. Secondary outcomes were incidence and incidence density of hospital-associated MRSA bacteremia, 30-day and inpatient mortality, readmission rate, treatment failure, and recurrence.

Sarma et al.[23] conducted an interrupted time series study to determine the impact of universal MRSA screening on MRSA bacteremia in an NHS Trust in northeast England comprising three acute general and seven community hospitals. Screening and decolonization was initiated as part of an improvement program established by the Department of Health.

In the pre-intervention period, from 2003 to 2007, patients were selected for MRSA screening based on risk factors including pre-operative patients in elective surgery, emergency orthopedics and trauma surgery, critical care, patients known to be MRSA positive, oncology/chemotherapy inpatients, and patients admitted from high-risk settings. In the intervention period, beginning in 2007, universal MRSA screening and decolonization was introduced to include all adult elective, day case and emergency admissions. MRSA positive patients were isolated and received octenisan or 2% triclosan body wash once daily and mupirocin nasal ointment three times daily. Patients were rescreened 48 hours after decolonization if they were still in the hospital.

Swabs were tested by latex slide test and antibiotic sensitivity by the Vitek 2 system; average turnaround for testing was 48 hours. Hospital-associated bacteremia was defined as a positive test at or after 48 hours of hospitalization.

The time-series analysis included 19 pre-and 15 post-intervention quarterly data points. The primary outcome was the incidence of hospital acquired MRSA bacteremia.

Outcomes

MRSA bacteremia

Lawes et al.[20] reported results of a multivariate analysis (R^2, 0.45–0.68) in which universal screening was associated with a 19% reduction in the prevalence density of MRSA bacteremia (absolute change, 0.189 to 0.154 [-0.035, 95% CI, -0.049– -0.021]/1000 acute occupied bed days; $p < 0.001$) and a 29% reduction in the incidence of HA MRSA bacteremia (0.10 to 0.071 [-0.029, 95% CI, -0.035– -0.023]/1000 acute occupied bed days; $p<0.001$).

Sarma et al.[23] reported a reduction in MRSA bacteremia from 23 cases in 2007 to 0 cases by the end of 2010. The interrupted time-series analysis indicated that this reduction represented an immediate and sustained effect of the intervention for MRSA bacteremia (level change between pre- and post-intervention periods was -0.554 [$p = 0.000$] and declining trend was -0.393 [$p = 0.048$]). A similar effect was observed for incidence of HA bacteremia, which dropped from 15 cases in 2007 to 0 by the end of the second quarter of 2009. The interrupted time-series analysis indicated also that this drop represented an immediate effect of the intervention (level change between pre and post-intervention was -0.577 [$p = 0.001$], but the declining trend was not statistically significant -0.216 [$p = 0.298$].

Mortality

Lawes et al.[20] reported a 46% reduction in 30-day mortality (34% to 18.4% [-15.6%, 95% CI, -24.1%– -7.1%]; $p<0.001$).

MSSA bacteremia

Sarma et al.[23] reported no statistically significant reduction in MSSA bacteremia between pre- and post-intervention periods ($R^2 = 0.09$) and a statistically significant increase in MSSA isolates from non-blood culture ($R^2 = 7.3$).

Mupirocin resistance

Sarma et al.[23] reported that mupirocin resistance increased from 1.7% to 2.3% over the study period.

Targeted screening vs. no screening

Three studies (one cluster RCT,[18] and two retrospective cohort,[19]) compared targeted screening (on high-risk location or population) with no screening.

Huang et al.[18] conducted a cluster randomized controlled trial (ClinicalTrials.gov identifier NCT00980980) to determine the screening, isolation, and decolonization strategy that works best to reduce MRSA and other pathogens in ICUs. The trial randomized 72 adult (aged 13 years and older) ICUs in 42 Hospital Corporation of America (a for-profit manager/operator of health care facilities) hospitals in 16 states in the United States with a total of 71,609 patients. All ICUs in a given hospital were assigned to the same strategy.

Group 1 (16 hospitals, 23 ICUs) implemented screening and isolation that employed bilateral nares screening for MRSA performed on ICU admission, and contact precautions for patients with a history of MRSA colonization or infection and for those who had any positive MRSA test (standard of care in the study hospitals beginning in 2007). Group 2 (13 hospitals, 20 ICUs) implemented targeted decolonization consisting of MRSA screening and contact precautions similar to those in Group 1. In addition, patients known to have MRSA colonization or infection underwent a 5-day decolonization regime consisting of twice-daily intranasal mupirocin and daily bathing with chlorhexidine-impregnated cloths. Group 3 (13 hospitals, 29 ICUs) implemented universal decolonization in which no admission screening was performed, contact precautions similar to those in Group 1, and all patients received twice-daily intranasal mupirocin and daily bathing with chlorhexidine-impregnated cloths for the entire ICU stay.

There was a 12-month baseline period, a 3-month phase-in period, and an 18-month intervention period (April 8, 2010–September 30, 2011). Contact precautions (based on CDC guidance) were identical and unchanged in all hospitals. Results of cultures obtained on admission were available the next day.

The primary outcome was ICU-attributable MRSA-positive clinical cultures. Pathogens were attributed to an ICU if the collection date occurred during the period from third day after ICU admission through second day after discharge. Secondary outcomes included ICU-attributable MRSA bloodstream infection and ICU-attributable bloodstream infection caused by any pathogen.

Kjonegaard et al.[19] conducted a retrospective cohort study to compare the effectiveness and costs of active MRSA screening and contact precautions with no screening in a Southern California acute-care community hospital. The study involved 3341 admissions.

In the pre-intervention period (before January 7, 2009), medical intensive care unit (MICU) and surgical intensive care unit (SICU) patients were cultured for an infection when symptoms were present and there was a physician order. Patients who tested positive or had a known history of MRSA were placed in contact precautions but were not routinely decolonized. In the comprehensive active surveillance period (January 7–August 4, 2009) all patients admitted or transferred to the MICU or SICU had samples taken from both nares and from the perineal area, with the goal of

obtaining specimens within 24 hours of admission. Patients who had a negative admission screen were also screened upon discharge from the MICU and SICU. Rapid polymerase chain reaction (PCR) was used for MRSA screening. During the state-mandated surveillance period (August 5, 2009–March 4, 2010; the State of California enacted Bill 1058 [effective January 7, 2009] that required each patient admitted to an ICU to be tested for MRSA with 24 hours of admission), patients were screened in the nares upon admission to the MICU or SICU, but there was no perineum or discharge screening.

The primary outcome was the rate of HA MRSA infection, defined as those with a previous negative result and now positive. Community acquired MRSA was defined as a positive result less than 3 days following admission. Infection of unknown origin was defined as a positive result after 48 hours in the hospital and no previous admission result.

Mehta et al.[22] conducted a retrospective cohort study to determine the impact of a preadmission screening and decolonization protocol on MRSA colonization rates at the New York University Hospital for Joint Disease, a specialty orthopedic hospital. Rates at the hospital were compared with those from an adjacent university hospital and acute rehabilitation hospital that did not implement screening and decolonization but that had similar institutional policies regarding infection control. The study was conducted between January 2007 and July 2010 and observed 64,327 patient days pre-intervention and 63,860 patient days post-intervention.

Infection control measures to prevent MRSA transmission, such as use of isolation precautions and environmental cleaning, did not change during the study period. During the intervention period (November 2008–July 2010), the orthopedic hospital implemented a preadmission screening and decolonization protocol for MRSA. All scheduled admissions for elective arthroplasty or spine fusion surgery had nares screening. Swabs were screened by disc diffusion or chromagar methods. Screen results were available on the day of surgery. Regardless of culture result, all patients received a 5-day course of twice-daily mupirocin nasal ointment and chlorhexidine shower the night before surgery (October 2008–2009) or chlorhexidine wipes the night before and day of surgery (October 2009–June 2010). MRSA negative patients received standard perioperative antibiotic. MRSA positive patients received intravenous vancomycin 30-minutes before incision and every 12 hours thereafter for 24 hours.

The primary outcomes were change in MRSA and MSSA prevalence density.

Outcomes

MRSA acquisition

Huang et al.[18] reported that universal decolonization reduced MRSA –positive clinical cultures by 37%: Hazard ratio (HR) 0.63 (95% CI, 0.52–0.75) in Group 3 and HR 0.92 (95% CI, 0.77–1.10) in Group 1.

Mehta et al.[22]reported a reduction in MRSA-positive clinical cultures from 1.23/1000 patient days to 0.83/1000 patient-days ($p = 0.026$) in the intervention hospital and no statistically significant reduction in the control hospitals over the same period: 1.27/1000 patients-days vs. 1.24/1000 patients-days ($p = 0.787$).

MRSA infection

Kjonegaard et al.[19] reported that the rate of HA MRSA infection in the prescreening period was significantly lower than that in the intensive screening period: average 0.8 infections/1000 admissions vs. 1.6 infections/1000 admissions ($p = 0.037$). There was no statistically significant

difference between HA MRSA infection rates in the comprehensive and state-mandated periods (1.6/1000 admissions vs. 1.1/1000 admissions). There was no statistically significant difference between HA MRSA infection rates in the prescreening and state-mandated periods (0.8/1,000 admissions vs. 1.1/1,000 admissions).

MRSA bloodstream infection

Huang et al.[18] reported no statistically significant differences in MRSA bloodstream infection rates among the three strategies (p = 0.11).

Bloodstream infection (any pathogen)

Huang et al.[18] reported that universal decolonization reduced bloodstream infection by any pathogen by 44%, HR 0.56 (95% CI, 0.49–0.65), compared with a 22% reduction for targeted decolonization, HR 0.78 (95% CI, 0.66–0.91, p = 0.03). No significant reductions were seen for universal screening and isolation: HR 0.99 (95% CI, 0.84–1.16).

Other outcomes

MSSA acquisition

Mehta et al.[22] reported no statistically significant reduction in MSSA prevalence after implementation of the preadmission screening and decolonization protocol: 1.57/1000 patient-days vs. 1.86/1000 patient-days (p = 0.205).

ESBL screening studies

Universal screening/high-risk screening vs. no screening

Lowe et al.[21] conducted a retrospective cohort study at 12 Toronto hospitals (six screening, six non-screening) to determine if admission screening (universal and risk-factor) for ESBL-producing Enterobacteriaceae was associated with a reduction in the incidence of hospital-onset (HO) ESBL-E. Data on all positive clinical and screening specimens positive for ESBL-E were collected from 2005 to 2009. Four of the hospitals used risk-factor based screening and two used universal screening. Risk-factors varied, though all included travel to an endemic country, and risk-factors included previous colonization/infection, previous hospitalization, transfer from a long-term care facility, admission to a specific ward or increased risk of environmental contamination (for example diarrhea, draining wound). Screening practices were in place prior to the start of the study and no non-screening hospitals had previously had admission screening. Control screening (screening regularly after admission) was not conducted at any hospital. Most screening hospitals were community hospitals and most non-screening hospitals were academic hospitals.

The six screening hospitals used admission rectal swabs. Infection control strategies (for example use of contact precautions) were similar at both screening and non-screening hospitals, though use of a private room for infected/colonized patients was more common in screening hospitals. Hospitals varied in the duration of precautions, from discontinuation after 1 negative culture to 3 negative cultures separated each by 1 week to continuation for entire admission.

Adult in patients from all clinical services with a clinical culture and/or an admission rectal screen positive for Ambler Class A ESBL-producing *Escherichia coli, Klebsiella pneumoniae,* and *Klebsiella oxytoca* were included. All hospitals used similar standard culture methods for identification of ESBL-E positive isolates. Patients were considered to have hospital-onset (HO)-ESBL-E if an ESBL-E was identified from a clinical specimen obtained >72 hours after admission without any prior cultures yielding ESBL.

The primary outcome was incidence of HO ESBL-E/1,000 patient-days. Secondary outcomes were incidence of HO ESBL-E stratified by organism (for example *E. coli* or *K. pneumoniae*), incidence of HO ESBL-E bacteremia, and ratio of HO to community-onset cases.

Outcomes

ESBL acquisition

The authors found that the incidence of HO ESBL-E was higher among non-screening than screening hospitals from the first year (0.098 vs. 0.034/1000 patient-days) to the final year (0.184 vs. 0.097/1000 patient-days). The results indicated a 49.1% ($p < 0.001$) reduction in HO ESBL cases for screening hospitals compared with non-screening hospitals. The HO/community-onset ratio for non-screening compared with screening hospitals was 0.88 vs. 0.45.

ESBL bacteremia

Hospitals employing ESBL screening showed a 64.1% reduction in HO ESBL bacteremia cases.

