Comparative Effectiveness Research Review Disposition of Comments Report

Research Review Title: *Screening for Methicillin-Resistant Staphylococcus Aureus (MRSA)*

Draft review available for public comment from March 15, 2012 to April 12, 2012.

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Comments to Research Review

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The tables below include the responses by the authors of the review to each comment that was submitted for this draft review. The responses to comments in this disposition report are those of the authors, who are responsible for its contents, and do not necessarily represent the views of the Agency for Healthcare Research and Quality.

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Commentator & Affiliation	Section	Comment	Response
Reviewer #1 (Peer)	Executive Summary	Executive Summary: I feel recommendations by AHRQ at a minimum should state the following: "The preponderance of evidence supports active MRSA surveillance and isolation/decolonization in high risk populations, selected categories of surgical patients and in hospital wards which are at risk for developing MRSA outbreaks. The preponderance of evidence also supports Universal surveillance in facilities servicing communities with a significant rate of MRSA colonization in the general population." All of the articles studied in the White Paper showed a decrease in MRSA transmission and infection when effective (eliminating the studies of Harbarth, et al, and Huskins, et al.) MRSA surveillance, isolation/decolinization was instituted. I feel this white paper provides strong evidence in favor of surveillance; and we strongly urge AHRQ and the CDC to take an active role in setting standards, which include at a minimum surveillance for all high-risk populations, preoperative patients and patients admitted to the ICU for the prevention of MRSA. Universal surveillance with effective isolation and intervention should also be performed on all patients entering a facility from communities with a high MRSA colonization rate in the general population. As pointed out by Andreas Vos (BMJ, 2004, PMID:15345601): "Randomised controlled trials are useful for investigating a limited number of variables and when randomisation can be accomplished. Infection control measures are habitually complicated and depend on multiple factors. Therefore I still have some faith in the strength of common sense, microbiological experiments, and careful observation of success and failure when evaluating infection control measures." After all, it took decades of research and arguing with the tobacco industry regarding the validity of studies which demonstrated health risks associated with tobacco use before effective action was taken that limited sales and secondhand smoke exposure. Despite the flaws that exist in biomedical research, Surgeon General Dr. Luther Terry acted much earlier and in 1964 determined that smoking is dangerous to your health. I strongly urge AHRQ to follow suit and set standards, calling for surveillance to be used as a major tool in combating the epidemic of healthcare associated infections.	There is low strength of evidence that universal screening of hospital patients decreases MRSA infection. However, there is insufficient evidence on other outcomes of universal MRSA screening, including morbidity, mortality, harms and resource utilization. There is also insufficient evidence on any outcomes of MRSA screening in other settings. The literature that evaluates screening for MRSA carriage predominantly employs a quasi-experimental design. Much of that literature does not control for confounders or secular trends or does not do so adequately. Because the incidence of MRSA infection has been decreasing in recent years, studies that do not adequately control for secular trends may show a decrease in the incidence of MRSA infection with screening, though that decrease may actually be attributable to a secular trend. Similarly, interventions designed to decrease health care-associated infection more generally (e.g., interventions to reduce surgical site infections) may also reduce MRSA surgical site infections. Failure to control for such a confounder show a decrease in the incidence of MRSA infection with screening, though that decrease may actually be attributable to a confounder.
Reviewer #1 (Peer)	General	General Comments: The reviewers did a nice job defining the key questions. I think it could be more clear that this applies to endemic settings -- not outbreak settings etc where the impact of screening might differ.	Though studies conducted during outbreaks were not excluded from this comparative effectiveness review, we have clarified in the discussion that the results of the comparative effectiveness review apply to endemic settings.
Reviewer #2 (TEP)	General	General Comments: The authors of the report are to be commended for synthesizing such a complex and heterogenous content area. This will be an extremely valuable resource for policy decisions at the facility, local and national levels and will also greatly inform decisions regarding funding of additional studies.	None needed.

Commentator & Affiliation	Section	Comment	Response
Reviewer #2 (TEP)	General	General Comments: While the individual parts of the report are extremely well written, I found that the ordering of the different sections made it difficult to read the report. Specifically, reading the report from front to back without first reading the in-depth report made reading the brief report somewhat difficult to follow from a methodological standpoint.	The report follows a fairly standard structure. We have clarified the methodology, particularly with respect to assessment of study quality and rating of strength of evidence. Strength of evidence assessments were based only on those studies that attempted to control for confounding and/or secular trends, as only those studies that have the potential to support causal inferences.
Reviewer #2 (TEP)	General	General Comments: I thought the report's methodological descriptions were lacking in some areas (e.g., strength of evidence determination criteria provided but the application of those criteria was not, nor was there any detail on how consensus was achieved. Was this same as was done for the individual quality of each study?). I also found the application of the different USPSTF quality criteria to be somewhat subjective and this came through in several sections of the report (e.g., the assignment of a "poor" quality grade to the Jain et al. paper while the Robiscek et al. paper was assigned a "good" quality score.)	We have clarified the methodology, including the assignment of strength of evidence and study quality. In particular, we have clarified the decision rules used to determine the SOE. Please see the tables depicting the Strength of Evidence Rating Domains, the Strength of Evidence Categories and Rules, and the Summary of Outcomes Measures and SOE. Greater detail about rating of individual study quality has been added to each Key Question, with new tables describing key aspects of all studies that attempted to control for secular trends and confounding. In the Results chapter, each Key Question has a strength of evidence section that has been revised to give clarity to the key domains of risk of bias, consistency, directness and precision.
Reviewer #3 (Peer)		General Comments: The authors of this systematic literature review should be commended for the breadth and depth of this review on the data regarding screening for MRSA. This thorough review demonstrates how little is known about the benefit of MRSA screening and the need for more high quality studies. This is a necessary piece of work not only for infection control practitioners and researchers, but also to show policy makers and funding agencies the need for large studies before mandates on MRSA screening are implemented.	None needed.
Reviewer #4 (Peer)	General	General Comments: This is an extremely complete and well-presented review of 21 years of medical literature (1990-2011) addressing the benefits and/or harms of screening for MRSA. It is clinically important, the target population and audience are clearly defined, and the key questions are clearly stated. The conclusion is depressing but nonetheless important to state clearly, as the authors have done: we simply do not have enough high-quality studies to come to any conclusion about the benefits of routine MRSA screening for infection prevention. The most important impact of this review should be to help encourage and direct future research on MRSA screening approaches (see below).	None needed

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Reviewer #5 (Peer)	General	General Comments: In general the report: Screening for Methicillin-Resistant Staphylococcus aureus (MRSA) is very well written and systematically reviews all relevant literature on the topic. The topic is extremely important for both clinicians and healthcare administrators. The conclusion of the review is similar to other recently published meta-analyses, however, the scope of this review is far more comprehensive and provides the reader with a nice grasp of the limitations of the published work on this topic. The target population and audience are explicitly defined in the preface, page iii as those who develop health plans, providers, purchasers, government programs, and the healthcare system as a whole. Essentially, this would include the population AHRQ serves. I believe the key questions are appropriately generated based on what is known to exist in the literature. The key questions are clearly stated in theory. I have some specific comments regarding how the results relate to the key questions in my comments below.	None needed.

Commentator & Affiliation	Section	Comment	Response
Reviewer #6 (Peer)	General	General Comments: The review is well-organized, well-written and informative. The audience and target population could be identified more clearly. The key questions are important and comprehensive, although Key Questions 3C and 4 should be clarified. The methods are adequate, although the application of the study quality and strength of evidence criteria should be clarified and there was no formal assessment of agreement in the identification of studies, data abstraction, or assessment of the study quality and the strength of evidence. The results are clear and well-described, although the synthesis of the strength of evidence appears almost nonsensical in some instances and strengths and limitations of individual key studies are not discussed in any depth. The conclusions are appropriate overall and meaningful, but could be strengthened.	We followed a careful and transparent process to develop PICOTS (population, intervention, comparator, outcomes, timing, setting) and key questions, with expert and public input, so we have not revised these components. We have clarified that KQ 3C evaluates screening of high-risk patients (e.g., patients transferred from another health care facility) compared to no screening. We have also clarified that KQ 4 evaluates screening of a broader patient population for MRSA-Carriage (expanded screening) compared to screening of a narrower patient population (limited screening). We have clarified the methodology, including the assignment of strength of evidence and study quality. In particular, we have clarified the decision rules used to determine the SOE. Please see the tables depicting the Strength of Evidence Rating Domains, the Strength of Evidence Categories and Rules, and the Summary of Outcomes Measures and SOE. Greater detail about rating of individual study quality has been added to each Key Question, with new tables describing key aspects of all studies that attempted to control for secular trends and confounding. We have added a discussion of the importance of controlling for confounding and secular trends to both the Introduction and Discussion sections. In the Results chapter, each Key Question has a strength of evidence section that has been revised to give clarity to the key domains of risk of bias, consistency, directness and precision.