Discussion of evidence from primary studies

This updated search for studies on ARO screening identified six studies (one RCT and five quasi-experimental studies) that were published subsequent to the literature searches of the most recent systematic reviews. The evidence from the primary studies provides an unclear picture of the benefits of screening (Table 2 below), similar to that provided by the evidence from the systematic reviews. No studies examined the effectiveness of universal screening vs. no screening. The results of the single, large cluster randomized trial by Huang et al.[18] strongly suggests that, in the short term, screening and isolation and screening and targeted decolonization are not as effective as a protocol of no screening and universal decolonization in reducing MRSA colonization and infection in ICU patients. This is consistent with the results of the single cluster RCT included in the review by Glick et al.[14] that showed that universal screening had no significant impact on short-term rates of MRSA infection when compared with no screening. The strengths of the study by Huang et al. include its large size and rigorous design and the results of the study have led some experts to conclude that hospitals ought to discontinue screening as a strategy for controlling endemic MRSA.[6] Nevertheless, researchers have also pointed to the following weaknesses of the study, which may limit the usability of the results: generalizability of results, long term impact, and risk of inducing mupirocin resistance. This last weakness is a potential drawback with universal decolonization that may reduce its potential benefits. Widespread use of chlorhexidine and mupirocin could possibly engender resistance has been reported in some studies of MRSA decolonization.[18,32] Universal screening and decolonization may play a role in reducing hospital rates of MRSA infection, but it can also result in a tremendous screening and treatment burden. In addition to the allocation of financial and human resources that universal screening requires, subsequent mass decolonization may place selection pressure for the development of resistance to commonly used agents such as mupirocin or chlorhexidine.

The remaining retrospective studies provide some information on reduction in MRSA incidence, which is an intermediate or proxy outcome for the benefits of screening, namely, reduced likelihood of infection and, ultimately, fewer cases of HA ARO-associated morbidity and mortality.

Table 2: Summary of results for primary screening studies

ARO and Strategy Quality rating	Population and setting	Study authors' conclusions	Support for ARO screening
MRSA			
Universal screening vs. targeted screening			
Lawes et al. 2012[20] NOS score: 9/9	All admissions to Scottish tertiary referral and teaching hospital	Screening reduced MRSA bacteremia rate Screening reduced 30-day mortality	+ +
Sarma et al. 2013[23] NOS score: 9/9	All adult elective, day case, and emergency admissions in acute and community hospitals	Screening reduced MRSA bacteremia rate	+
Targeted screening vs. no screening			
Huang et al. 2013[18] Risk of bias: Unclear	Adult ICU patients in 32 HCA hospitals	Universal decolonization (no screening) reduced rate of MRSA positive cultures Universal decolonization (no screening) reduced rate of bloodstream infection by any pathogen No strategy reduced rate of MRSA bloodstream infections	- - Neutral
Kjonegaard et al. 2013[19] NOS score: 9/9	Adult ICU in single community hospital	Screening did not reduce MRSA infection rate	-
Mehta et al. 2013[22] NOS score: 8/9	Adults undergoing elective orthopedic surgery in specialty orthopedic hospital	Screening associated with a reduction in MRSA colonization rate	+
ESBL			
Universal screening vs. no screening			
Lowe et al. 2013[21] NOS score: 8/9	All admissions to 12 academic and community hospitals in Toronto, ON.	Screening associated with reduction in ESBL incidence Screening associated with reduction in ESBL bacteremia rate	+ +

HCA = Hospital Corporation of America

As was noted in the review of systematic reviews of reviews, ARO screening is never independent from other infection prevention activities and is always a part of a set of infection prevention practices (contact precautions, decolonization).[19] Uncoupling the effects of the many components of infection detection and prevention protocols is crucial because, as Ho et al.[15] noted, individual components, such as isolation, can be not only costly due to the extra use of resources and staffing, but also may be one of the sources of potential harm for patients, in the case of isolation practices, of increased anxiety and depression. However, a recent systematic review[15] of the clinical evidence on the effectiveness of patient isolation and decolonization strategies for VRE and ESBL found very little evidence with which to draw conclusions regarding the impact of these strategies on psychosocial outcomes. In institutions with endemic AROs, it is unclear how much of the reduction of HA AROs infection may be attributed to screening versus other infection control interventions.

Limitations

As was noted above, the "bundles" of measures implemented in conjunction with screening (hand hygiene, barrier or contact precautions, environmental cleaning, and antimicrobial decolonization), limit our ability to be confident that reduction in ARO infection is a result of the effect of screening. The results of the three-arm trial by Huang et al.[18] provide good evidence of the lack of effectiveness of screening compared with other "bundles" that do not include screening. Importantly for infection prevention practice, the study provides evidence of the greater effectiveness of horizontal approaches (not pathogen specific) over vertical strategies (pathogen specific), which are considered to be resource intensive and costly.[6] The remaining studies, though well reported and conducted, are retrospective studies; hence, the results of these should be interpreted in light of the well-known weaknesses of retrospective designs.

Based on predetermined criteria, we omitted studies conducted in countries designated as "economies in transition" or "developing economies" to minimize including studies, the results of which, may not be generalizable due to major structural and institutional differences. However, some countries, most especially those designated "economies in transition," have characteristics that could place them in more than one category.[2] Schwaber et al.[33,34] conducted an ambispective study (retrospective and prospective data collection) to examine the effectiveness of a nation-wide intervention to contain the spread of CROs in Israel (which is classified as a "developing economy"). In 2006, acute care hospitals in Israel reported outbreaks of carbapenem-resistant *K. pneumoniae* (though to have been introduced via the United States 1 year prior). Because there was no national detection system for the emergence or spread of AROs, the outbreak went unnoticed for a year (2005-2006) without concerted intervention; the outbreaks accelerated and, by 2007, CRE was endemic. All acute-care hospitals in Israel fall under the jurisdiction of the Ministry of Health, so, from April 2007 to May 2008, the Ministry implemented a three-part intervention: (1) mandatory reporting to public health authorities of every patient with a laboratory specimen that grew CRE and mandatory isolation of hospitalized carriers of CRE; (2) hospital guidelines that mandated strict adherence to contact isolation measures and placement of patients in self-contained nursing units (either single rooms or cohorts); (3) the creation of a task force composed of specialists in infection control, clinical microbiology, and public health, reporting directly to the Ministry Director-General. The task force collected data from hospitals and was given the authority to intervene as necessary to contain the outbreak. The results showed that, immediately following the intervention, there was a steady and continuous downward trend in incidence of CRE acquisition (as detected by clinical culture) beginning with a 29% reduction from the peak incidence in the first month of the intervention. Results also showed that there was almost universal compliance with the guidelines during the intervention period. Compliance with the guideline for dedicated staffing was associated with lower incidence: For each 10% in compliance, there was a decrease in incidence of 0.6 cases per 100,000 patient days ($p = 0.02$). Assessment of the reasons for continued nosocomial transmission of CRE by the task force led to two additional interventions: (1) intervention in long-term care facilities, and (2) distribution of guidelines for active CRE surveillance in acute care hospitals.[34] The authors concluded that all components of the intervention (adherence to principles of standard precautions and contact isolation, physical separation of carriers from non-carriers, and dedicated nursing staff), and the fact that the intervention was centrally coordinated, succeeded in containing the CRE outbreak after local measures had failed.

In addition, though it is unlikely that this search update has missed any large, well-designed, multi-centre studies, it is possible that the search has missed unpublished smaller studies from researchers in single institutions or in non-academic settings that may help to shed light on the effectiveness of

ARO screening strategies. This update was limited to studies published in the English language. Hence, there may be published reports of studies in countries with developed market economies that were published in a language other than English; however, we are unable to estimate both the number of reports this may represent and the impact this potential omission may have on the review results. Finally, there was no search of clinical trials databases for recently completed but unpublished trials or of ongoing trials. Hence, this summary represents a reasonably complete, but still limited, overview of the state of the science of screening for AROs. The systematic reviews examined in this report had similar limitations. Additional methodological limitations that affect the results of this entire summary (for example, a single reviewer) are considered in greater detail in the final Discussion section below.

CLINICAL PRACTICE GUIDELINES

Summary of Clinical Practice Guidelines

Five clinical practice guidelines (CPGs) from Canada,[1,24] Europe,[27] the United States,[26] and the United Kingdom[25] were identified that addressed screening for endemic AROs. These CPGs were published in 1997,[24] 2006,[25] 2012,[26] 2013,[1] and 2014.[27] In other words, only three CPGs[1,26,27] may be relevant to current clinical practice. No quality assessment was conducted of the guidelines; however, the inclusion criteria, which were based on the Institute of Medicine's definition of a practice guideline[8] acted as a de facto quality filter by excluding those guidelines that were not informed by a systematic review of evidence or did not use an explicit and transparent process involving a multidisciplinary panel of experts. The most recent and comprehensive CPG was produced by Public Health Ontario[1], published in 2013, and covered four AROs: MRSA, VRE, CPE, and ESBL-E. The other four CPGs focused on a specific ARO or class of ARO: MRSA,[25] VRE,[24] CRE,[26] and Gram-negative bacteria.[27] Three guidelines[1,25,27] used an explicit system for indicating the strength of the recommendations and evidence grading schemes; however, one guideline[1] did not report the grading for individual recommendations regarding ARO screening. Specific recommendations on screening and the grading systems used are described in Appendix 9, Tables 1-4.

Overall, all but one[27] of the CPGs recommended admission screening of high-risk patients in endemic settings. No CPG recommended a universal screening strategy for selected AROs. None of the guidelines recommended routine staff screening for AROs.

MRSA Screening

Two CPGs[1,25] provided recommendations on screening for MRSA. One guideline[25] provided evidence grades to indicate the strength of the recommendations being made and the quality of the evidence upon which the recommendations were based.

Coia et al.[25] produced a guideline under the auspices of the Joint Working Part of the British Society of Antimicrobial Chemotherapy, the Hospital Infection Society, and the Infection Control Nurses Assocation. The guideline authors concluded that there was sufficient epidemiological evidence and a theoretical rationale to suggest implementing admission MRSA screening targeted toward patients at high risk of MRSA carriage, unless the patients are being admitted directly to isolation facilities and there is no plan to clear the patient of MRSA carriage. In addition, all patients, regardless of risk status, should be screened upon admission to high-risk units. Whether to screen patients upon admission to other wards should be decided by local infection control teams.

Public Health Ontario[1] (the Ontario Agency for Health Protection and Promotion) produced a guideline jointly with the Provincial Infectious Diseases Advisory Committee on Infection Prevention and Control. The guidelines recommended that all patients at increased risk for MRSA carriage should be screened upon admission. In addition, point prevalence screens should be conducted on units/areas (burn units, ICU, etc.) where patients are at high risk for acquiring MRSA during their stay. No grades were provided for individual recommendations.

VRE Screening

Two CPGs[1,24] provided recommendations on screening for VRE. Neither guideline provided evidence grades for the individual recommendations.

Public Health Agency of Canada[24] recommended period culture surveys of critically ill patients at high risk of VRE infection or colonization. The guideline authors also concluded that screening surveys are not a mandatory component of an infection control program and that the utility of universal screening is unknown and, therefore, not recommended.

Public Health Ontario[1] (the Ontario Agency for Health Protection and Promotion) produced a guideline jointly with the Provincial Infectious Diseases Advisory Committee on Infection Prevention and Control. The guidelines recommended that all patients at increased risk for VRE carriage should be screened upon admission. In addition, point prevalence screens should be conducted on units/areas (dialysis, transplantion, ICU, etc.) where patients are at high risk for acquiring VRE during their stay.

CPO Screening

Two CPGs[1,26] provided recommendations on screening for CPO. Neither guideline provided evidence grades for the individual recommendations.

The U.S. National Center for Emerging and Zoonotic Infectious Diseases[26] guideline does not specifically address admission screening. It does, however, recommend that point prevalence surveys should be conducted in situations where a review of clinical cultures using laboratory records identifies unreported CRE patients in certain wards.

Public Health Ontario[1] (the Ontario Agency for Health Protection and Promotion) produced a guideline jointly with the Provincial Infectious Diseases Advisory Committee on Infection Prevention and Control. The guidelines recommended that admission screening be conducted and pre-emptive contact precautions used for individuals with risk factors for CPE.

ESBL Screening

Two CPGs[1,27] provided recommendations on screening for ESBL. Taconelli et al.[27] used the GRADE system for grading of recommendations.

Taconelli et al.[27] developed a guideline under the auspices of the European Society for Clinical Microbiology and Infectious Diseases. After evaluation of the evidence, the guidelines authors agreed that the implementation of active surveillance screening for Gram-negative bacteria in the endemic setting should be suggested only as an additional measure and not included as part of the basic measures to control the spread of multidrug-resistant Gram-negative bacteria.

Public Health Ontario[1] (the Ontario Agency for Health Protection and Promotion) produced a guideline jointly with the Provincial Infectious Diseases Advisory Committee on Infection Prevention and Control. The guidelines recommend that local epidemiology should govern decision-making regarding routine screening of patients/residents for ESBL-producing bacteria. If the local

prevalence of ESBL-producing bacteria is high, the authors contend there is some value to routinely screening patients, particularly those admitted to ICUs.

Discussion of Clinical Practice Guidelines

Five guidelines on ARO screening were identified that met the IOM's definition of a guideline. One guideline provided recommendations on the four AROs of interest for this consensus conference: MRSA, VRE, CPE, and ESBL. The remaining guidelines each focused on a specific ARO. Three of the five guidelines used established frameworks for grading the strength of the recommendations.

Overall, the guidelines recommend admission screening of high-risk patients for MRSA, VRE, and CPO. Hence, for at least these three AROs, admission screening of high-risk patients is considered a crucial component of infection prevention and control. However, the guidelines that provided explicit grading of the recommendations uniformly noted the weak evidence based upon which this guidance is based. No guidelines recommended routine screening for ESBL, and one guideline[27] noted explicitly the lack of research evidence to support the development of recommendations for this particular ARO. However, as at least one commentator[35] has pointed out, much of what is included in recommendations for the prevention and control of MRSA (and, by extension, other AROs) is both logical and self-evidence. The effectiveness at least some interventions, when implemented, can be seen on countries where the prevalence of AROs is low.

The guidelines also highlight the importance of adherence to good hygiene practices and contact precaution protocols, including patient cohorting. Futher, the guideline recommendations underline the multifactorial nature of successful infection prevention and control through screening, testing, and surveillance and the close connection between these activities and contact precautions and communication.[35] The guidelines also discuss the importance of environmental cleaning and antibiotic stewardship, topics that are beyond the scope of this report.

DISCUSSION

This review of systematic reviews, primary studies, and guidelines on screening practices for endemic AROs is the most up-to-date summary of the evidence to date. The results indicate that research in this area has focused overwhelmingly on MRSA, with only three studies identified that addressed screening for VRE and ESBL. None have addressed the most recent emerging ARO, CPO. This does not mean, however, that no studies have examined that particular ARO, only that no studies meeting our inclusion criteria did so. As noted in the Discussion of the primary studies, there is at least one study[33,34] that examined interventions for CPO that may provide relevant information, though it did not meet the inclusion criteria. Additionally, the focus on AROs occurring endemically within hospital settings in developed market economies means that the conclusions drawn here should not be extrapolated to outbreak scenarios, situations in which aggressive admission screening and surveillance may be warranted. Despite the tremendous effort clinical researchers have put into developing and determining effective components of infection prevention and control protocols, few studies have provided solid ground upon which to base recommendations regarding ARO screening. And several reports have cautioned against the overemphasis of ARO (specifically, MRSA) screening at the expense of other important precautions.[19]

Almost all of the primary studies identified in this summary employed a quasi-experimental design. As was pointed out in the review of reviews and review of primary studies, these designs can vary in their ability to provide a reliable estimate of the impact of an intervention.[36] Nevertheless, well

designed and conducted quasi-experimental studies, especially the interrupted time-series design, can be strong alternatives to experimental randomized designs, when RCTs are not feasible, and provide good evidence regarding causal effects. As was highlighted in the summary of systematic reviews, our confidence in the results of quasi-experimental studies depends on our confidence that rival hypotheses that might explain the observed effect have been ruled out. Features that give us this confidence include addressing autocorrelation, knowledge of exactly when and to what extent an intervention was implemented, and having a sufficient number of observations before and after the implementation of the intervention.[36] Additional design features, such as a non-equivalent no-treatment control group as was done by Mehta et al.[22] (though in the context of a cohort study rather than a time-series), can also be employed to help discount rival hypothesis based on secular trends.

Overall, the conditions required for reliable results from time-series designs were satisfied for the time-series studies included in this report. However, a deficiency of all studies, both experimental and quasi-experimental designs, was the bundling together of different measures for prevention and control of AROs. The bundling of measures makes it difficult to ascertain the contribution screening may make to prevention and control of AROs. Indeed, Taconelli et al.[27] conclude that the simultaneous implementation of several measures made it impossible to establish which measure (in that case, admission screening, contact precautions, or environmental cleaning) was the most effective. Hence, the strength of the study conducted by Huang et al.[18] was in the choice and design of comparisons. It is possible that a single component of an ARO screening strategy, for example, decolonization of patients found through screening to be ARO positive, may produce an independent, clinically significant benefit. However, the influence of other important factors, such as the testing strategy (PCR vs. culture), knowledge of its corresponding test turnaround time, management of patients before screening test results are known, and the use of concomitant infection prevention strategies and treatments, could not be determined.[7] A systematic review[37] of nine studies comparing conventional (chromogenic agar) with rapid testing (PCR) for targeted MRSA screening found MRSA colonization, infection and transmission rates were lower using PCR than chromogenic agar, but often differences were not statistically significant. The review authors point out that additional factors that may influence turnaround times and that ought to be considered include the infrastructure of the laboratory that provides the service, prevalence rate of MRSA in the hospital setting and the number of specimens that will be processed, available laboratory hours, and the laboratory staff on-hand to process the screening test.[37] The authors concluded that the number and quality of studies provided insufficient evidence upon which to draw conclusions regarding the effectiveness of PCR for MRSA screening in hospitalized patients. They emphasize, as we have, that screening is only one component of an ARO infection prevention and control programme, and it is difficult to accurately determine its relative contribution to overall control. Finally, studies must be adequately reported so that researchers, clinicians, and policy makers can assess the merits and demerits of any single study, including the transferability of the findings. The Outbreak Reports and Intervention Studies Of Nosocomial Infection (ORION) Statement[38] provides guidance on reporting to help researchers ensure that all relevant information needed to assess validity and applicability is provided in their research reports.

The difficulty in drawing conclusions because of the "bundling" of interventions in all studies has been a recurring theme of this summary. A promising approach for future research would be to employ designs that might "unbundle" the intervention effects and provide some indication of the relative contribution of and interaction between different prevention and control measures.[36] One class of such designs is factorial trials, which allow for two or more intervention comparisons to be carried out simultaneously. So, for example, a factorial study design would be able to compare

targeted screening, contact precautions, and universal decolonization with various combinations of no screening, and no universal decolonization. (The existing evidence supporting the use of contact precautions and ethical issues around exposures to environmental risks would likely prevent the removal of many contact precautions.) This design has been used in simulation modeling studies to assess the effects of hand hygiene and nurse-to-patient ratio on MRSA acquisition.[39]

Despite the shortcomings in the evidence base for ARO screening described above, some form of active surveillance for MRSA has become routine in almost all Canadian hospitals.[4] Research on strategies used in Canadian hospitals[4] combined with the research results examined in this review suggest screening may add little, if anything, to the effective control of endemic AROs achieved by infection precautions and control. Simor et al.[4] examined whether institutional characteristics or infection prevention and control policies were associated with prevalence of MRSA, VRE, and CDI. Lower prevalence of MRSA and VRE were found in facilities that routinely used private rooms to accommodate patients with these AROs. The routine use of an antiseptic soap, such as chlorhexidine, for daily washing of patients with MRSA was associated with lower MRSA infection rates, and a policy of enhanced environmental cleaning of rooms used for patients with VRE was associated with lower VRE rates. All results were considered consistent with existing research findings. The study authors noted that the apparent association of prevalence with particular infection prevention and control strategies and practices warrants closer study.[4]

LIMITATIONS

The expedited process used to prepare this evidence summary has a number of methodological shortcomings that could potentially affect the results. First, a single reviewer only was involved at all stages of the review from literature screening and selection, quality assessment, and data extraction to analysis and summary. Hence, though there is a potential for bias, the possibility for selection bias was minimized by having members of the expert advisory group, some of whom were authors of the included studies, examine the list of included studies for obvious omissions. The involvement of a second reviewer for quality assessment and data extraction, though certainly helpful to identify human errors, is unlikely to change risk of bias assessments.[40] Second, the review of reviews did not disaggregate the primary studies included in the reviews in an attempt to resynthesize the evidence (for example, by listing studies common or unique to each review). By not doing so, it is unclear if there were studies that, in all reviews in which they were included, provided the support for a conclusion in support of or refuting the potential benefits of screening. The criticisms of at least one review[29] suggest that this may be an issue worth investigating more closely.

Heterogeneity among the studies with respect to outcome measure, institutional policies, and other potential confounders, precluded statistically combining the results of similar studies. Because the results were summarized narratively, there was no opportunity to conduct sensitivity or subgroup analyses to investigate potential differences in effect based on characteristics of study design or risk of bias, or characteristics of study populations, interventions, or study setting. For example, we did not investigate potential differences in the timing of screening results (culture or PCR) nor did we examine the differences in effectiveness based on number or location of screening (nares, anus, perineum, etc.), aspects of screening that may influence the effectiveness of ARO prevention and control.

This review has focused on HA AROs; however, as a Canadian prevalence study has shown us, although MRSA, VRE, and *C. difficile* are acquired predominantly in healthcare settings, MRSA is, in some parts of Canada, more often and, in some locations (for example, Alberta), predominantly

community associated than is VRE or CDI.[41] Hence, there is also a need to better understand the transmission between the community and hospital settings and the contribution community-acquired AROs make to HA ARO colonization, infection, and their sequelae.

As noted above, we omitted the studies conducted in countries designated as "economies in transition" or "developing economies" that may, despite that designation, be relevant to addressing this issue. Some countries, most especially those designated "economies in transition," have characteristics that could place them in more than one category.[2] For example, a nation-wide intervention to contain the spread of CROs was implemented in Israel[34] (which is classified as a "developing economy").

Relatedly, most of the literature regarding screening and decolonization is focused on MRSA and to a lesser extent, VRE. There are few studies examining the impact on other ARO's such as ESBL or CPO. The single guideline[27] addressing this topic concluded that there was insufficient evidence from which to derive strong recommendations for the wide application of chlorhexidine in hospitalized patients colonized or infected with multidrug-resistant Gram-negative bacteria. The single primary study[21] that assessed the use of screening for ESBL-E had acknowledged limitations, hence, the results showing a benefit were considered suggestive only.

An important topic in successful ARO infection prevention and control, but one unaddressed by this report, is the role of antimicrobial stewardship. Antimicrobial stewardship programmes aim to reduce antimicrobial resistance through optimized antibiotic usage, which will hopefully improve patient health and help to contain health care costs.[42]

Finally, screening and surveillance strategies raise a number of ethical issues with respect to underlying evaluation of benefit (individual autonomy vs. communitarianism), obligations regarding informed consent, and appropriate payers (in the context of the US healthcare system).[43] In Canada, one of the most salient issues will be the opportunity cost incurred by pursuing screening. This review has not sought to identify or consider the ethical issues involved in infection prevention and control strategies, though doing so is certainly relevant to the development of robust clinical practice guidelines.

FUTURE RESEARCH NEEDS

Based on the results of the AHRQ comparative effectiveness review[14] described above and input from various experts and stakeholders, Noorani et al.[7] identified gaps in the systematic review evidence that limited the ability to answer the initial key research questions regarding the effectiveness of screening for MRSA. Likewise, this summary of reviews and additional primary studies, has identified similar important gaps related to assessing the effectiveness of ARO screening. Noorani et al.[7] suggested the following prioritized list of seven research questions to address the identified research gaps (needs):

1. For surgical admissions, what is the most effective strategy for reducing MRSA acquisition and infection rates and improving morbidity, mortality, patient flow and resource use?
2. For surgical admissions what factors are associated with increased risk of MRSA acquisition and infection?
3. For intensive care populations, what is the most effective strategy for reducing MRSA acquisition and infection rates and improving morbidity, mortality, patient flow and resource use?

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

EPIC2,[41] the guidelines for preventing HA infections in NHS hospitals in England (which was not included because it did not provide guidance on screening) and perhaps the most rigorous evidence-based CPG, lists, among other things, the following three areas for future research:

1. Develop appropriate and realistic methods and tools to facilitate local surveillance of HA infections.
2. The role of screening for HA infection microorganisms as a means of controlling HA infections.
3. Further research on community MRSA colonization and its impact on acute care.

Likewise, Taconelli et al.[27] highlighted that their review of the evidence identified clear "grey" areas where appropriately designed studies are required: contact precautions for high-risk patients colonized or infected with ESBL-producing *E. coli,* cohorting of patients and staff, and antimicrobial stewardship programmes.

CONCLUSIONS

Despite much research having been conducted in this area, there is currently little high-quality evidence that screening of patients (whether universal or targeted, and primarily relating to MRSA) is associated with reduction in HA ARO incidence, infection, mortality or morbidity in endemic settings. Results from a single, large RCT suggest that universal (or horizontal) approaches to infection control may be more effective than approaches that aim to target single pathogens (vertical). Current CPGs recommend that admission screening of high-risk patients be conducted for MRSA, VRE, and CROs. No guidelines currently recommend screening for ESBL-producing organisms.

Given the serious impact ARO infections can have on patients and hospital staffing and resources and the cost and resources required for effective prevention and control of endemic AROs and the current lack of reliable research evidence with which to guide decisions regarding screening, future research should focus on conducting well-designed, prospective studies that can disentangle the relative contributions of the measures employed in infection prevention and control programmes to better allocate health care resources.