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Reviewer #8 (Peer)	General	General Comments: The authors of the comparative effectiveness review report dealing with screening for methicillin-resistant Staphylococcus aureus (MRSA) obviously spent a considerable amount of time in reviewing pertinent literature and in analyzing a large body of information utilizing rigid criteria for stratifying the level of evidence provided in the individual studies reviewed. It is the most comprehensive review of this topic, which is of considerable interest to healthcare administrators and policy makers. As an infectious diseases specialist involved in diagnosis and treatment of patients with MRSA infections over a period of 34 years, and a hospital epidemiologist involved in the prevention and control of health-care-associated MRSA infections over a period of 30 years, I appreciate the opportunity to review and comment on this important report. I have serious concerns about the overall conclusion drawn by the reviewers, and have listed these concerns among the comments provided below.	None needed.
Reviewer #10 (Peer)	General	General Comments: The report is clinically meaningful and focuses on the evidence for screening for MRSA. This is an increasingly important topic as it affects many patients, but also is being adopted by institutions and states without complete evaluation of the available evidence. The key questions are appropriate, though data to draw meaningful conclusions is limited on many components or the statistical methods were not strong enough and the studies were downgraded or not included. The text is extremely well written and outlines the challenges and limitations, as well as the need for a document like this.	None needed

Commentator & Affiliation	Section	Comment	Response
Reviewer #11 (Peer)	General	General Comments: This is a comprehensive comparative effectiveness review prepared for AHRQ on the topic of screening tests for MRSA carriage in the inpatient and outpatient settings. This is a topic of particular importance to hospital epidemiologists, infectious diseases experts, hospital administrators, and policymakers, in particular because of the increasing public awareness of MRSA colonization and infection, as well as the evolution of public policy toward mandated screening. The importance of having high-quality literature to guide this policymaking cannot be understated, and a comprehensive review such as this is key to understanding the current status of our knowledge on the topic. It's also a difficult subject to digest because of the complexity of the science and the methods used to generate these published works, such as key differences in patient populations, epidemiologic settings, screening strategies, and alternative MRSA control efforts, all of which can have significant impacts on the outcomes observed. One of the strengths of this report is that it clearly and explicitly states the target populations, audience, and key questions, all of which are appropriate to this topic, and serves to highlight the heterogeneity and overall low quality of the published work in this field. This manuscript does a nice job addressing these complexities. Within this context, there are some key points made that limit the usefulness of the information presented -- specifically, the lack of information provided in most studies about (a) decolonization practices at facilities where screening was implemented; (b) the presence of other simultaneous campaigns to reduce health care-associated infections; and, perhaps most importantly, (c) adherence to the intervention under study (e.g., screening, isolation, etc). Without this information from these studies, we are left with the inability to make sound, unconfounded causal inferences about the impact of MRSA screening. The result is that readers are left with the sense that there are practically no studies that provide sufficient detail to make accurate inferences about MRSA screening -- a point which is made by this manuscript, but one is left wondering if the entire exercise was worth the tremendous effort.	None needed.

Commentator & Affiliation	Section	Comment	Response
Reviewer #12 (Peer)	General	General Comments: In the grading of the strength of evidence, there appears to be lack of distinction between the terms consistency and precision. According to the referenced article (#37), consistency refers to the situation in which study findings appear to have the same direction of effect. Precision, on the other hand, refers to the degree of certainty surrounding an effect estimate (e.g., do the confidence intervals allow for the possibility of both inferiority and superiority?). In several locations, the definition of precision seems to have been applied to the term consistency. Specific examples are included in my comments for the Results section.	We have clarified that a body of evidence that is consistent possesses studies with the same direction of effect. We have also clarified that a body of evidence that is precise possesses either 1) uncertainty around an effect compatible with only one of these: clinically important superiority, inferiority or noninferiority; or 2) in the absence of meta-analysis, individual studies consistently report statistically significant results. We have clarified the methodology, including the assignment of strength of evidence. In particular, we have clarified the decision rules used to determine the SOE. Please see the tables depicting the Strength of Evidence Rating Domains, the Strength of Evidence Categories and Rules, and the Summary of Outcomes Measures and SOE. In the Results chapter, each Key Question has a strength of evidence section that has been revised to give clarity to the key domains of risk of bias, consistency, directness and precision.

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Reviewer #7 (Public, Lahue/Durack)	General	BD Recommendation 1: BD urges the AHRQ to re-phrase statements in the structured abstract, executive summary, and main document that address the implications of this review's conclusions for clinical decision-makers to more accurately represent practical options based on the existing body of evidence. In the executive summary, the authors state that: "There is insufficient evidence to support the benefits of routine implementation of screening for MRSA carriage as part of organizational infection control in all settings" (AHRQ, 2012). This concluding statement is made based on the Strength of Evidence (SOE) assessment conducted using the Grading of Recommendations Assessment, Development and evaluation (GRADE) Working Group system. BD commends the AHRQ for using this best practice tool to evaluate the strength of existing evidence, and suggests that the implications of an "insufficient" evidence recommendation must be more accurately represented in the discussion portion of the document. Specifically, BD recommends the statement be modified to state: "There is insufficient evidence to support or refute the benefits of routine implementation of screening for MRSA-carriage as part of organizational infection control in all settings" For many of the key questions, the strength of evidence assessment was impacted by the limited number of studies that met inclusion criteria and demonstrated an attempt to control for confounding and/or secular trends (CCS studies). This limited pool of available evidence resulted in the inability to make strong evidence recommendations based on risk of bias, consistency, directness, and precision. BD respects the authors' decisions to declare there to be an insufficient amount of information to make a SOE decision. Despite the limited amount of high-quality evidence to demonstrate the comparative effectiveness of MRSA screening, clinical stakeholders must still make informed decisions about whether to adopt MRSA screening in various areas within their organizations. The current evidence pool, although small, does suggest that MRSA screening can be a beneficial component of an effective infection control strategy. The large multi-centre study by Robiscek in 2008 (rated good quality), for example, suggests that positive gains in intermediate outcomes and health outcomes (MRSA acquisition, MRSA infection) in various settings can be made. The results and conclusions of studies like this one should not be diminished, and should be considered by decision-makers who are seeking to implement MRSA screening as an infection control mechanism. In the absence of large amounts of high-quality evidence, it is important to communicate transparently to decision-makers on how to interpret insufficient evidence scores.	We have changed this language to read "There is low strength of evidence that universal screening of hospital patients decreases MRSA infection. However, there is insufficient evidence on other outcomes of universal MRSA screening, including morbidity, mortality, harms and resource utilization. There is also insufficient evidence to support or refute the effectiveness of MRSA screening on any outcomes in other settings." The Robicsek study was an observational study of good quality. However, in the group of studies that addressed health care-associated infection overall and health care-associated bacteremia/bloodstream infection, there were no other studies of good or fair quality. In addition, because the findings of the studies that addressed health care-associated infection overall and health care-associated bacteremia/bloodstream infection do not consistently report statistically significant results, the findings are imprecise. Because the evidence base for these outcomes includes only one good quality observational study (the Robicsek study) without any other study of good or fair quality, the starting level for the strength of evidence is low. Strength of evidence is lowered by the high risk of bias and the lack of precision. In summary, the Robicsek study alone does not provide a sufficient level of evidence to draw a conclusion about the strength of evidence for/against screening for MRSA-carriage on health care-associated infection overall or on health care-associated bacteremia/bloodstream infection.