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APPENDICES

Appendix 1: Glossary of Potentially Relevant AROs

Sources: http://www.cdc.gov/HAI/organisms/organisms.html

http://www.phac-aspc.gc.ca/amr-ram/dis-mal-eng.php

Acinetobacter

Acinetobacter is a group of bacteria commonly found in soil and water. Outbreaks of Acinetobacter infections typically occur in intensive care units and healthcare settings housing very ill patients. *Acinetobacter baumannii* accounts for about 80% of reported infections. Acinetobacter infections rarely occur outside of healthcare settings.

Carbapenem-resistant Enterobacteriaceae (CRE)

Carbapenem-resistant Enterobacteriaceae are a family of bacteria that are difficult to treat because they have high levels of resistance to antibiotics. *Klebsiella* species and *Escherichia coli (E. coli)* are examples of Enterobacteriaceae, a normal part of the human gut bacteria, that can become carbapenem-resistant. In healthcare settings, CRE infections most commonly occur among patients who are receiving treatment for other conditions. Patients whose care requires devices like ventilators (breathing machines), urinary (bladder) catheters, or intravenous (vein) catheters, and patients who are taking long courses of certain antibiotics are most at risk for CRE infections. There is significant geographic variability currently in the distribution of KPC and NDM, the two most common mechanisms underlying CRE, with increasing global spread feared.

Extended spectrum β-Lactamase producing bacteria (ESBL)

ESBL are gram-negative bacteria that produce an enzyme, β-lactamase that can break down commonly used antibiotics, such as penicillin and cephalosporins, making infections with ESBL-producing bacteria more difficult to treat. Enterobacteriaceae, E. coli*, and* K. pneumoniae *are common producers of ESBL, and they most commonly cause urinary tract infections and bacteraemia.*

Staphylococcus aureus

S. aureus (staph), is a bacterium commonly found on the skin and in the nose of about 30% of individuals. Most of the time, staph does not cause any harm. Infections can look like pimples, boils, or other skin conditions and most are able to be treated. Types of staph infections:

Methicillin-resistant *S. aureus* (MRSA)

Methicillin-resistant *S. aureus* (MRSA) is a type of staph bacteria that is resistant to certain antibiotics called β-lactams. These antibiotics include methicillin and other more common antibiotics such as oxacillin and cephalosporins. In the community, most MRSA infections are skin infections. More severe or potentially life-threatening MRSA infections occur most frequently among patients in Healthcare Settings.

Vancomycin-resistant *S. aureus* (VRSA)

Vancomycin-intermediate *S. aureus* (also called VISA) and vancomycin-resistant *S. aureus* (also called VRSA) extend the resistance of MRSA to include vancomycin. Persons who develop this type of staph infection may have underlying health conditions (such as diabetes and kidney disease), tubes going into their bodies (such as catheters), previous infections with methicillin-resistant *S. aureus (MRSA),* and recent exposure to vancomycin and other antimicrobial agents.

Vancomycin-resistant Enterococci (VRE)

Enteroccocci are bacteria that are normally present in the human intestines and in the female genital tract and are often found in the environment. These bacteria can sometimes cause infections. Vancomycin-resistant Enterococci (VRE) are specific types of antimicrobial-resistant bacteria that are resistant to vancomycin, the drug often used to treat infections caused by enterococci. Most VRE infections occur in hospitals.

Appendix 2: Literature Searches

The literature search was conducted by IHE Research Librarians for publications published between 2003 and 2013. The search was further limited to human studies and to Systematic Reviews and Clinical Practice Guidelines. Language was restricted to English. Animal studies were excluded.

Database	Edition or date searched	Search Terms ††
Core Databases		
Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations and Ovid MEDLINE(R) 1946 to August Week 3 2013	30 Aug 2013 Reviews: 250 Guidelines: 830 Primary Studies Search: 04Nov2013 Unique Results in addition to scoping search: 2215	1. drug resistance, microbial/ or exp drug resistance, bacterial/ 2. ((antimicrobial or antibiotic*) adj2 resistan*).ti. 3. Methicillin-Resistant Staphylococcus aureus/ 4. MRSA.ti,ab. 5. Methicillin Resistance/ 6. (met?icillin adj2 resist*).ti,ab. 7. or/5-6 8. Staphylococcus aureus/ 9. Staphylococcal Infections/ 10. (Staphylococc* adj2 (infect* or aureus)).ti,ab. 11. ("s.aureus" or "s aureus" or "staph aureus").ti,ab. 12. or/8-11 13. 7 and 12 14. exp Enterobacteriaceae Infections/ 15. exp Enterobacteriaceae/ 16. (((Carbapenem* adj (resistan* or produc*)) or CRE) adj5 Enterobacteriaceae).ti,ab. 17. exp β-Lactamases/ 18. exp β-Lactam Resistance/ 19. or/17-18 20. ((extended or expanded) adj5 (spectrum or spectra)).ti,ab. 21. Gram-Negative Bacterial Infections/ 22. gram negative.mp. 23. or/20-22 24. 19 and 23 25. ((extended or expanded) adj5 (spectrum or spectra) adj5 (lactam or βlactam*)).ti,ab. 26. (ESBL or ESBLs).ti,ab. 27. or/24-26 28. exp Vancomycin Resistance/ 29. (Vancomycin adj5 resistan*).ti,ab. 30. or/28-29 31. Enterococcus/ 32. Enterococc*.ti,ab. 33. exp Gram-Positive Bacterial Infections/ 34. gram positive.ti,ab. 35. or/31-34 36. 30 and 35 37. (VRE or VREs).ti,ab. 38. 1 or 2 or 3 or 4 or 13 or 14 or 15 or 16 or 24 or 27 or 36 or 37 39. exp Mass Screening/ 40. (test or tests or testing or tested or swab or swabs).mp. 41. (screen* or surveill*).ti,ab. or exp Population Surveillance/ 42. pc.fs. 43. or/39-41 44. 38 and 43 45. limit 44 to animals

		46. limit 44 to humans 47. 45 not (45 and 46) 48. 44 not 47 49. (rat or rats or rodent or mice or mouse or sheep or murine or lamb or lambs or dog or dogs or cats or monkey or primate* or pig or pigs or piglet* or porcine or rabbit* or bovine or hamster* or zebra*).ti,ab. 50. 48 not 49 51. meta-analysis.pt. 52. (meta-anal$ or metaanal$).mp. 53. ((quantitativ$ adj3 review$1) or (quantitativ$ adj3 overview$)).mp. 54. ((systematic$ adj3 review$) or (systematic adj3 overview$)).mp. 55. ((methodologic adj3 review$1) or (methodologic adj3 overview$)).mp. 56. (integrat$ adj5 research).mp. 57. (quantitativ$ adj3 synthes$).mp. 58. or/51-57 59. review.pt. or (review$ or overview$).mp. 60. (medline or medlars or pubmed or index medicus or embase or cochrane).mp. 61. (scisearch or web of science or psycinfo or psychinfo or cinahl or cinhal).mp. 62. (excerpta medica or psychlit or psyclit or current contents or science citation index or sciences citation index).mp. 63. (hand search$ or manual search$).mp. 64. ((((electronic adj3 database$) or bibliographic) adj3 database$) or periodical index$).mp. 65. (pooling or pooled or mantel haenszel).mp. 66. (peto or der simonian or dersimonian or fixed effect$).mp. 67. ((combine$ or combining) adj5 (data or trial or trials or studies or study or result or results)).mp. 68. or/60-67 69. 59 and 68 70. 58 or 69 71. (hta$ or health technology assessment$ or biomedical technology assessment$).mp. 72. technology assessment, biomedical/ or biomedical technology assessment/ 73. 71 or 72 74. 70 or 73 75. 50 and 74 - SRS 76. exp practice guideline/ or Health Planning Guidelines/ or guideline*.ti. or (practice adj3 parameter*).ti,ab. or clinical protocols/ or guidance.ti,ab. or care pathway*.ti,ab. or critical pathway/ or (clinical adj3 pathway*).ti,ab. or algorithms/ or consensus development conference.pt. or consensus development conference nih.pt. or (protocol or policy).ti. 77. 50 and 76 78. 75 not 77 79. (latin or latina or latinae or latinamericanos or latinas or latine or latines or latini or latino or latinoamericana or latinoamericanas or latinoamericano or latinoamericanos or africa or africain or africaine or africaines or africains or african or africana or africas or africasia or afrika

		or afrikaanse or afrique asia or Asian or chinese or china or india or indian).ti,jw. 80. 77 not 79 81. 78 not 79 82. limit 80 to english language 83. remove duplicates from 82 – GUIDELINES **PRIMARY STUDIES** 1. drug resistance, microbial/ or exp drug resistance, bacterial/ 2. ((antimicrobial or antibiotic*) adj2 resistan*).ti. 3. Methicillin-Resistant Staphylococcus aureus/ 4. MRSA.ti,ab. 5. Methicillin Resistance/ 6. (met?icillin adj2 resist*).ti,ab. 7. or/5-6 8. Staphylococcus aureus/ 9. Staphylococcal Infections/ 10. (Staphylococc* adj2 (infect* or aureus)).ti,ab. 11. ("s.aureus" or "s aureus" or "staph aureus").ti,ab. 12. or/8-11 13. 7 and 12 14. exp Enterobacteriaceae Infections/ 15. exp Enterobacteriaceae/ 16. ((((Carbapenem* adj (resistan* or produc*)) or CRE) adj5 Enterobacteriaceae).ti,ab. 17. exp β-Lactamases/ 18. exp β-Lactam Resistance/ 19. or/17-18 20. ((extended or expanded) adj5 (spectrum or spectra)).ti,ab. 21. Gram-Negative Bacterial Infections/ 22. gram negative.mp. 23. or/20-22 24. 19 and 23 25. ((extended or expanded) adj5 (spectrum or spectra) adj5 (lactam or βlactam*)).ti,ab. 26. (ESBL or ESBLs).ti,ab. 27. or/24-26 28. exp Vancomycin Resistance/ 29. (Vancomycin adj5 resistan*).ti,ab. 30. or/28-29 31. Enterococcus/ 32. Enterococc*.ti,ab. 33. exp Gram-Positive Bacterial Infections/ 34. gram positive.ti,ab. 35. or/31-34 36. 30 and 35 37. (VRE or VREs).ti,ab. 38. 1 or 2 or 3 or 4 or 13 or 14 or 15 or 16 or 24 or 27 or 36 or 37 39. exp Mass Screening/ 40. (test or tests or testing or tested or swab or swabs or cultur*).ti,ab. 41. (screen* or surveill*).ti,ab. or exp Population Surveillance/ 42. or/39-41 43. ((control or prevent*) adj (intervention or program* or strategy or measure* or precaution*)).ti,ab. 44. pc.fs. 45. infection control/mt, st 46. (infection adj3 (intervention or control or prevention)).ti,ab. 47. universal precautions/ 48. or/43-47 49. 38 and 42 and 48 50. ((control or prevent*) adj (intervention or program* or strategy or measure*)).ti,ab.