Commentator & Affiliation	Section	Comment	Response
Reviewer #7 (Public, Lahue/Durack)	General	Review Process Considerations BD Recommendation 3: For future evidence reviews, BD recommends that the AHRQ provide opportunity for qualitative feedback on evidence included in draft reports. BD applauds the authors' use of a well-defined systematic approach to identify the most appropriate evidence to answer key research questions. Despite all efforts to appropriately assess the quality of studies for inclusion into the body of evidence, it is often difficult to understand whether described study design was adhered to during the execution phase. In these situations, only stakeholders directly involved in the execution of studies can comment on the analysis and interpretation of results. For example, in the case of this review, a qualitative feedback process would have allowed the authors to learn of additional limitations of the study published by Huskins et al in 2011. In this study, all samples from multiple sites were sent to one center for processing. Because of this approach, the test turnaround time was an average of 5.2 days, during which colonized patients in the ICU were only isolated for 41% of the time (Peterson 2011). This lengthy time delay may well have impeded the effectiveness of the screening program. This important issue in the study's execution was not adequately addressed in the publication. BD recommends that the AHRQ provide a formal process for authors to hear additional qualitative feedback about the studies included in draft reports. By doing so, the AHRQ can better commit to delivering conclusions that are evidence-based and can be supported by the research community. BD applauds AHRQ's efforts in conducting this comparative effectiveness review. The results demonstrate an increased need for conducting unbiased, high-quality comparative effectiveness research in this field. As clinical decision-makers plan and implement infection control strategies, they should be enabled with the most appropriate evidence. If evidence gaps exist, it is important for organizations like the AHRQ to invest in further research to address key questions and challenges. BD commends the Agency for Healthcare Quality and its associated Evidence-based Practice Centers for using an evidence-based approach to recommend the optimal practices for the management of MRSA and appreciates the ability to provide comments for the authors to consider.	AHRQ provides ample opportunity for interested parties to comment on draft reports. The Huskins study was judged to be of good quality overall because it presented baseline characteristics for the intervention and control groups, conducted appropriate analyses (tested for trend, addressed autocorrelation and controlled for at least one confounder) and reported on an health care-associated outcome. When studies reported test turnaround time, we included this data in the comparative effectiveness review. Because test turnaround time is an important metric, studies that reported this metric should not be penalized disproportionately to studies that did not. However, we expanded both the results and the discussion section to address this limitation of the Huskins study. We used the method developed by the US Preventive Services Task Force to assess the quality of individual studies. We point out this flaw of the Huskins study in the Discussion. ("The one cluster randomized trial (a design that minimizes the risk of bias) to examine the impact of MRSA surveillance failed to show a favorable impact of screening, though concerns about the lengthy turnaround time of the screening modality used and the failure to implement barrier precautions, isolation and/or decolonization while awaiting screening test results limit the applicability of this study's findings.")

Commentator & Affiliation	Section	Comment	Response
Reviewer #7 (Public, Persing)	General	Thank you for the opportunity to comment on AHRQ's Draft Comparative Effectiveness Report (CER) of Screening for Methicillin-Resistant Staphylococcus aureus (MRSA). We commend the Agency's effort to compile data across a wide variety of sources and support its mission to "to improve the quality, safety, efficiency, and effectiveness of health care for all Americans." We do, however, have serious concerns on two levels: 1) the conclusions regarding the utility of MRSA screening programs and 2) the assessment of clinical evidence related to the evaluation of the value of diagnostics and infection control programs. Our first request is that AHRQ consider extending the comment period for a minimum of an additional 30 days. After consulting with key opinion leaders, we are concerned that a period of 29 calendar days was insufficient for interested parties to fully digest the review and compile a comprehensive response to some of the conclusions.	Thank you for your comments. However, the comment period cannot be extended.
Reviewer #7 (Public, Persing)	General	Should a revised assessment conclude that MRSA surveillance positively impacts health outcomes in terms of a reduction in either infections or transmission events, Cepheid highly recommends that AHRQ work with its sister Agencies, such as CDC and CMS, to establish both updated practice guidelines and innovative payment incentives that reward positive processes (e.g., MRSA testing and compliance with infection control procedures) that contribute to improved patient outcomes and maximize the efficient use of healthcare resources.	The creation of guidelines does not fall within the purview of the EHC program. Therefore, the goal of this effort is not to create a guideline, though ideally, to inform the subsequent creation of a guideline.
Reviewer #7 (Public, Rattiff)	General	There needs to be more of a distinction between hospital-acquired MRSA and community-acquired MRSA and not lump them together. I am surprised in the search terms that these two were not separated in the search. Also if you are looking at prevention, there is no mention of environmental surfaces as a source of spread especially in athletic facilities.	This comparative effectiveness review evaluated the impact of screening for MRSA-carriage on health care-associated infection. We were unable to restrict our search to teams related to health care-associated acquisition or infection, as this would have eliminated all studies conducted during the period in which community-acquired MRSA infection was unknown. (In other words, health care-associated acquisition/infection is a terminology only recently developed. Because community-acquired MRSA was unknown during the earlier period of the literature search, we chose to search for MRSA more broadly. In this way, we were able to identify articles that evaluated health care-associated MRSA infection before this terminology was developed.) We have modified the introduction to include the mention of environmental surfaces as a source of spread.

Commentator & Affiliation	Section	Comment	Response
Reviewer #7 (Public, Schoomaker)	General	Please see attached comment. Thank you.	None needed.
Reviewer #7 (Public, Kavanagh)	General	References: Reference 66 (Rodriguez-Bano, et al) appears to be wrong. The reference should be: (Rodriguez-Bano, et al., 2010, PMID 20524852) Some of the references need PMID numbers. Some of these are listed below (I added the PMID for these.) 42. Holzmann-Pazgal G, Monney C, Davis K, et al. Active surveillance culturing impacts methicillin-resistant Staphylococcus aureus acquisition in a pediatric intensive care unit. Pediatric Critical Care Medicine. 2011;12(4):e171-e5. PMID:20838355 46. Boyce JM, Havill NL, Kohan C, et al. Do infection control measures work for methicillin-resistant Staphylococcus aureus? Infect Control Hosp Epidemiol. 2004;25(5):395-401. PMID:15188845 47. Clancy M, Graepler A, Wilson M, et al. 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. Infect Control Hosp Epidemiol. 2006;27(10):1009-17. PMID: 17006806 60. Supriya M, Shakeel M, Santangeli L, et al. Controlling MRSA in head and neck cancer patients: what works? Otolaryngol Head Neck Surg. 2009;140(2):224-7. PMID:19201293 68. Pan A, Carnevale G, Catenazzi P, et al. Trends in methicillin-resistant Staphylococcus aureus (MRSA) bloodstream infections: effect of the MRSA “search and isolate” strategy in a hospital in Italy with hyperendemic MRSA. Infect Control Hosp Epidemiol. 2005;26(2):127-33. PMID PMID:15756881	We have corrected the Rodriguez-Bano references and have added the PMID numbers.
Reviewer #7 (Public, Kavanagh)	General	Abbreviations: Table 6, uses “NSS” for the abbreviation for not statistically significant. To be consistent “NS” should be used.	We chose to use NSS (rather than NS) throughout the manuscript.
Reviewer #1 (Peer)	Introduction	Introduction: Introduction reviews the issue well	None needed.
Reviewer #2 (Peer)	Introduction	Introduction: Very well written. Nicely summarizes the current gap in knowledge and the significance of the current report.	None needed
Reviewer #3 (Peer)	Introduction	Introduction: The first paragraph of the executive summary and the introduction seem outdated. 2012-1961= much more than 3 decades, and the sentence that says that the incidence of MRSA infections has steadily increased does not take into account recent papers such as Kallen JAMA. 2010;304(6):641-647 and Burton JAMA. 2009;301(7):727-736.	We have revised the introduction to include these recent papers. In particular, we have noted that while the incidence of MRSA infection at US hospitals steadily increased for many years, it is now decreasing.

Commentator & Affiliation	Section	Comment	Response
Reviewer #4 (Peer)	Introduction	Introduction: The intro covers the essential background literature well. In my view, perhaps the key theme that should be given even more attention (though the authors do recognize and discuss it) is the important distinction between (1) screening as a means to guide isolation and transmission prevention, and (2) screening as a means to guide decolonization of carriers. The first is meant to keep non-colonized individuals from acquiring and becoming infected with MRSA, while the second is meant to prevent the already colonized from becoming infected. It seems extremely important that future research tries to disentangle these two approaches. For example, it may be that screening/isolation alone is not particularly effective as an adjunct to other mechanisms of transmission prevention (e.g. hand hygiene, single rooms, environmental disinfection), while suppression of organism carriage in those who do carry MRSA effectively prevents infection. This distinction is extremely important, because suppression/decolonization can be applied in the absence of screening (e.g. chlorhexidine bathing of ICU patients), or more broadly than for MRSA alone (e.g. screening for all S. aureus perioperatively). In addition, many of the potential harms of screening are linked closely to the isolation intervention, rather than to the decolonization intervention.	We have clarified these points. In the Introduction we write, “By detecting the larger population of colonized individuals, at the very least conventional precautions can be implemented in a broader and a more timely manner so as to interrupt horizontal transmission of MRSA. Detection of colonized patients also permits consideration of more aggressive interventions, including attempts at microbiological eradication or decolonization in order to prevent colonized individuals from becoming infected, as is discussed later.”
Reviewer #5 (Peer)	Introduction	Introduction: The introduction is appropriate for the review as it clearly outlines the significance of the pathogen with regards to its impact on the patient and the healthcare system. The epidemiology is briefly discussed as are conventional strategies for MRSA control. The authors state that the effectiveness of hand hygiene in preventing the spread of MRSA has been most convincingly demonstrated in quasi-experimental observational studies...Would these hand hygiene studies have qualified as good, precise, direct, etc if subjected to the same rigorous criteria used for the screening studies in this report? Importantly the introduction discusses how the effectiveness of the majority of commonly employed measures for MRSA control depend on provider or patient compliance. I dont think this could be overstated enough. The introduction also describes the potential benefits of MRSA screening as well as potential harmful effects. One additional advantage that could be explored is if there is potential benefit to knowing ones colonization status with regards to empiric treatment.	We have modified the language used to discuss the evidence for hand hygiene. In particular, because the effectiveness of hand hygiene to prevent the spread of MRSA has been demonstrated in quasi-experimental studies we have changed the language as follows: “The effectiveness of hand hygiene in preventing the spread of MRSA has been demonstrated in quasi-experimental observational studies in which hand hygiene-promotion campaigns were associated with subsequent reductions in the incidence of MRSA among hospitalized patients. Pittet and colleagues demonstrated a significant reduction in MRSA bloodstream infections in one especially robust investigation. The benefit of hand hygiene appears to be consistent, whether the use of soap and water or alcohol-based hand rubs is promoted. The ease of adherence associated with the latter method suggests that this approach may be especially fruitful.”

Commentator & Affiliation	Section	Comment	Response
Reviewer #5 (Peer)	Introduction	Introduction: The objective of the review is clearly stated and of course appropriately ambitious.In general the key questions are appropriate but it isnt entirely clear what is being reported regarding adverse events such as allergic reactions, other toxicities and antimicrobial resistance. Does this refer exclusively to agents that would be used for decolonization? Additionally, it isnt clear why the key questions specifically state that ambulatory patients are being included when the studies discussed in the sections are clearly among inpatients and ICUs. I can understand the comparison using ambulatory patients when analyzing screening studies of surgical patients; however, its more difficult to understand the comparison when the analysis is of the effect of screening ICU patients. The PICOTS discussion of the key questions is excellent.	We were prepared to consider any harms reported by studies meeting eligibility criteria. This included, though was not limited to, agents that would be used for decolonization. Because ambulatory patients may undergo screening prior to a scheduled admission that will require an ICU stay (e.g., elective cardiac surgery), this comparative effectiveness review included studies that included evaluation of hospitalized and/or ambulatory patients. Several studies, especially those of elective surgical patients, conducted screening for MRSA carriage in the outpatient setting. This information is captured in the text of the results section. Because any of the KQs had the potential to include ambulatory and hospitalized patients, we have not categorized the PICOTs by KQ. In the PICOTs section, we have more explicitly specified which outcomes are related to harms.
Reviewer #6 (Peer)	Intro/ES	Introduction Executive Summary: [page ES-1, lines 16-19] The sentence beginning “Despite the adoption of infection control measures.” ignores an important study that contradicts the statement made in the sentence (Burton DC, et al. JAMA. 2009;301:727-36). NHSN data indicate the incidence of MRSA infection, specifically bloodstream infection, has been decreasing since 2001. This is particularly important since so many of the studies cited in the review are quasi-experimental studies without concurrent controls. Studies, particularly those reporting decreases in MRSA infections (e.g., Robicsek [15], Jain [16]), must be interpreted in this larger context.	We have revised the introduction to include the Burton study. In addition, we changed the Introduction to read, “Despite the adoption of a number of measures to prevent spread, the incidence of MRSA infection at most U.S. hospitals steadily increased for many years but is now decreasing.”
Reviewer #6 (Peer)	Intro/ES	Introduction Executive Summary: [page ES-1, lines 19-21] The methodology for determining attributable mortality and cost of care associated with MRSA infection is complex (Graves N, et al. Clin Infect Dis 2010;50:1017-21). Earlier studies of the mortality and cost associated with MRSA infection may have resulted in over-estimates. A more recent study found no increased attributable mortality or cost (Ben-David D, et al. Infect Control Hosp Epidemiol 2009;30:453-60).	We have revised the introduction to include these studies. In addition, we revised the Introduction to state, “Although not all studies concur, a number of analyses suggest that MRSA infections are associated with increased mortality and cost of care when compared with those due to strains that are susceptible to methicillin.”

Commentator & Affiliation	Section	Comment	Response
Reviewer #6 (Peer)	Intro/ES	Introduction Executive Summary: [page ES-1, lines 33-48] While the review distinguishes the outcomes of healthcare associated MRSA acquisition vs. MRSA infection, this paragraph focuses exclusively on interventions to prevent MRSA acquisition. Interventions to prevent healthcare associated infections (HAI) caused by all pathogens, including MRSA, should also be discussed since efforts to reduce HAIs cause by all pathogens, particularly central line associated bloodstream infections and surgical sites infections, have been remarkably successful during the past decade. As noted in Comment 1, the results of quasi-experimental studies reporting reduced rates of MRSA infection must be interpreted in this larger context.	We have revised the introduction to include the potential impact of interventions to prevent healthcare associated infections.
Reviewer #6 (Peer)	Intro/ES	Introduction Executive Summary: [page ES-1, lines 33-48] The text does not discuss interventions to "decolonize" or reduce the density of colonization. This is important because Key Question 4 appears to focus on the additional benefit of decolonization.	The text discusses both decolonization and attempted eradication. Key Question 4 actually addresses the comparative effectiveness of screening a limited group of patients compared to a broader group of patients. We have enhanced the explanation of KQ 4 in the PICOTs
Reviewer #6 (Peer)	Intro/ES	Introduction Executive Summary: [pages ES-1, line 53-ES-2, line 6] Additional studies have addressed negative consequences of screening and isolation. While the findings are not conclusive, this topic should be discussed in more depth.	Given limitations of space in the Executive Summary, we are not able to explore this topic in more depth. This subject is discussed in the Introduction.
Reviewer #6 (Peer)	Intro/ES	Introduction Executive Summary: [page ES-2, lines 15-19] The value of surveillance cultures in identifying patients who were not previously recognized to be colonized with MRSA is well-quantified by several studies (e.g., Robicsek [15], Jain [16], Huskins [21]). The statements could be more specific about the sizable proportion of colonized patients detected by surveillance cultures only.	Given limitations of space in the Executive Summary, we are not able to explore this issue in more depth. However, the introduction to the main body of the document notes that the purpose of surveillance cultures is to identify asymptomatic patients who are colonized with MRSA.
Reviewer #6 (Peer)	Intro/ES	Introduction Executive Summary: [page ES-4, lines 9-10] Regarding Key Question 3C, what is the definition of "high-risk" patients? How are they distinguished from ICU and surgical patients? Do they include patients admitted from long-term care facilities, patients with chronic indwelling devices (e.g., tracheostomy, g-tube), or immunocompromised patients?	The definition of high risk was provided by the authors of each study and is included in the results section of the comparative effectiveness review. In addition, we have provided some examples of high risk populations in the PICOTs (e.g., patients transferred from another health care facility, patients receiving hemodialysis).
Reviewer #6 (Peer)	Intro/ES	Introduction Executive Summary: [page ES-4, lines 22-25] Regarding Key Question 4, the definitions of "expanded" vs. "limited" strategies should be clarified. Figure ES-2 appears to indicate that an "expanded" strategy includes interventions to decolonize patients, but this is not explicit from the test or Figure ES-1.	An expanded strategy represented a broader screening strategy, though did not necessarily include decolonization. The screening strategies used were defined by study authors and are included in the results section of the comparative effectiveness review. In addition, we have provided an example of an expanded and limited screening strategy in the description of KQ 4.

Commentator & Affiliation	Section	Comment	Response
Reviewer #8 (Peer)	Introduction	Introduction: Pages 1-2. The introduction briefly discusses the serious nature of MRSA infections and alludes to several of the well accepted modes of transmission of MRSA in healthcare settings.	None needed.
Reviewer #8 (Peer)	Introduction	Introduction: Page 2. It is noteworthy that the report states that the effectiveness of hand hygiene in preventing the spread of MRSA has been most convincingly demonstrated in quasi-experimental observational studies. Having reviewed many of such studies in my role as a member of a core group of experts working with the World Health Organization on its hand hygiene guidelines, I suspect that many of the studies would have been considered non-CCS studies using the strict criteria employed in this report. Nonetheless, the authors of the present report seemed to have found the evidence dealing with hand hygiene convincing, in contrast to quasi-experimental observations studies dealing with MRSA screening.	We have clarified the language used to discuss this issue in the introduction. In particular, because the effectiveness of hand hygiene to prevent the spread of MRSA has been demonstrated in quasi-experimental studies we have clarified the language used to describe the effectiveness of this practice. “The effectiveness of hand hygiene in preventing the spread of MRSA has been demonstrated in quasi-experimental observational studies in which hand hygiene-promotion campaigns were associated with subsequent reductions in the incidence of MRSA among hospitalized patients. Pittet and colleagues demonstrated a significant reduction in MRSA bloodstream infections in one especially robust investigation. The benefit of hand hygiene appears to be consistent, whether the use of soap and water or alcohol-based hand rubs is promoted. The ease of adherence associated with the latter method suggests that this approach may be especially fruitful.”