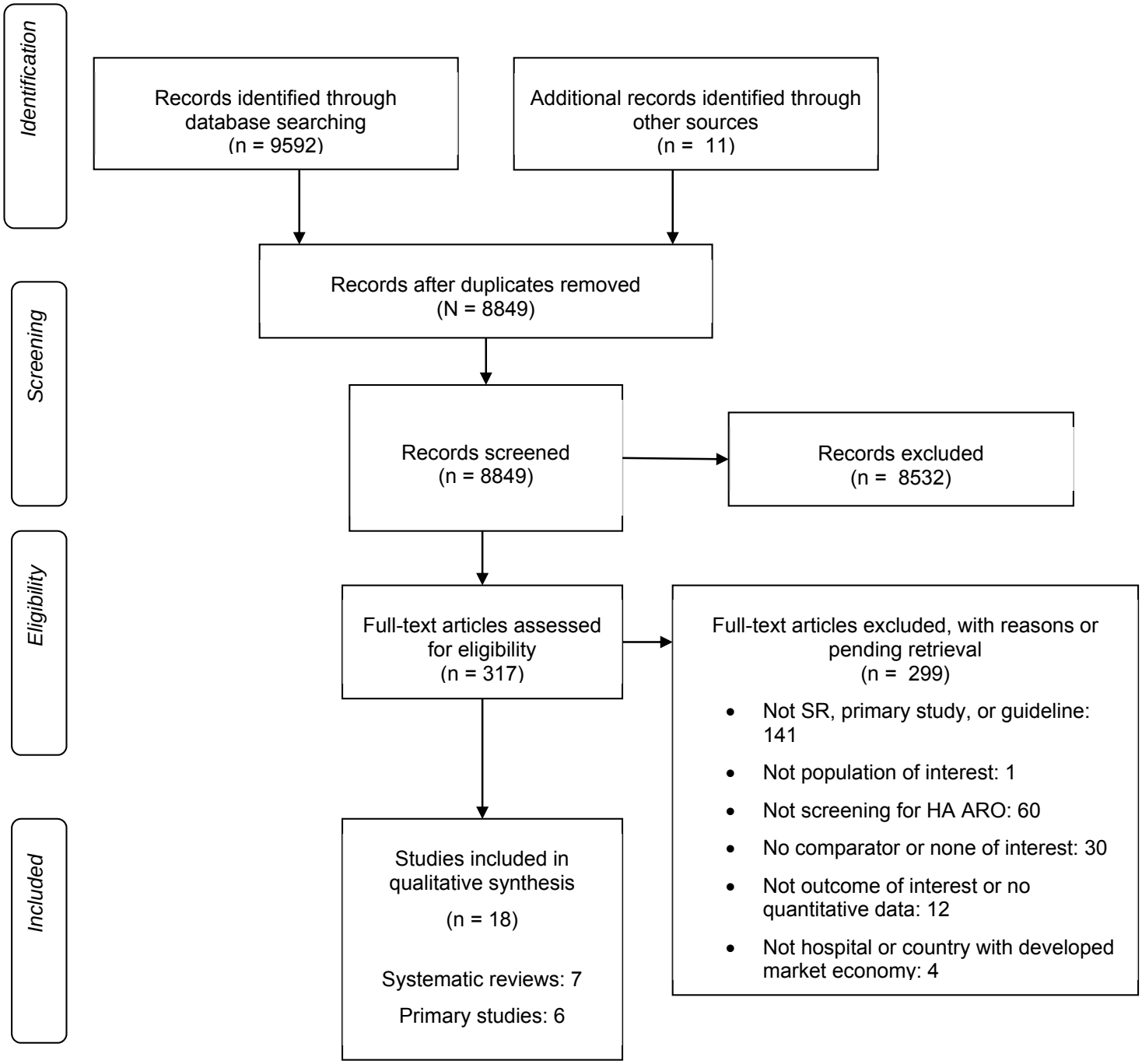
		51. ("randomized controlled trial" or "controlled clinical trial" or "Comparative Study " or "EvaluationStudies " or clinical trial).pt. 52. randomized controlled trials/ or random allocation/ or double-blind method/ or placebos/ or single-blind method/ or clinical trials/ or research design/ or follow-up studies/ or exp cohort studies/ or prospective studies/ or Program Evaluation/ or exp case-control studies/ or cross-sectional studies/ 53. "clinical trial".ti,ab. 54. ((singl* or doubl* or trebl* or tripl*) and (mask* or blind*)).mp. 55. (placebo* or random* or prospectiv* or volunteer* or control or controlled or controls).mp. 56. "Sensitivity and Specificity"/ or "Predictive Value of Tests"/ or (sensitiv* or specific* or (predictive adj2 value*) or likelihood or ((false or true) adj2 (positiv* or negativ*))).ti,ab. or di.fs. or (diagnostic or diagnosis).ti. 57. or/51-56 58. 49 and 57 59. Comment/ or Letter/ or Editorial/ or News/ 60. animal/ not (animal/ and human/) 61. (rat or rats or rodent or mice or mouse or horse* or cow or cows or sheep or murine or lamb or lambs or dog or dogs or cats or monkey or primate* or pig or pigs or piglet* or swine* or porcine or rabbit* or bovine or hamster* or zebra*).ti,ab. 62. In vitro/ not (In vitro/ and human/) 63. or/59-62 64. 58 not 63 65. limit 64 to (english language and yr="2003 -Current") 66. remove duplicates from 65 - PRIMARY STUDIES
Embase 1974 to 2013 Week 34	03 Sep 2013 Results: 1608 guidelines 637 Reviews	1. antibiotic resistance/ 2. ((antimicrobial or antibiotic*) adj2 resistan*).ti. 3. Methicillin-Resistant Staphylococcus aureus/ 4. Methicillin-Resistant Staphylococcus aureus infection/ 5. MRSA.ti,ab. 6. Penicillin Resistance/ 7. (met?icillin adj2 resist*).ti,ab. 8. or/6-7 9. Staphylococcus aureus/ 10. Staphylococcus Infection/ 11. (Staphylococc* adj2 (infect* or aureus)).ti,ab. 12. ("s.aureus" or "s aureus" or "staph aureus").ti,ab. 13. or/9-12 14. 8 and 13 15. exp Enterobacteriaceae Infection/ 16. exp Enterobacteriaceae/ 17. (((Carbapenem* adj (resistan* or produc*)) or CRE) adj5 Enterobacteriaceae).ti,ab. 18. exp β-Lactamases/ 19. ((extended or expanded) adj5 (spectrum or spectra)).ti,ab. 20. Gram-Negative Bacterial Infections/ 21. gram negative.mp. 22. or/19-21 23. 18 and 22 24. extended spectrum β lactamase producing Enterobacteriaceae/ 25. extended spectrum β lactamase/ 26. ((extended or expanded) adj5 (spectrum or spectra) adj5 (lactam or βlactam*)).ti,ab. 27. (ESBL or ESBLs).ti,ab. 28. or/23-27 29. exp Vancomycin Resistant Enteroccocus/

		30. (VRE or VREs).ti,ab. 31. (Vancomycin adj5 resistan*).ti,ab. 32. Enterococcus/ 33. Enterococc*.ti,ab. 34. exp Gram-Positive Bacterial Infections/ 35. gram positive.ti,ab. 36. or/32-35 37. 31 and 36 38. 1 or 2 or 3 or 4 or 5 or 14 or 15 or 16 or 17 or 23 or 28 or 29 or 30 or 37 39. Mass Screening/ or Screening/ or Screening Tests/ 40. (test or tests or testing or tested or swab or swabs).mp. 41. (screen* or surveill*).ti,ab. 42. pc.fs. 43. or/39-41 44. 38 and 43 45. limit 44 to animal 46. exp animal/ 47. 44 and 46 48. 45 or 47 49. limit 44 to human 50. 45 not (48 and 49) 51. 44 not 50 52. (rat or rats or rodent or mice or mouse or sheep or murine or lamb or lambs or dog or dogs or cats or monkey or primate* or pig or pigs or piglet* or porcine or rabbit* or bovine or hamster* or zebra* or veterinary or animal*).ti,ab. 53. 51 not 52 54. "systematic review"/ 55. "meta analysis"/ 56. (meta-anal$ or metaanal$).mp. 57. ((quantitativ$ adj3 review$1) or (quantitativ$ adj3 overview$)).mp. 58. ((systematic$ adj3 review$) or (systematic adj3 overview$)).mp. 59. ((methodologic adj3 review$1) or (methodologic adj3 overview$)).mp. 60. (integrat$ adj5 research).mp. 61. (quantitativ$ adj3 synthes$).mp. 62. or/54-61 63. review.pt. or (review$ or overview$).mp. 64. (medline or medlars or pubmed or index medicus or embase or cochrane).mp. 65. (scisearch or web of science or psycinfo or psychinfo or cinahl or cinhal).mp. 66. (excerpta medica or psychlit or psyclit or current contents or science citation index or sciences citation index).mp. 67. (hand search$ or manual search$).mp. 68. ((((electronic adj3 database$) or bibliographic) adj3 database$) or periodical index$).mp. 69. (pooling or pooled or mantel haenszel).mp. 70. (peto or der simonian or dersimonian or fixed effect$).mp. 71. ((combine$ or combining) adj5 (data or trial or trials or studies or study or result or results)).mp. 72. or/64-71 73. 63 and 72 74. 62 or 73 75. (hta$ or health technology assessment$ or biomedical technology assessment$).mp. 76. biomedical technology assessment/ 77. 75 or 76 78. 74 or 77 79. 53 and 78 – SYSTEMATIC REVIEWS 80. exp practice guideline/ or Health Care Planning/ or guideline*.ti. or (practice adj3 parameter*).ti,ab. or guidance.ti,ab. or ((critical or care or

		clinical) adj3 (pathway* or protocol*)).ti,ab. or (protocol* or policy or policies).ti. 81. 53 and 80 82. 79 not 81 83. (latin or latina or latinae or latinamericanos or latinas or latine or latines or latini or latino or latinoamericana or latinoamericanas or latinoamericano or latinoamericanos or africa or africain or africaine or africaines or africains or african or africana or africas or africasia or afrika or afrikaanse or afrique asia or Asian or chinese or china or india or indian).ti,jx. 84. 81 not 83 85. limit 84 to english language 86. remove duplicates from 85 87. limit 86 to letter 88. 86 not 87 – GUIDELINES
EBMR Reviews - ACP Journal Club Cochrane Library (CDSR, DARE, HTA, NHS EED)	09 Sep 2013 Results: 112 ACPJC: 2 CDSR: 11 HTA: 12 NHS EED: 74	1. drug resistance, microbial/ or exp drug resistance, bacterial/ 2. ((antimicrobial or antibiotic*) adj2 resistan*).ti. 3. Methicillin-Resistant Staphylococcus aureus/ 4. MRSA.ti,ab. 5. Methicillin Resistance/ 6. (met?icillin adj2 resist*).ti,ab. 7. or/5-6 8. Staphylococcus aureus/ 9. Staphylococcal Infections/ 10. (Staphylococc* adj2 (infect* or aureus)).ti,ab. 11. ("s.aureus" or "s aureus" or "staph aureus").ti,ab. 12. or/8-11 13. 7 and 12 14. exp Enterobacteriaceae Infections/ 15. exp Enterobacteriaceae/ 16. (((Carbapenem* adj (resistan* or produc*)) or CRE) adj5 Enterobacteriaceae).ti,ab. 17. exp β-Lactamases/ 18. exp β-Lactam Resistance/ 19. or/17-18 20. ((extended or expanded) adj5 (spectrum or spectra)).ti,ab. 21. Gram-Negative Bacterial Infections/ 22. gram negative.mp. 23. or/20-22 24. 19 and 23 25. ((extended or expanded) adj5 (spectrum or spectra) adj5 (lactam or βlactam*)).ti,ab. 26. (ESBL or ESBLs).ti,ab. 27. or/24-26 28. exp Vancomycin Resistance/ 29. (Vancomycin adj5 resistan*).ti,ab. 30. or/28-29 31. Enterococcus/ 32. Enterococc*.ti,ab. 33. exp Gram-Positive Bacterial Infections/ 34. gram positive.ti,ab. 35. or/31-34 36. 30 and 35 37. (VRE or VREs).ti,ab. 38. 1 or 2 or 3 or 4 or 13 or 14 or 15 or 16 or 24 or 27 or 36 or 37 39. exp Mass Screening/ 40. (test or tests or testing or tested or swab or swabs).mp. 41. (screen* or surveill*).ti,ab. or exp Population Surveillance/ 42. pc.fs. 43. or/39-41 44. 38 and 43

GREY LITERATURE		
National Guidelines Clearinghouse	10 Sep 2013 Results: 11	VRE or CRE or MRSA or ESBL
Dynamed	10 Sep 2013	VRE or CRE or MRSA or ESBL
Websites – CDC www.cdc.gov	September 10, 2013 8	VRE or CRE or MRSA or ESBL
Identified by EAG members or other researchers	3	

Appendix 3: Literature Search and Selection



Appendix 4: Excluded Studies

From the 316 reports retrieved and evaluated based on the full text, a total of 299 reports were excluded. The reasons for exclusion and numbers of reports excluded for those reasons were as follows: not an original report of a systematic review, primary study, or guideline (141 reports); not a population of interest, for example, health care professionals (one report); not a screening strategy aimed at endemic AROs, for example, outbreak or contact precautions (60 reports); not a comparator of interest, for example, different methods for identifying AROs (30 reports); not an outcome of interest or no quantitative data (12); not set in a country with a developed market economy (four reports); not published in the English language (six reports); study included in a systematic review included in the review of reviews (34 reports). At the time the review was completed, 11 reports had not been retrieved and evaluated and were considered "pending."

Not original report of an SR, primary study, or guideline (n = 141)

1. Guidelines for the control of epidemic methicillin-resistant Staphylococcus aureus. Report of a combined working party of the Hospital Infection Society and British Society for Antimicrobial Chemotherapy. *Journal of Hospital Infection* 1986;7(2):193-201.
2. Guidelines for the prevention and control of vancomycin resistant enterococci (VRE) in long-term care facilities. Sioux Falls Task Force on Antimicrobial Resistance. *South Dakota Journal of Medicine* 1998;51(4):127-32.
3. Surveillance for antimicrobial resistance: DEFRA sets out its strategy. *Veterinary Record* 2004;154(21):642-3.
4. Screening for MRSA and isolating carriers doesn't reduce ICU infections. *BMJ* 2013;346:f3581.
5. Almario V. Use of a room placement algorithm for safe placement of patients with MRSA and/or VRE colonization in a long-term acute care (LTAC) hospital setting. *American Journal of Infection Control Conference: APIC 37th Annual Educational Conference and International Meeting New Orleans, LA United States Conference Publication: (var pagings) 38 (5) ()(pp E7* 2010;(var.pagings):E78. Available: http://dx.doi.org/10.1016/j.ajic.2010.04.106.
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10. Bootsma MC, Diekmann O, Bonten MJ. Controlling methicillin-resistant Staphylococcus aureus: quantifying the effects of interventions and rapid diagnostic testing. *Proceedings of the National Academy of Sciences of the United States of America* 2006;103(14):5620-5.
11. Boyce JM, Jackson MM, Pugliese G, Batt MD, Fleming D, Garner JS, et al.