Commentator & Affiliation	Section	Comment	Response
Reviewer #8 (Peer)	Introduction	Introduction: Page 3. The discussion on page 3 of aggressive MRSA containment programs utilized in northern Europe is very brief, and describes such programs as draconian in nature, of view that would not be shared by many knowledgeable epidemiologists and infectious disease experts working in the Netherlands and in Scandinavia. The AHRQ report makes no mention of the extremely low MRSA prevalence rates (often < 3%) maintained over a period of years in countries that utilize MRSA screening combined with other preventive measures. It would be more appropriate if the report at least alluded to the effectiveness of such MRSA bundles in maintaining very low rates of MRSA when the bundles are utilized by a majority of hospitals. The discussion on page 3 does appropriately point out that using MRSA screening to identify colonized individuals promotes more complete and more timely implementation of additional preventive measures designed to interrupt horizontal transmission. Again, I was impressed that the authors believed that "some of the most compelling evidence for the effectiveness of active surveillance in controlling the spread of antibiotic-resistant organism comes from experience with vancomycin-resistant Enterococcus (VRE)." I have also been very impressed by the Ostrowsky study, However some of the compelling evidence that the AHRQ authors cite comes from VRE studies that apparently did not take into account all potential confounding variables, did not use multiple regression analysis and did not represent a cluster-randomized trial (Ostrowsky BE et al. NEJM 2001;344:1427), and would likely have been considered non-CCS studies which would not have been considered worthy of including in strength of evidence analyses by the comparative effectiveness team. It seems as though the authors of the present report are holding the evidence regarding MRSA screening to a different standard than they have the evidence dealing with hand hygiene and VRE transmission.	The purpose of this review was to evaluate the comparative effectiveness of screening for MRSA-carriage. Given the study findings, it would be inappropriate to suggest that "using MRSA screening to identify colonized individuals promotes more complete and more timely implementation of additional preventive measures designed to interrupt horizontal transmission." In the introduction, we have clarified the language used to discuss screening for VRE. In particular, because the effectiveness of screening for VRE has been demonstrated in quasi-experimental studies we have modified the language used to describe the effectiveness of this practice. "Some of the evidence for the effectiveness of active surveillance in controlling the spread of antibiotic-resistant organisms came from experience with vancomycin-resistant Enterococcus (VRE). In quasi-experimental studies, rectal screening for this pathogen was associated with decreased transmission at the level of individual units and wards, whole hospitals, and even across an entire region."
Reviewer #8 (Peer)	Introduction	Introduction: Page 4. I agree with the authors' comments that MRSA screening, by itself, would not be expected to affect MRSA transmission rates, and that additional prevention measures such as improved hand hygiene, compliance with contact precautions, and environmental cleaning and disinfection are necessary elements of a bundle of measures that are required to effectively reduce MRSA transmission and infections.	None needed.
Reviewer #8 (Peer)	Introduction	Introduction: Pages 5-8. The key questions and PICOTS outlined in the report are well-formulated and defined.	None needed
Reviewer #10 (Peer)	Introduction	Introduction: Well written and clear. Defines objectives and scope. Key questions are clear. I wonder if a table summarizing more simply the Key Question number, overall theme such as "Universal vs no screening," "Universal vs. targeted screening," "High risk vs. no screening," etc. It would be a good reference to refer back to throughout the document.	We have added table summarizing the Key Questions and their results (Table A and Tables 5, 8, 11, 14, 17, and 20).

Commentator & Affiliation	Section	Comment	Response
Reviewer #11 (Peer)	Introduction	Introduction: The Introduction is extremely comprehensive and effectively covers most of the important issues in MRSA screening and control, and presents the case well that existing strategies such as hand hygiene and contact isolation have been insufficient to check the spread of MRSA (and other pathogens) in the setting of "passive" surveillance. There is also good coverage of alternative strategies in other countries, such as the "search and destroy" approach in some European countries. Importantly, there is a nice discussion of many of the issues related to the methodology of screening strategies, such as type of test used, approach to patients while awaiting test results, and the limitations imposed by deficiencies in study design on the interpretation of study outcomes.	None needed.
Reviewer #12 (Peer)	Intro/ES	Introduction: 1. ES-1, line 10 and page 1, line 10: What exactly is meant by "aggressive" bacterium? More scientifically accepted terms might be "pathogenic" or "virulent."	We have changed "aggressive" to "virulent."
Reviewer #12 (Peer)	Intro/ES	Introduction: Executive summary: ES-2, line 17 and page 3, line 19-20: The manuscript states "Because routine clinical cultures may identify as few as 18% of patients overtly infected with …MRSA,…" This is incorrect. The statistics to which the authors are referring address the proportion of patients with asymptomatic MRSA carriage that are identified by routine clinical cultures. Clinical cultures have a much higher yield among patients with overt MRSA infection. The number provided is also incorrect. The percentage of colonized patients detected by routine clinical cultures may actually be even lower than 18%. The Jain study (reference #39) found that the ratio of persons with MRSA colonization or infection identified by active surveillance to those identified by clinical culture was 10:1.	We have clarified this statement to read "Because routine clinical cultures may identify as few as 18 percent of patients with asymptomatic carriage of MRSA, there exists a large reservoir of patients who are silent carriers of these organisms."
Reviewer #12 (Peer)	Intro/ES	Introduction: Executive summary: ES-2, line 24 and page 3, line 30: The meaning of the phrase "conventional precautions" is not clearly explained. Are the authors referring to contact precautions? If so, it would be preferable to use that more common, routinely accepted terminology.	We have clarified this statement. Specifically, we have changed the language to read, "Based on the failure of conventional control strategies (hand hygiene, barrier precautions and isolation) to adequately control MRSA…"
Reviewer #12 (Peer)	Intro/ES	Introduction: Executive summary: ES-3, line 23; ES-3, line 38; ES-4, line 10; ES-4, line 24; page 6, line 7; page 6, line 22; page 6, line 36; page 6, line 49; page 7, line 10: In the descriptions of Key Questions 2-4, the wording seems to imply that screening had to include screening, isolation, and eradication/decolonization when, in fact, that is not correct. Perhaps it would be more appropriate as "(screen, isolate, +/-eradicate/decolonize).	We have clarified that screening included screening +/- isolation +/- eradication/decolonization.
Reviewer #12 (Peer)	Intro/ES	Introduction: Executive summary: ES-7 (Figure ES-2); page 11, Figure 2: (1) The text in this figure is nearly illegible. (2) The framework seems to include only the negative potential outcomes of screening. It suggests that all paths lead to infection and death. Aren't other options such as "no MRSA transmission" and "clearance of MRSA" appropriate for inclusion in the framework?	We have replaced Figure ES-2 with a version that is clearer (i.e., less blurry). The framework is meant to show the possible path from MRSA acquisition to death, which screening aims to interrupt.

Commentator & Affiliation	Section	Comment	Response
Reviewer #12 (Peer)	Intro/ES	Introduction: Executive summary: Page 3, line 14: The term “draconian” has a derogatory connotation and denotation (“unusually severe or cruel”) and its use in a reportedly non-biased assessment of a medical intervention seems judgmental and inappropriate.	We use a more neutral word in place of “draconian.”
Reviewer #1 (TEP)	Methods	Methods: Could the authors be more explicit about their quality ratings? On page 60 they highlight three characteristics that constitute a good quality study - baseline characteristics, had an important outcome, and appropriate analyses. A poor study basically does not do the appropriate analysis. I think several of the poor quality studies probably meet the three qualities for a good study (e.g., Ellingson, Jain, etc). Is this because there isnt a control group? If that is the case you should explicitly state this.	We have clarified the methodology, including the assignment of study quality.
Reviewer #1 (TEP)	Methods	Methods: I am wondering about your reporting of consistency in the SOE reviews. It appears that if you have two or more studies that have an point estimate in the same direction they will still be inconsistent if at least one of them is not statistically significant (eg, key question 2, 3A). In reviewing the paper that you cite by Owens et al (number 37) for this methodology this is not consistent with what is shown in the example (Table 4) --here two articles with an effect in the same direction where one is significant and the other not significant appear to be judged consistent. In addition, since another criteria is precision -- this would seem to be penalizing articles twice for the same problem.	We have clarified that a body of evidence that is consistent possesses studies with the same direction of effect. We have also clarified that a body of evidence that is precise possesses either 1) uncertainty around an effect compatible with only one of these: clinically important superiority, inferiority or noninferiority; or 2) in the absence of meta-analysis, individual studies consistently report statistically significant results. We have clarified the methodology, including the assignment of strength of evidence and study quality. In particular, we have clarified the decision rules used to determine the SOE. Please see the tables depicting the Strength of Evidence Rating Domains, the Strength of Evidence Categories and Rules, and the Summary of Outcomes Measures and SOE. Greater detail about rating of individual study quality has been added to each Key Question, with new tables describing key aspects of all studies that attempted to control for secular trends and confounding. In the Results chapter, each Key Question has a strength of evidence section that has been revised to give clarity to the key domains of risk of bias, consistency, directness and precision.
Reviewer #1 (TEP)	Methods	Methods: Figure ES2 is not clear and not readable	We have replaced Figure ES-2 with a version that is clearer (i.e., less blurry).

Commentator & Affiliation	Section	Comment	Response
Reviewer #2 (TEP)	Methods	Methods: The sections on application of criteria in arriving at an overall assessment of strength of evidence could provide more detail. Examples might also be considered here.	We have clarified the methodology, including the assignment of strength of evidence and study quality. In particular, we have clarified the decision rules used to determine the SOE. Please see the tables depicting the Strength of Evidence Rating Domains, the Strength of Evidence Categories and Rules, and the Summary of Outcomes Measures and SOE. Greater detail about rating of individual study quality has been added to each Key Question, with new tables describing key aspects of all studies that attempted to control for secular trends and confounding. In the Results chapter, each Key Question has a strength of evidence section that has been revised to give clarity to the key domains of risk of bias, consistency, directness and precision.
Reviewer #2 (TEP)	Methods	Methods: I found the assignment of quality scores to individual studies to be fairly subjective despite the detail provided. I never felt convinced, either in the methods or results sections, that the Jain and Robiscek paper were that different in quality. Both suffer from bias arising from unmeasured confounding (aspects of the interventions components other than the screening potentially explain observed results more than the screening aspects). Beyond that, the Robiscek paper had moderately more rigorous statistical methodology and a better description of the study population. That does not seem to be enough to merit a difference between “good” and “poor” quality. I realize there is not a perfectly “objective” method for weighting the quality of papers but this difference in quality grading lacks face validity in my opinion. This is one example, I suspect there may be others among the other 42 included studies.	We have clarified the methodology, including the assignment of strength of evidence and study quality. In particular, we have clarified the decision rules used to determine the SOE. Please see the tables depicting the Strength of Evidence Rating Domains, the Strength of Evidence Categories and Rules, and the Summary of Outcomes Measures and SOE. Greater detail about rating of individual study quality has been added to each Key Question, with new tables describing key aspects of all studies that attempted to control for secular trends and confounding. In the Results chapter, each Key Question has a strength of evidence section that has been revised to give clarity to the key domains of risk of bias, consistency, directness and precision.
Reviewer #3 (Peer)	Methods	Methods: The study was performed very well. The only downside is that I would have liked to see more of an assessment of publication bias. I was very impressed by the quality scoring.	As noted in the methods section, to evaluate the possibility of publication bias, we conducted a search of the grey literature.
Reviewer #4 (Peer)	Methods	Methods: Good. Inclusion/exclusion critera justifiable, search strategies well outlined and appropriate, definitions and criteria used for outcomes are proper.	None needed

Commentator & Affiliation	Section	Comment	Response
Reviewer #5 (Peer)	Methods	Methods: The methods in general are easy to follow and very well described. The analytical framework is clearly shown in figures 1 and 2. These are very helpful for the reader. The literature search strategy is comprehensive and logicial and appropriately stated in the document. I particularly liked the way the authors describe the grey literature search. The inclusion and exclusion criteria are justifiable. The definitions and ratings criteria are very well described. The outcome measures are described well but of course not obtainable with the literature available. This is still important as it helps to identify gaps in knowledge and research opportunities. There are no statistics performed as no studies could be combined. It is interesting that the authors describe what they "would have done" if the data had allowed (page 17- data synthesis). Is this necessary to include?	We consider it important to discuss the plan for meta-analysis, had this been feasible.
Reviewer #6 (Peer)	Methods/ES	Methods Executive Summary: The inclusion and exclusion criteria are appropriate, the search strategies are explicitly described, and the definitions or diagnostic criteria for the outcome measures appropriate and clear. There was no formal meta-analysis.	None needed
Reviewer #6 (Peer)	Methods/ES	Methods Executive Summary: [page ES-8] Somewhere in the text, either in the Introduction or Methods, it should be acknowledged that most, if not all, studies report group-level (i.e., unit- or hospital-level) results, as opposed to subject-level results or risks. This is important for at least two reasons. First, because the outcomes of individual patients within a unit or hospital may be correlated, studies that fail to adjust for clustering may under-estimate the alpha-error (i.e., report a difference when a difference is not present). This represents an additional methodologic concern that is separate from controlling for confounding or secular trends. Second, single center studies reporting group-level results are essentially "N=1" studies; multi-center studies reporting group-level results have greater power and are likely to be more generalizable. Multicenter studies should be given more weight for this reason-or at least an acknowledgment that single center studies have limited generalizability should be included.	We have added a discussion of these issues to the introduction.
Reviewer #6 (Peer)	Methods/ES	Methods Executive Summary: [pages ES-8, ES-9] The methods do not include any formal assessment of agreement among reviewers with respect to the identification of studies (page ES-8, line 50-52), data abstraction (page ES-9, lines 5-7), or assessment of the quality of the study (page ES-9, lines 18-21) and the strength of evidence (page ES-9, lines 48-50). This is a significant limitation.	We reached agreement by consensus, during discussion among team members. The Methods chapter states, "The quality of the abstracted studies and the body of evidence was assessed by two independent reviewers. Discordant quality assessments were resolved with input from a third reviewer, if necessary."

Commentator & Affiliation	Section	Comment	Response
Reviewer #6 (Peer)	Methods/ES	Methods Executive Summary: [page ES-9, lines 13-21 and lines 41-50] The distinction between the quality of the study as assessed by the US Preventative Services Task Force and the strength of evidence provided by the findings as assessed by the GRADE system is not clear. It appears that the former was used to select studies and the latter was used to synthesize the data, but this distinction is unclear and perhaps somewhat redundant. Neither approach, even with the modifications described by Deeks (page 16, lines 54-55), seems adequate to assess the quality of quasi-experimental studies. Was the ORION guideline considered (Stone SP, et al, Lancet Infect Dis 2007;7:282-8)?	We have clarified the methodology, including the assignment of study quality and strength of evidence. Greater detail about rating of individual study quality has been added to each Key Question, with new tables describing key aspects of all studies that attempted to control for secular trends and confounding. In the Results chapter, each Key Question has a strength of a body of evidence section that has been revised to give clarity to the key domains of risk of bias, consistency, directness and precision. We did not use the ORION guidelines, as Stone's paper notes, "ORION should be considered a "work in progress", which requires ongoing dialogue for successful promotion and dissemination."