Methicillin-resistant Staphylococcus aureus (MRSA): a briefing for acute care hospitals and nursing facilities. The AHA Technical Panel on Infections Within Hospitals. *Infection Control & Hospital Epidemiology* 1994;15(2):105-15.

12. Buchan BW, Ginocchio CC, Manii R, Cavagnolo R, Pancholi P, Swyers L, et al. Multiplex identification of gram-positive bacteria and resistance determinants directly from positive blood culture broths: evaluation of an automated microarray-based nucleic Acid test. *PLoS Medicine / Public Library of Science* 2013;10(7):e1001478, 2013.
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14. Calfee DP. Methicillin-resistant Staphylococcus aureus and vancomycin-resistant enterococci, and other Gram-positives in healthcare. *Current Opinion in Infectious Diseases 201*2;25(4):385-94.
15. Canadian Agency for Drugs and Technologies in Health (CADTH). Pre-Operative Screening for Methicillin-Resistant Staphylococcus aureus (MRSA) Infection: A Review of the Clinical-Effectiveness and Guidelines. *CADTH Technology Overviews* 2010;1(2):e0114, 2010.
16. Centre for Reviews and Dissemination. Cost-effectiveness of a Staphylococcus aureus screening and decolonization program for high-risk orthopedic patients (Structured abstract). *NHS Economic Evaluation Database (NHSEED)* Critically appraised economic evaluations. 2013 Issue 3, John Wiley & Sons, Ltd. Chichester, UK. Division: ST.
17. Centre for Reviews and Dissemination. Cost-effectiveness of different MRSA screening methods (Structured abstract). *NHS Economic Evaluation Database (NHSEED)* Critically appraised economic evaluations. 2013 Issue 3, John Wiley & Sons, Ltd. Chichester, UK. Division: ST.
18. Centre for Reviews and Dissemination. Active screening in high-risk units is an effective and cost-avoidant method to reduce the rate of methicillin-resistant Staphylococcus aureus infection in the hospital (Structured abstract). *NHS Economic Evaluation Database (NHSEED)* Critically appraised economic evaluations. 2013 Issue 3, John Wiley & Sons, Ltd. Chichester, UK. Division: ST.
19. Centre for Reviews and Dissemination. Optimizing treatment of antimicrobial-resistant Neisseria gonorrhoeae (Structured abstract). *NHS Economic Evaluation Database (NHSEED)* Critically appraised economic evaluations. 2013 Issue 3, John Wiley & Sons, Ltd. Chichester, UK. Division: ST.
20. Centre for Reviews and Dissemination. Effectiveness of a multifaceted infection control policy in reducing vancomycin usage and vancomycin-resistant enterococci at a tertiary care cancer centre (Structured abstract). *NHS Economic Evaluation Database (NHSEED)* 2013;Critically appraised economic evaluations. 2013 Issue 3, John Wiley & Sons, Ltd. Chichester, UK. Division: ST.
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aureus: bad news and good news from the European Antimicrobial Resistance Surveillance Network (EARS-Net, formerly EARSS), 2002 to 2009. *Euro Surveillance: Bulletin Europeen sur les Maladies Transmissibles = European Communicable Disease Bulletin* 2011;16(11).

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new, rapid molecular test (EMMS). *BMC Health Services Research* 2007;7:160, 2007.

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Not hospital setting or country with developed market economy (n = 4)

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Pending retrieval and assessment (n = 11)

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11. Widmer AF, Mertz D, Frei R. Necessity of screening of both the nose and the throat to detect methicillin-resistant Staphylococcus aureus colonization in patients upon admission to an intensive care unit. *Journal of Clinical Microbiology* 2008;46(2):835, 2008.

Appendix 5: Summary of Quality Assessment of Systematic Reviews

Item	Aboelela et al. 2006[12]	Chen et al. 2013[13]	Glick et al. 2013[14]	Halcomb et al. 2008[5]	Ho et al. 2012[15]	Loveday et al. 2006[16]	McGinigle et al. 2008[17]
A1. A priori design	Can't answer	Can't answer	Yes	Yes	Yes	Yes	Yes
A2. Duplicate selection and data extraction	Yes	Can't answer	Yes	No	Yes	No	Can't answer
A3. Lit search	Yes	No	Yes	Yes	Yes	Yes	Yes
A4. Inclusion criteria	No	No	Yes	Yes	Yes	No	Yes
A5. Studies list	No	No	Yes	Yes	Yes	No	No
A6. Study characteristics	No (partial)	Yes	Yes	Yes	Yes	Yes	No (partial)
A7. QA conducted	Yes	Yes	Yes	Yes	Yes	Yes	Yes
A8. QA considered in conclusions	Yes	Yes	Yes	Yes	Yes	Yes	Yes
A9. Pooled results	NA	NA	NA	NA	NA	NA	NA
A10. Publication bias	No	No	No	No	No	No	No
A11. Conflict of interest	No	No	No	No	No	No	No
Overall score /11	4	3	9	8	9	6	5

NA = not applicable; QA = quality or risk of bias assessment

Appendix 6: Characteristics of Included Systematic Reviews

Primary author, year, country Strategies compared, AMSTAR score	Databases and search date Grey Lit search Search limits	Number and design of studies included	Outcomes	Conflict of Interest Additional comments
Aboelela et al. 2006[12] United States Universal screening vs. no screening 4/11	PubMed, Cochrane CENTRAL, Cochrane Library 2004—Jun 30, 2005 Published studies only English language only	21 studies: quasi-experimental design with or without a control group	Infection rates and colonization rates	Not reported
Chen et al. 2013[13] United States Targeted vs. no screening 3/11	PubMed, Cochrane database of systematic reviews and CENTRAL, DARE, HTA database Inception—December 2012 Published after 1968	19 studies: three RCTs,six prospective and 10 retrospective observational studies	Surgical site infection rate	Not reported
Glick et al. 2013[14] United States (AHRQ) Universal vs. no screening Universal vs. targeted screening Targeted vs. no screening 9/11	MEDLINE, Embase, Cochrane Database of Systematic Reviews 1990–Mar 30, 2012 Website search of NICE, NHS HTA program, National Guideline Clearinghouse, clinical trial registries	32 studies: one RCT and 15 observational studies included in summary of evidence and additional 16 observational studies described, but not considered in SOE due to high-risk of bias	Incidence of hospital acquired infection, morbidity, mortality, harms and resource utilization of screening	Funded by AHRQ. Potential conflicts of interest for members of technical expert panel and peer reviewers reported.
Halcomb et al. 2008[5] Australia Targeted vs. no screening 8/11	MEDLINE, Embase, CINAHL, Cochrane Library and Joanna Briggs institute Library 1990–Aug 2005 Reference lists Internet search English language only	five “exploratory descriptive” or comparative studies	Incidence of hospital acquired acquisition	Not reported **Comment:** Assessment of study quality focused on quality of reporting rather than on conduct and risk of bias.

Ho et al. 2012[15] Canada (CADTH) Targeted vs. no screening 9/11	MEDLINE, Embase, PubMed and Cochrane Library 2002–Mar 26, 2012 Grey literature and Google search English language only	one retrospective cohort study	Incidence of hospital acquired VRE bacteremia or blood infection	Funded by CADTH. Potential COI not reported.
Loveday et al. 2006[16] United Kingdom Targeted vs. no screening 6/11	MEDLINE, Embase, CINAHL, DARE, Cochrane CENTRAL, and Health Information Management Consortium 1996–2006 National Research Register Published studies data only English language only	No studies included	Primary: Reduction in colonization/infections Secondary: Length of stay, antimicrobial prescribing	Not reported
McGinigle et al. 2008[17] United States Targeted vs. no screening 5/11	MEDLINE, Web of Science, CINAHL and Cochrane Library Inception–Sept 2007 Reference lists Website search of CDCP and Healthcare Improvement	16 observational studies: two controlled, 14 no control	Incidence of hospital acquired infection, incidence of MRSA colonization	Not reported

CDCP = Centers for Disease Control and Prevention

APPENDIX 6: REVIEW CHARACTERISTICS (CONT'D)

Primary author, year, country Strategies compared, AMSTAR score	Population and setting	Interventions and comparators	Quality assessment and grading of evidence	Reviewer's Conclusions
Aboelela et al. 2006[12] United States Universal screening vs. no screening 4/11	Adults in tertiary care or long-term care	Surveillance cultures (that is screening upon admission and weekly or more frequent screening) for MRSA or VRE **Comparator:** No screening	**Study quality:** Tool developed from quality assessment instruments used in previous reviews. Quality assessment examined 5 domains: representativeness, bias, confounding, description of intervention, outcomes assessment, and statistical analysis. Studies given overall numerical score. **Grading:** No grading system used	Studies to date assessing the impact of surveillance cultures and barrier precautions on transmission of multidrug resistant organisms are generally consistent but methodologically flawed and subject to multiple biases. Because the majority of interventions tested have included many components, it is not yet possible to determine whether there is a specific set of interventions that is essential and to identify those minimum components necessary to reduce risk of transmission.
Chen et al. 2013[13] United States Targeted vs. no screening 3/11	Orthopedic surgery patients	Screening for MRSA and/or decolonization in orthopedic procedures **Comparator:** No screening	**Study quality:** assessed by type of study, year study conducted, and sample size (> 1000 participants considered more favorably). Studies were categorized as good, fair, and low. **Grading:** No grading system used	All studies showed a reduction in SSIs or wound complications by instituting a screening and decolonization protocol in elective orthopedic and trauma patients. Preoperative screening and decolonization in orthopedic patients is a cost-effective means to reduce SSIs.

Glick et al. 2012[14] United States (AHRQ) Universal vs. no screening Universal vs. targeted screening Targeted vs. no screening 9/11	Inpatient (hospital wards and ICUs) and ouptient (ambulatory clinics, urgent care centres, and emergency departments)	MRSA screening strategy applied to all patients in a setting (universal) or applied to particular wards, units or patients (targeted) and used a testing modality with rapid, intermediate, or longer (culture) turnaround **Comparator:** No screening or targeted screening	**Study quality:** USPSTF framework. QA assessed 6 domains: assembly of groups, maintenance of comparable groups, loss to followup, outcome measurement, definition of intervention, and outcomes considered. Studies rated good, fair, or poor. **Grading:** AHRQ modified GRADE system. Assesses 4 domains: risk of bias, consistency, directness, and precision.	There is low strength of evidence that universal screening of hospital patients decreases MRSA infection. Insufficient evidence for other outcomes for universal screening. Insufficient evidence to support or refute claims of the effectiveness of MRSA screening for any outcomes in other settings (that is, targeted screening).
Halcomb et al. 2008[5] Australia Targeted vs. no screening 8/11	Adult, pediatric or neonatal clients in acute care setting in hospitals in Italy, UK, and Germany.	Screening prior to hospital admission for elective surgical patients or following admission. Screening cultures varied from single nasal cultures to nasal passages and a combination of rectal, axilla and groin swabs; throat, skin, lesions, and invasive devices. **Comparator:** No screening	**Study quality:** Instrument developed by review team that assessed description of sample, setting, method of sampling, history of MRSA, type of study, method of data collection, cleaning regime, research design, blinding, type of analysis, clinical significance and consistency with results. **Grading:** Evidence hierarchy developed by the National Health and Medical Research Council. Included studies were classified as either level III or IV.	Many included studies had significant limitations. The lack of information in the studies on patient diagnosis and study setting limits the ability to generalize the findings to other settings.
Ho et al. 2012[15] Canada (CADTH) Targeted vs. no screening 9/11	Patients in high-risk units, for example hematology-oncology, transplant, and ICU wards.	Active screening (3 weeks) Weekly rectal swabs from all patients **Comparator:** No screening	**Study quality:** Downs and Black checklist **Grading:** No grading system used	Evidence from a limited number of observational studies showed that active surveillance with weekly rectal swabs in high-risk units was associated with lower VRE bacteremia rates.

Loveday et al. 2006[16] United Kingdom Targeted vs. no screening 6/11	Acute care patients (all including high-risk groups, e.g, previous known MRSA/elective orthopedic or cardiac surgery)	Preadmission screening and on-admission screening **Comparator:** No screening	**Study quality:** Process developed by Scottish Intercollegiate Guidelines Network **Grading:** Evidence hierarchy developed by Eccles and Mason	No studies reported screening as the primary intervention. In an SR of isolation policy studies, those that included screening as an additional intervention to isolating patients were considered by the reviewers to provide insufficient data to assess the individual effects of the screening of patients as a component of broader infection control strategies to prevent and control MRSA transmission.
McGinigle et al. 2008[17] United States Targeted vs. no screening 5/11	Adult medical or surgical ICU patients	Admission screening and at least weekly screening thereafter **Comparator:** No screening	**Study quality:** UK NHS Centre for Reviews and Dissemination guideline for observational studies. Studies rated good, fair, or poor. **Grading:** No grading system used	Existing evidence may favor the use of active surveillance cultures (screening), but the evidence is of poor quality, and definitive recommendations cannot be made.