Commentator & Affiliation	Section	Comment	Response
Reviewer #6 (Peer)	Methods/ES	Methods Executive Summary: [page ES-9, lines] The quality ratings need to be better clarified and justified. For example, of the 4 CCS studies categorized as "good" quality studies, 1 was a multicenter cluster randomized trial involving 18 ICUs (Huskins [21]), 1 was a non-randomized, controlled cross-over study involving 12 surgical units in 1 hospital (Harbarth [30]), 1 was a non-randomized, controlled study involving 2 hospitals (Leonhardt [17]), and 1 was a quasi-experimental study with no concurrent control involving 3 hospitals (Robiscek [15]). It is hard to understand how these 4 studies are regarded as methodologically equivalent with respect to control of confounding variables and secular trends. Wouldn't it be more appropriate to classify the Huskins and Harbarth studies as "good" and the Robiscek and Leonhardt studies as "fair?" Moreover, it is unclear how the non-randomized, uncontrolled studies quasi-experimental studies-such as the "good" Robiscek (15) study-are differentiated from other quasi-experimental studies-such as the "poor" Huang (20) study. The distinction between these two studies appears to be based solely on the lack of control of confounding in the Huang study since this study did use an interrupted times series analysis to control for secular trends. However, while the Robiscek study reported data on the characteristics of patients (confounding variables) during different periods, it is not apparent that the regression analysis controlled for these variables. What then is the basis for the distinction between these two studies? This lack of clarity in the reasons for the quality rankings of individual studies is especially concerning because of the lack of a formal assessment of agreement between reviewers. While I believe the authors made a good faith effort to be both systematic and fair, this weakness the credibility of the data synthesis.	We have further clarified the methodology, including the assignment of study quality and strength of evidence. Greater detail about rating of individual study quality has been added to each Key Question, with new tables describing key aspects of all studies that attempted to control for secular trends and confounding. In the Results chapter, each Key Question has a strength of evidence section that has been revised to give clarity to the key domains of risk of bias, consistency, directness and precision. Using the US Preventive Services Task Force method of assessing study quality, we identified 4 studies as good (Robicsek, Huskins, Harbarth and Leonhardt). These studies were judged to be of good quality overall because they presented baseline characteristics for intervention and control groups, conducted appropriate analyses (tested for trend, addressed autocorrelation and controlled for at least one confounder) and reported on an important (health care-associated) outcome. While it is possible to make finer distinctions within this group of studies, the AHRQ Methods Guide does not recommend it. While the Huang study tested for trend and for autocorrelation, it did not control for any confounders. Therefore, it was rated as poor quality. In contrast, the Robicsek study controlled for at least one confounder (admitting hospital). We have clarified this distinction in the Results section. We reached agreement by consensus, during discussion among team members.
Reviewer #8 (Peer)	Methods	Methods: Pages 9-11. The sections on topic development and the analytic framework figures are clear.	None needed
Reviewer #8 (Peer)	Methods	Methods: Page 12. Perhaps the text should point out that having a single reviewer apply study selection criteria for the initial screen of titles and abstracts could potentially bias the studies selected for further evaluation.	We do not consider this is a significant limitation of the comparative effectiveness review. In addition to rigorous application of the study criteria by a trained reviewer, experts in the field (members of the TEP panel) were asked to identify potential studies for inclusion that might have been overlooked.

Commentator & Affiliation	Section	Comment	Response
Reviewer #8 (Peer)	Methods	Methods: Page 13. Although I believe I read somewhere in the report that studies that included MRSA screening as one of a number of measures utilized during an MRSA outbreak were excluded from the analysis, I didn't see this exclusionary criteria mentioned on Page 13. While it is true that the characteristics of MRSA outbreaks are quite variable, and may make it difficult to generalize findings to diverse healthcare settings, much experience has been gained from using bundles of prevention measures (including screening) to control or eliminate MRSA outbreaks. Rejecting all such studies ignores many examples of successful control of MRSA transmission (e.g., Thompson RL et al. Ann Intern Med 1982;97:309). I consider this a shortcoming of the present report.	This comparative effectiveness review did not exclude studies conducted during an outbreak. We did however exclude studies published prior to 1990, due to differences in the understanding of health care-associated MRSA infection, its prevalence and management prior to that time.
Reviewer #8 (Peer)	Methods	Methods: Page 16. The Definitions of Ratings Based on Criteria section is clearly written and the three categories are reasonably well-defined.	None required.
Reviewer #8 (Peer)	Methods	Methods: Page 17. I strongly disagree with the statement by authors that observational studies that do not attempt to control for confounding or secular trends do not provide evidence that supports causal inference (implying that they provide no useful information to influence prevention measures used to interrupt transmission of infectious agents). Much has been learned about prevention and control of transmissible diseases such as tuberculosis, pneumonic plague, smallpox, hemorrhagic fevers, cholera and severe acute respiratory syndrome (SARS) from studies that were not randomized controlled trials and that did not take into account all or most potential confounding variables or secular trends. Knowledge of the suspected or proven modes of transmission of such diseases, combined with a combination (bundle) of measures designed to interrupt the mode(s) of transmission have been effective in controlling diseases occurring in epidemic or endemic settings. Perhaps the authors who feel only studies adhering to the strict criteria employed in this report would have recommended a cluster-randomized trial of the use of screening of patients and healthcare workers for signs/symptoms of acute respiratory illness, and the use (or lack of use by a control group) of personal protective equipment during the SARS outbreak. Or perhaps all the was learned from the non-randomized interventions that were employed to control and eliminate the SARS outbreak should be ignored if a further outbreak occurs because the interventions would be considered non-CCS according to standards outlined in this comparative effectiveness report. Perhaps the authors should consider stating not only that non-CCS studies were not considered of sufficient quality to add to the strength of evidence for the purposes of this report, but that useful information regarding prevention of other transmissible agents has been gained from studies or interventions that would not meet the criteria of a CCS study.	It is well-established that causal inference is possible using observational studies, but such studies must protect against bias and confounding through features of design, conduct and analysis. Studies that perform simple statistical tests of before after designs without attempts to control for trend or confounding generate hypotheses that can be evaluated by more sophisticated studies.

Commentator & Affiliation	Section	Comment	Response
Reviewer #10 (Peer)	Methods	Methods: Inclusion and exclusion criteria Search strategies are logical. Wonder about including the Healthcare Infection Society in the search for meeting abstracts. (Not in list on p. 49 and 50 of text (p. 50 and 51 pdf), line 33.)	As noted, we did not include the Healthcare Infection Society in our search of the grey literature.
Reviewer #10 (Peer)	Methods	Methods: p. 48: Figure 2 (also ES-2) would be very helpful but is extremely blurry and hard to read. Not sure if this is just a problem with pdf conversion.	We have replaced Figure ES-2 with a version that is clearer (i.e., less blurry).
Reviewer #10 (Peer)	Methods	Methods: Typo on p. ES-10 (pdf p. 20), line 43: “y Question 1:” should be “Key Question 1:”	We have corrected this typo
Reviewer #10 (Peer)	Methods	Methods: Definitions of diagnostic criteria for outcome measures are outlined and bulletted list on p. 52 is helpful.	None required.
Reviewer #10 (Peer)	Methods	Methods: Statistical methods and grading of studies are clear. In table ES-1, would consider putting table footnotes/abbreviations on both pages (add to p. ES-12).	We have added table abbreviations to both pages of Table ES-1.
Reviewer #11 (Peer)	Methods	Methods: The methods are also quite comprehensive and explicitly stated. Given that this is a literature review, it is important that the authors define and describe their literature search strategy, the criteria used for inclusion/exclusion of articles, the data extraction process, and the methods used for quality assessment of individual studies. All of these were done quite well, with sufficient detail to understand the process. The only comment about the chosen study outcomes would relate to the use of health care-associated MRSA infection: given that MRSA screening would only have an indirect effect on actual infection, the use of infection as an outcome is going to be heavily confounded by other health care practices that may have a more direct impact on MRSA infection, such as decolonization, so perhaps more explicit acknowledgement of this would be prudent.	In the Background, Methods, and Results sections, we describe that health care-associated infection is the outcome of interest.
Reviewer #11 (Peer)	Methods	Methods: The inclusion of Figures 1 and 2 to describe the analytic framework were useful, although the resolution on Figure 2 was poor, making the diagram difficult to read.	We have replaced Figure ES-2 with a version that is clearer (i.e., less blurry).

Commentator & Affiliation	Section	Comment	Response
Reviewer #11 (Peer)	Methods	Methods: Another point is that, in some of the Tables (for instance, Table ES-1 in the Executive Summary on page ES-12, or Table 3 in the full manuscript on page 29), ratings for categories such as "risk of bias" are sometimes provided not for individual studies, but rather for groups of studies combined, and it is not clear if the Methods section describes how ratings of different studies were combined into a single rating.	Bodies of evidence consisting of at least one good quality RCT had risk of bias of low. Bodies of evidence consisting of at least one fair quality RCT or one good quality quasi-experimental study and one additional study of fair or good quality had a risk of bias of medium. Bodies of evidence that did not meet minimum requirements for low or medium had a risk of bias of high. We have clarified the methodology, including the assignment of strength of evidence and study quality. In particular, we have clarified the decision rules used to determine the SOE. Please see the tables depicting the Strength of Evidence Rating Domains, the Strength of Evidence Categories and Rules, and the Summary of Outcomes Measures and SOE. Greater detail about rating of individual study quality has been added to each Key Question, with new tables describing key aspects of all studies that attempted to control for secular trends and confounding. In the Results chapter, each Key Question has a strength of evidence section that has been revised to give clarity to the key domains of risk of bias, consistency, directness and precision.
Reviewer #11 (Peer)	Methods	Methods: It is notable that the authors made the effort to differentiate between studies that attempted to control for confounding and secular trends and those that did not, and considerable discussion is devoted to both groups. That said, since the non-CCS studies were not included in the strength of evidence syntheses, it tends to create a bit of confusion since so much of the narrative addresses this group of studies that contribute almost nothing to the overall recommendations and conclusions. If there were somehow a more effective way to separate out this information in the narrative, it might improve the clarity of the presentation.	We chose to report the results of all included studies, which does add to the text of the results section. However, we felt this presentation would be more concise that including two separate results sections (one for CCS studies and one for non-CCS studies).
Reviewer #12 (Peer)	Methods	Methods: ES-12, Table ES-1: The abbreviations "L" and "M" are not defined in the footnote. Definitions should be provided.	We have provided definitions for these abbreviations.
Reviewer #7 (Public, Lahue/Durack)	Methods	Methodological Considerations BD Recommendation 2: BD suggests that the AHRQ and the Oregon Evidence-Based Practice Center distinguish between different MRSA screening technologies when designing future research questions to assess the impact of MRSA screening approaches on clinical and patient outcomes. In the Population-Intervention(s)-Comparator-Outcome-Timeframe (PICOT) statement section of the systematic review protocol document published in	We agree with the concern that not only is test turnaround time important, but that the interventions taken while waiting for test results and the fidelity to those interventions are also important. These issues were inconsistently and often inadequately addressed in the available literature. Therefore, there were too few studies to