NHS = National Health Service; QA = quality assessment; USPSTF = United States Preventive Services Task Force

Appendix 7: Risk of Bias Assessment Primary Studies

Table 1: Risk of bias assessment of controlled trial

Huang et al.[18]		
Domain	**Description**	**Reviewer Judgment**
Sequence generation	Randomization stratified to balance patient volume and baseline prevalence of MRSA carriage. Hospitals ranked according to ICU volume and grouped. Each group of three consecutive hospitals randomly assigned one to each strategy group using block randomization. Generation of sequence not described.	Unclear
Allocation concealment	Allocation concealment not described.	Unclear
Blinding	Blinding not possible but unlikely to affect outcomes, which, as a class, were assessed independently in a lab.	Yes
Incomplete outcome data	Reasons for missing outcome data unlikely to be related to true outcome	Yes
Selective outcome reporting	Reported data for all outcomes reported in clinical trial registry (ClinicalTrials.gov).	Yes
Other sources of bias	Funding source (AHRQ and CDCP) reported and unlikely to bias results.	Yes
Overall risk of bias	Unclear risk of bias for one or more key domains	Unclear

Appendix 7: Risk of Bias Assessment Primary Studies (Cont'd)

Table 2: Newcastle-Ottawa Cohort Assessment Tool

Domain	Kjonnegaard et al.[19]	Lawes et al.[20]	Lowe et al.[21]	Mehta et al.[22]	Sarma et al.[23]
Representativeness of exposed cohort	Truly representative	Truly representative	Truly representative	Truly representative	Truly representative
Selection of non-exposed cohort	Same community	Same community	Same community	Same community	Same community
Ascertainment of exposure	Secure record	Secure record	Secure record	Secure record	Secure record
Outcome not present	Yes	Yes	Yes	Yes	Yes
Comparability	Multivariate regression analysis	Poisson regression tests used to assess secular trends	Controls for baseline ESBL incidence and year No specific statistical adjustment reported	No statistical adjustment reported.	Durbin-Watson correction for autocorrelation
Outcome assessment	Lab/hospital records	Lab/hospital records	Lab/hospital records	Lab/hospital records	Lab/hospital records
Follow-up	Yes	Yes	Yes	Yes	Yes
Adequacy of follow-up	Complete	Complete	Complete	Complete	Complete
Overall score /9	9	9	8	8	9

CO = community-onset

Appendix 8: Characteristics of Primary Studies

Primary author year, country, study design, comparison, funding source	Objective Clinical setting	Intervention strategy, No. patients Comparator, No. patients Duration	Outcomes	Results
Huang S 2013[18] United States Cluster RCT Targeted vs. no screening **Funding:** U.S. AHRQ, CDCP	To determine what type of decolonization strategy works best to reduce MRSA and other pathogens in ICUs. Adult ICUs in Hospital Corporation of America hospitals	G1: Universal MRSA screening and isolation 16 hospitals (23 ICUs and 23,480 patients) G2: Targeted decolonization (screening, isolation, and decolonization of MRSA carriers) 13 hospitals (20 ICUs and 22,105 patients) G3: Universal decolonization (no screening and decolonization of all patients 13 hospitals (29 ICUs and 26,024 patients) Study period: April 8, 2010–September, 2011	**Primary:** ICU-attributable MRSA positive cultures **Secondary:** ICU-attributable MRSA bloodstream infection, ICU-attributable bloodstream infection from any pathogen Pathogens attributed to an ICU if collection date occurred during the period from third day after ICU admission through second day after discharge.	Universal decolonization reduced MRSA-positive clinical cultures by 37%: HR 0.63 (95% CI, 0.52–0.75). No significant reduction between G1 and G2. No statistically significant differences in MRSA infection rates among G1–G3 (p = 0.11). Universal decolonization reduced bloodstream infection by any pathogen by 44%: HR 0.56 (95% CI, 0.49–0.65), targeted decolonization by 22%, HR 0.78 (95% CI, 0.66–0.91, p = 0.03). No significant reductions were seen for Group 1: HR 0.99 (95% CI, 0.84–1.16).
Kjonegaard et al. 2013[19] United States Retrospective cohort Targeted vs. no screening **Funding:** Not reported	To evaluate the effectiveness and costs of active MRSA screening and contact precautions on the transmission rate of HA MRSA in ICU patients ICU in a Southern California acute care community hospital	Pre-active surveillance: MICU and SICU patients were cultured for an infection when symptoms were present and there was physician order. Before January 7, 2009 Active surveillance: all patients admitted or transferred into MICU or SICU were screened for MRSA colonization. 1,654 admissions	**Primary:** HA MRSA infection rates HA MRSA defined as previous negative results and now positive; CA defined as positive result less than 3 days following admission; unknown defined as positive result after 48 hours in the hospital and no previous admission result	Rate of HA MRSA infection lower in prescreening period than in intensive screening period: average 0.8 infections/1000 admissions vs. 1.6 infections/1,000 admissions (p = 0.037). No statistically significant difference in HA MRSA infection rates between comprehensive and state-mandated periods (1.6/1000

		January 7–August 4, 2009 State-mandated active surveillance: All patients admitted to MICU or SICU were screened using method in previous period. 1,687 admissions August 5, 2009–March 4, 2010		admissions vs. 1.1/1000 admissions). No statistically significant difference in HA MRSA infection rates between the prescreening and state-mandated periods (0.8/1000 admissions vs. 1.1/1000 admissions).
Lawes et al. 2012[20] United Kingdom (Scotland) Retrospective cohort Universal vs. targeted screening **Funding:** Scottish government Health Directorate	To evaluate impact of infection control measures, including universal MRSA admission screening on MRSA bacteremia rates All admissions to Aberdeen Royal Infirmary (tertiary referral and teaching hospital)	MRSA screening was performed on selected high-risk patients only, including intensive care and elective surgical admissions with the same strategy of isolation and decolonization as was used in the intervention period. Universal admission screening of all overnight admissions to acute specialties by nasal swab, isolation, or cohorting of all patients with known or new colonization or infection with MRSA and decolonizing of all MRSA positive patients admitted to any specialty. Elective patients were screened at preadmission assessment or on admission. 420,452 admissions Study period: January 1,2006–December 30,2010	**Primary:** Prevalence density of MRSA and methicillin-sensitive SA (MSSA) bacteremia **Secondary:** Incidence and incidence density of hospital-associated MRSA bacteremia, 30-day and inpatient mortality, readmission rate, treatment failure, and recurrence	Prevalence density of MRSA bacteremia: 19% reduction (absolute change, 0.189 to 0.154 [-0.035, 95% CI, -0.049– -0.021]/1000 acute occupied bed days; p <0.001) Incidence density of HA MRSA bacteremia: 29% reduction (0.10 to 0.071 [-0.029, 95% CI, -0.035– -0.023]/1000 acute occupied bed days; p<0.001). 30-day mortality: 46% reduction (34% to 18.4% [-15.6%, 95% CI, -24.1%– -7.1%]; p<0.001)
Lowe et al. 2013[21] Canada Retrospective cohort Universal vs. no screening **Funding:** Physician Services Incorporated Foundation	To determine effect of admission screening (universal and risk-factor) for ESBL-E on incidence of hospital acquired ESBL-E isolates 12 academic and community hospitals (six screening, six non-screening) in Toronto, ON.	Admission screening (no control screening) Median admissions/year: 18,055 (range: 13,188–25,875) No screening Median admissions/year: 21,270 (range: 9,882–26,317) Study period: 5 years (2005–2009)	**Primary:** Incidence of HO ESBL-E/1,000 patient-days. **Secondary:** Incidence of hospital-onset ESBL-E stratified by organism (for example *E. coli* or *K. pneumoniae*), incidence of HO ESBL-E bacteremia and ratio of HO to community-onset cases	Incidence of HO-ESBL-E (non-screening vs. screening) first year: 0.098 vs. 0.034/1000 patient-days Incidence of HO-ESBL-E (non-screening vs. screening) final year: 0.184 vs. 0.097/1,000 patient-days 49.1% (p < 0.001) reduction in HO-ESBL cases

			HO or CO defined as culture positive after or before 72 hours.	64.1% reduction in HO-ESBL bacteremia HO/CO ratio (non-screening vs. screening): 0.88 vs. 0.45
Mehta et al. 2013[22] United States Retrospective cohort Targeted vs. no screening **Funding:** No external funding	To determine the MRSA prevalence density rate before and after implementation of a screening and decolonization protocol Adults undergoing elective orthopedic surgery in specialty orthopedic hospital	Preadmission nasal screening of elective orthopedic patients and decolonization. 63,860 patient-days January 2007–October 2008 No screening, but infection control measures such as isolation precautions and environmental cleaning. 64,327 patient-days November 2008–July 2010	**Primary:** MRSA prevalence density (colonization rate)	MRSA colonization rate pre-implementation 1.23/1000 patient-days, post-implementation 0.83/1000 patient-days (p = 0.026) No statistically significant differences in MSSA rates.
Sarma et al. 2013[23] United Kingdom (England) Interrupted time series Universal vs. targeted screening **Funding:** Unrestricted educational grant from Novartis Pharmaceuticals UK Ltd.	To determine the impact of specific and non-specific interventions (including universal screening) to reduce the incidence of MRSA bacteremia. NHS Trust comprising 3 acute and 7 community hospitals	Universal screening and decolonization (all adult elective, day case, and emergency admissions) Risk-factor screening (elective surgery, emergency orthopedics, trauma surgery, known MRSA positive, oncology/chemotherapy patients Study period: 2003–2008	**Primary:** Incidence of MRSA bacteremia **Secondary:** Incidence of HA MRSA bacteremia and MSSA bacteremia, number MRSA isolates from non-blood cultures, mupirocin resistance HA bacteremia defined as positive test ≥48 hours hospitalization.	Reduction in MRSA bacteremia cases from 23 to 0. ITT analysis indicated significant reduction: level change -0.554 (p = 0.000) and declining slope -0.393 (p = 0.048). Reduction in HA bacteremia cases from 15 cases to 0. ITT analysis indicated significant reduction: level change -0.577 p = 0.001 and declining slope -.216 (p = 0.298). Mupirocin resistance increased from 1.7% to 2.3%. No statistically significant reduction in MSSA bacteremia (R^2 = 0.09).

AHRQ = Agency for Healthcare Research and Quality; CDCP = Centers for Disease Control and Prevention; CA = community acquired; CO = community onset; HA = hospital/healthcare acquired; HO = hospital onset; ICU = intensive care unit; ITT = interrupted time series; RCT = randomized controlled trial

Appendix 9: Guideline Recommendations for screening for AROs

Table 1: Clinical practice guidelines for the screening of MRSA

CPG	Recommendations	Grade for Recommendation
Coia et al. 2006[25] United Kingdom Joint Working Party of the British Society of Antimicrobial Chemotherapy, the Hospital Infection Society, the Infection Control Nurses Association	• Active screening for MRSA carriage should be performed and the results should be linked to a targeted approach to the use of isolation and cohorting facilities (Category 2). • Certain high-risk patients should be screened routinely, and certain high-risk units should be screened at least intermittently. • Selection of patients for screening should be determined locally by infection control teams and endorsed by the relevant hospital management structure. • Patients at high risk of carriage of MRSA may include: - Known to have been infected or colonized with MRSA in the past (Category 1b); - Frequent re-admissions to any healthcare facility (Category 1b); - Direct inter-hospital transfers (Category 1b); - Recent inpatients at hospitals abroad or hospitals in the UK which are known or likely to have a high prevalence of MRSA (Category 1b); - Residents of residential care facilities where there is a known or likely high prevalence of MRSA carriage (Category 1b). • All patients who are at high risk for carriage of MRSA should be screened at the time of admission unless they are being admitted directly to isolation facilities and it is not planned to attempt to clear them of MRSA carriage (Category 2). • Regular (for example, weekly or monthly, according to local prevalence) screening of all patients on high-risk units should be performed routinely (Category 2). • In addition, screening all patients (regardless of their risk-group status) should be considered on admission to high-risk units (Category 2). • Whether to screen patients on admission to other wards or regular screening of inpatients on their wards should be decided by the local infection control team in consultation with the senior clinical staff of the units, and as agreed with the relevant hospital management structure (Category 2). • **Screening of staff** is not recommended routinely, but if new MRSA carriers are found among the patients on a ward, staff should be asked about skin lesions. Staff with such lesions should be referred for screening and for consideration of dermatology treatment (Catogory 1b)	**Category 1a:** Strongly recommended for implementation and strongly supported by well-designed experimental, clinical or epidemiological studies. **Category 1b:** Strongly recommended for implementation and strongly supported by certain experimental, clinical or epidemiological studies and a strong theoretical rationale. **Category 1c:** Required for implementation, as mandated by federal or state regulation or standard. **Category 2:** Suggested for implementation and supported by suggestive clinical or epidemiological studies or a theoretical rationale. **No recommendation:** unresolved issue.

Public Health Ontario 2013[1]	• Regulated health professionals in health care facilities are expected to take screening specimens from patients at increased risk for MRSA on admission as part of an MRSA prevention and control program. • The following patients are at increased risk for MRSA and should be screened at admission for MRSA: - have previously been colonized or infected with MRSA; - have spent time in a health care facility outside of Canada in the last 12 months; - have been admitted to, or who have spent more than 12 continuous hours as a client/patient/resident in, any health care facility in the past 12 months; - have been transferred between health care facilities; - have recently been exposed to a unit/area of a health care facility with an MRSA outbreak; - other high-risk patient populations (s), for example, internal transfers, such as admission to an ICU. • Based on local epidemiology and risk factors, MRSA screening may be considered for those individuals who are: - receiving home health care services in the past year; - receiving treatment with an indwelling medical device; - receiving care in intensive care units, transplant units, burn units; - living in a communal setting (for example, shelter, halfway home, correctional facility); - with a history of injection drug use; - household contacts of people with MRSA; - immunocompromised; - from populations where community-associated MRSA is known to be a problem. • Monitor changes in the local epidemiology and local risk factors for MRSA and adjust screening accordingly. **Screening contact of MRSA cases:** • Any patient who is considered to be an MRSA contact should have follow-up screening specimens, with at least two specimens taken on different days, with one taken a minimum of seven days following the last exposure. • Patient contacts should be re-screened when new cases of MRSA continue to be identified despite active control measures. **Point prevalence screening:** • Point prevalence screens should be conducted on units/areas where patients are at high risk for acquiring MRSA during their stay in the healthcare setting. • Patients at high risk include those on burn units or other high-risk units such as ICU, transplantation units, or other units as defined by the ICP. • Point prevalence screens should be conducted, and should continue to be conducted, until no further transmission is detected; in general this means at least two prevalence screens, taken	Ranking system for recommendations is contained in the primary report to which the guideline is annexed.[44] No grading was reported for these recommendations. **Strength of recommendation** **A:** Good evidence to support a recommendation for use. **B:** Moderate evidence to support a recommendation for use. **C:** Insufficient evidence to support a recommendation for or against use. **D:** Moderate evidence to support a recommendation against use. **E:** Good evidence to support a recommendation against use. **Quality of evidence** **I:** Evidence from at least 1 properly randomized, controlled trial. **II:** Evidence from at least one well-designed non-randomized clinical trial, from cohort or case controlled analytic studies, preferably from more than one centre, from multiple time series, or from dramatic results in uncontrolled experiments. **III:** Evidence from opinions of respected authorities on the basis of clinical experience, descriptive studies, or reports of expert committees.

	after the last transmission was detected and at least a week apart, in any area where MRSA transmission is occurring. **Screening Staff for MRSA** Screening staff for MRSA should be considered when an outbreak of the same strain of MRSA continues despite adherence to control measures or when a staff member is epidemiologically linked to new acquisitions of MRSA.	

Table 2: Clinical practice guidelines for the screening of carbapenem-resistant Enterobacteriaceae (CRE) or carbapenemase-producing Enterobacteriaceae (CPE)

CPG	Recommendation	Grade for recommendation
National Center for Emerging and Zoonotic Infectious Diseases, Division of Healthcare Quality Promotion 2012 [26] United States	The screening for CRE generally involved stool, rectal, or peri-rectal cultures and sometimes cultures of wounds or urine (if a urinary catheter is present). CRE screening might include: • **Point prevalence surveys:** an effective way for facilities to rapidly evaluate the prevalence of CRE in particular wards/units and could be useful in a situation where a review of clinical cultures using laboratory records identifies unreported CRE patients in certain wards/units. It is generally conducted by screening all patients in that ward/unit. Depending on the extent of CRE colonization, point prevalence surveys could be done once only or serially. • **Screening of epidemiologically linked patients**: If previously unrecognized CRE carriers are identified, screening of patient contacts could be conducted to identify transmission instead of a wider point prevalence survey. Those patients considered contacts may include roommates of the unrecognized CRE patients as well as patients who might have shared healthcare personnel (HCP).	Not reported
Public Health Ontario 2013[1]	• All health care facilities should institute a screening program and targeted surveillance for CPE. In particular, admission screening and pre-emptive Contact Precautions are indicated for individuals with risk factors for CPE. Patients who have received health care outside of the country or who are known contacts of CPE should be screened. • If a single patient with CPE is identified, a full unit/ward prevalence screen should be conducted. If screening of the full unit/ward is not feasible, screening of patients in close proximity to the identified patient should be strongly considered. • In a CPE outbreak, there should be a full unit/ward prevalence screen. Periodic prevalence screening, for example, weekly, should continue until no new cases are identified, with at least three negative prevalence screens after the last new case. • Patients who have been transferred from the unit/ward should be screened and be placed on Contact Precautions pending screening results. For patients who have been transferred to another facility, the facility should be informed and the patients should be screened. • Patients with known CPE carriage should have their records flagged, should be placed on Contact Precautions and should be re-screened **on readmission.**	Ranking system for recommendations is contained in the primary report to which the guideline is annexed.[44] No grading was reported for these recommendations. **Strength of recommendation** **A:** Good evidence to support a recommendation for use. **B:** Moderate evidence to support a recommendation for use. **C:** Insufficient evidence to support a recommendation for or against use. **D:** Moderate evidence to support a recommendation against use. **E:** Good evidence to support a recommendation against use. **Quality of evidence** **I:** Evidence from at least 1 properly randomized, controlled trial. **II:** Evidence from at least one well-designed non-randomized

	Screening staff for CPE: Routine screening of staff for CPE is not recommended as no evidence that rectal colonization of health care providers contributes to transmission.	clinical trial, from cohort or case controlled analytic studies, preferably from more than one centre, from multiple time series, or from dramatic results in uncontrolled experiments. **III:** Evidence from opinions of respected authorities on the basis of clinical experience, descriptive studies, or reports of expert committees.

Table 3: Clinical practice guidelines for the screening of vancomycin-resistant Enterococci (VRE)

CPG	Recommendation	Grade for recommendation
Public Health Agency of Canada 1997[24] Canada	• Laboratories should routinely screen for vancomycin resistance in all clinically significant enteroccal isolates obtained within the facility from any body site. • In tertiary medical centres and other hospitals with many critical ill patients at high risk of VRE infection or colonization, periodic culture survey of stools or rectal swabs of such patients can detect the appearance of VRE. Fecal screening is recommended even when VRE infections have not been identified clinically, because gut colonization may occur in patients in a facility before infections are identified. • The findings of a first isolate of VRE should prompt fecal screening (stool survey or rectal swabs) for the identification of other colonized patients in an effort to establish the optimal and timely application of isolation precautions and control measures. • The use of screening surveys are merely a tool to elucidate the epidemiology of VRE within a given ward, patient population or facility are not considered a mandatory component of an infection control program. The optimal timing and extent of screening procedures remains unknown. In outbreak situations, it may be necessary to screen patients outside of the ward to avoid missing colonized patients. • The utility of massive screening efforts directed at all possible contact, entire health care facility patient populations and staff is unknown at this time and such efforts are not currently recommended.	Ranking system for recommendations is contained in the primary report to which the guideline is annexed.[44] No grading was reported for these recommendations. **Strength of recommendation** **A:** Good evidence to support a recommendation for use. **B:** Moderate evidence to support a recommendation for use. **C:** Insufficient evidence to support a recommendation for or against use. **D:** Moderate evidence to support a recommendation against use. **E:** Good evidence to support a recommendation against use. **Quality of evidence** **I:** Evidence from at least 1 properly randomized, controlled trial. **II:** Evidence from at least one well-designed non-randomized clinical trial, from cohort or case controlled analytic studies, preferably from more than one centre, from multiple time series, or from dramatic results in uncontrolled experiments. **III:** Evidence from opinions of respected authorities on the basis of clinical experience, descriptive studies, or reports of expert committees.

Public Health Ontario 2013[1]	• Regulated health professionals in health care facilities are expected to take screening specimens from patients at increased risk for VRE on admission as part of a VRE prevention and control program • The following patients are at increased risk for VRE and should be screened at admission for VRE: - have previously been colonized or infected with VRE; - have spent time in a health care facility outside of Canada in the last 12 months; - have been admitted to, or who have spent more than 12 continuous hours as a client/patient/resident in, any health care facility in the past 12 months; - transferred between health care facilities (for example, between hospitals or between a long-term care facility and a hospital), - have recently been exposed to a unit/area of a health care facility with a VRE outbreak, - other high-risk patient populations as identified by the ICP(s) (for example, internal transfers, such as admission to an ICU) or Public Health. • Monitor changes in the local epidemiology and local risk factors for VRE and adjust screening accordingly. **Screening Contacts of VRE Cases** VRE contacts should: • have follow-up specimens, with at least two specimens taken on different days, with one taken a minimum of seven days following the last exposure to VRE • be re-screened when new cases of VRE continue to be identified despite active control measures. **Point prevalence screening** • Point prevalence screens should be conducted on units/areas where patients are at high risk for acquiring VRE during their stay in the health care setting. • Patients at high risk include those on dialysis units or other high-risk units such as intensive care units, transplantation units, or other units as defined by the ICP(s). • Point prevalence screens should be conducted in any area where VRE transmission is occurring and should continue to be conducted until no further transmission is detected; in general, this means at least two prevalence screens taken at least one week apart after the last transmission was detected. **Screening Staff for VRE** The risk of staff colonization with VRE is extremely low and there is no evidence to support the need to screen staff for VRE.	Ranking system for recommendations is contained in the primary report to which the guideline is annexed.[44] No grading was reported for these recommendations. **Strength of recommendation** **A:** Good evidence to support a recommendation for use. **B:** Moderate evidence to support a recommendation for use. **C:** Insufficient evidence to support a recommendation for or against use. **D:** Moderate evidence to support a recommendation against use. **E:** Good evidence to support a recommendation against use. **Quality of evidence** **I:** Evidence from at least 1 properly randomized, controlled trial. **II:** Evidence from at least one well-designed non-randomized clinical trial, from cohort or case controlled analytic studies, preferably from more than one centre, from multiple time series, or from dramatic results in uncontrolled experiments. **III:** Evidence from opinions of respected authorities on the basis of clinical experience, descriptive studies, or reports of expert committees.

Table 4: Clinical practice guidelines for the screening of extended-spectrum β-lactamase-producing bacteria

CPG	Recommendation	Grade for recommendation
Public Health Ontario 2013[1]	• Local epidemiology should govern decision-making regarding routine screening of patients/residents for ESBL-producing bacteria. If the local prevalence of ESBL-producing bacteria is high, there is some value to routinely screening patients, particularly those admitted to ICUs. • An effective and consistent approach to surveillance is an important measure to prevent and control the spread of ESBLs. In an ESBL outbreak, protocols should be in place for screening patients in close proximity to colonized/infected patients who may have been exposed or who have risk factors for ESBL acquisition. • Patients with known ESBL carriage should have their records flagged and be placed on Contact Precautions and re-screened on readmission. • Routine screening of staff for ESBL is not recommended as no evidence that rectal colonization of health care providers contributes to transmission.	Ranking system for recommendations is contained in the primary report to which the guideline is annexed.[44] No grading was reported for these recommendations. **Strength of recommendation** **A:** Good evidence to support a recommendation for use. **B:** Moderate evidence to support a recommendation for use. **C:** Insufficient evidence to support a recommendation for or against use. **D:** Moderate evidence to support a recommendation against use. **E:** Good evidence to support a recommendation against use. **Quality of evidence** **I:** Evidence from at least 1 properly randomized, controlled trial. **II:** Evidence from at least one well-designed non-randomized clinical trial, from cohort or case controlled analytic studies, preferably from more than one centre, from multiple time series, or from dramatic results in uncontrolled experiments. **III:** Evidence from opinions of respected authorities on the basis of clinical experience, descriptive studies, or reports of expert committees.

Taconelli et al. 2013[27] European Society for Clinical Microbiology and Infectious Diseases	After evaluation of the evidence, the guidelines authors agreed that the implementation of active surveillance screening for Gram-negative bacteria in the endemic setting should be suggested only as an additional measure and not included as part of the basic measures to control the spread of multidrug-resistant Gram-negative bacteria. (No recommendation)	**Strength of recommendation** **Strong:** Large differences between the desirable and undesirable consequences. High confidence in the magnitude of estimates of effect of the interventions on important outcomes. **Conditional:** Small net benefit and low certainty for that benefit. Great variability in values and preferences, or uncertainty in values and preferences. High cost of an intervention. **Quality of evidence** **High:** Very confident that the true effect lies close to the estimated effect. **Moderate:** Moderately confident that the true effect lies close to the estimated effect, but there is a possibility that it is substantially different. **Low:** Confidence in the effect estimate is limited: the true effect may be substantially different from the estimate. **Very low:** Very little confidence in the effect estimate: true effect likely to be substantially different from the estimate.

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ISBN 978-1-926929-21-7 (on-line)