Commentator & Affiliation	Section	Comment	Response
		June 2011, the authors identified three separate types of technologies under the Interventions section based on the length of turnaround time associated with the testing modality: rapid turnaround (same day results), intermediate turnaround (between 1 and 2 days) and longer turnaround (greater than 2 days). Despite this differentiation in the PICOT statement, the authors subsequently combined studies that looked at all types of technologies during the strength of evidence assessment process. These substantial differences in turnaround time would likely have impacted the outcomes. The authors state that the differences in turnaround time associated with different types of technologies can be compensated for "by adopting a policy of early implementation of isolation precautions for all screened patients with the aim to discontinue these measures for those patients who test negative (irrespective of the assay employed)" (AHRQ, 2012). If these measures are adhered to in all environments and situations, this assumption is true, and the impact of all screening technologies can be comparatively assessed. In practice, however, the AHRQ points out that this approach "has presented logistical challenges at centers where the physical plant limits the availability of rooms and beds for such empirical isolation" (AHRQ, 2012). Given the logistical limitations of consistently adhering to the above approach (pre-emptive isolation), it is important to consider the differences that improvements in test sensitivity and turnaround time can have on clinical outcomes within health care settings. In a letter published in the Journal of Clinical Microbiology in 2010, Dr. Lance Peterson describes a useful outcomes measure: the percent (%) of MRSA isolation days captured, which is calculated as the number of days a colonized patient is isolated divided by the total colonization days (Peterson, 2010). He conducts an analysis of studies that evaluated the impact of test sensitivity and turnaround time on MRSA reduction, and assessed the % of MRSA isolation days captured in each publication. Studies with the highest percentage of MRSA days captured (above 85%) demonstrated the largest improvements in MRSA reduction. Studies using technologies with higher sensitivity and shorter test turnaround time increased the percentage of MRSA days that were captured (Peterson, 2010). In the concluding statements, BD recommends that the AHRQ consider suggesting that future reviews of MRSA screening should distinguish between screening technologies (and their testing modalities) as additional evidence in this field is contributed.	stratify by these variables. We have discussed these issues in the report.
Reviewer #7 (Public, Persing)	Methods	Preponderance of the Evidence We agree with AHRQ on the inclusion of well-designed, non-randomized, comparative studies in the evaluation, as they add to the robustness of the findings. Most studies of the effectiveness of an interventional program of diagnostic tests are not randomized, but are observational. With respect to	Despite the reviewer's conclusions about the strength of evidence, this comparative effectiveness review found low strength of evidence that universal screening of hospital patients decreases MRSA infection. However,

Commentator & Affiliation	Section	Comment	Response
		studies of the effectiveness of MRSA surveillance programs at reducing infections, most are a time-series design with historical controls. In fact, the intervention in the evaluation of infection control is as the Agency points out, complex due to the fact that the intervention consists of several components (eg., MRSA testing + hand hygiene + contact precautions + decolonization), which need to be carried out (or overseen) by multiple healthcare personnel in periods where the infection rate can vary over time due to secular trends and outbreaks. While we recognize the limitations and potential biases of studies using historical controls, these observational studies still can present significant findings, especially when they include multiple centers and large numbers of patients (see the Veterans Administration Study (Jain et. al. 2011). In fact, despite the lack of robust controls in the majority of studies evaluated, implementation of MRSA testing (universal and targeted) combined with an effective infection control bundle overwhelmingly demonstrate reductions in infections, cost and health resource utilization. These results were consistent across hundreds of hospitals, over a million patients, in multiple locations (globally), and across multiple time periods (including outbreaks and/or "off" seasons). Although each study may have individual flaws, we believe the consistency in the directionality of the results strongly support MRSA testing as part of a targeted infection control bundle, and are concerned that the AHRQ conclusion that the evidence is "insufficient to support … practice guidelines …. or legislation" will lead premature termination of such policy programs and the eventual increase in infections as a result. We further believe that such a conclusion would undermine the Department of Health and Human Services' (HHS) efforts to control healthcare associated infections as a priority expressed in the HHS Action Plan (http://www.hhs.gov/ash/initiatives/hai/introduction.html). MRSA strains cause a significant percentage of the general infections cited, and have specifically been targeted by goals for a 50% reduction in invasive MRSA infections in the population and 25% reduction in MRSA bacteremia in hospitals over a 5-year period. These reductions are unlikely to be achieved without continued diligence in identifying high risk, colonized patients, and applying effective infection control measures (e.g., hand hygiene, contact precautions, and decolonization) for patients who test positive. The entire intervention (testing + use and follow-up of results) needs to occur with a quick turnaround time to avoid transmission of the infection among patients and healthcare workers both in the health care facility and among community members. We would also recommend that the Agency consider other outcome measures to health resource utilization such as patient isolation time and impact on appropriate antibiotic use.	there is insufficient evidence on other outcomes of universal MRSA screening, including morbidity, mortality, harms and resource utilization. There is also insufficient evidence to support or refute the effectiveness of MRSA screening on any outcomes in other settings. Please see the SOE assessments for each KQ for further details.

Commentator & Affiliation	Section	Comment	Response
Reviewer #7 (Public, Persing)	Methods	In the "Data Sources and Selection" section (page ES-8) it states that "a single reviewer made the decision about a full text review" with consultation by a second or third reviewer as necessary. In future reviews of this nature and magnitude, it may be helpful to have a minimum of two initial reviewers – one with experience in study design considerations and one of a technical nature to the program at hand. Clearly, a well-designed study will be uninformative if the results of a surveillance test have no practical impact on patient management.	None required.
Reviewer #7 (Public, Kavanagh)	Methods	Methods: I am concerned that the White Paper is flawed in the analysis of the data and thus the conclusions it makes. This may have a disastrous effect by discouraging institutions from testing high-risk populations for MRSA carriage. Our review found that only four of the White Paper's studies were found to not observe a positive effect with surveillance. I believe the analysis of these four studies is flawed, one was even mis-referenced. The White Paper's main bias is that the effectiveness of intervention was not a parameter in the ranking of the research papers. This was a major factor in two of only three studies which were ranked as "Good". I believe these two studies (Habarth, 2008, PMID 18334690 & Huskins, 2011, PMID 21488763) had significant flaws in their intervention, which produced their negative results. I would also recommend excluding these two studies from the analysis. In the Huskins, 2011, study, it can be argued that effective intervention took place in less than 40% of the time. 1) Surveillance test results were not available for at least five days. 2) Staff compliance with isolation protocols was poor. 3) In addition, 2993 of the 5434 ICU patients were eliminated from the study because their stay in the ICU was less than 3 days. This would be expected to increase the spread of MRSA in the ICU. In the Harbarth, 2008 study, it can be argued ineffective intervention also took place. 1. 44% of the patients in the study did not have surgery. 2. Screening test results were not back before surgery in 31% of carriers. 3. Only 43% of the patients who were known to be MRSA carriers before surgery received appropriate antibiotics against MRSA. 4. Carriers were only placed in a, "flagged side or single rooms whenever available". 5. There is a question if the medical staff reliably follows institutional protocols with the article commenting that "especially in abdominal surgery, surgeons were reluctant to add vancomycin to the standard prophylactic regimen". One has to wonder if not giving preoperative antibiotics effective against MRSA to patients known to be colonized with MRSA even violates basic standards of care. In contradistinction, it can be argued that the Harbarth study even supports the need for surveillance since: 1) 5.1% of the patients who had MRSA on screening developed 47% of the MRSA infections. 2) All of the 26 patients who were identified as MRSA carriers on an outpatient basis underwent decolonization and had adequate prophylaxis. None of these patients developed an infection. In addition,	We have made clear that we do not conclude that screening is ineffective. Rather we find evidence to be insufficient to support OR refute its effectiveness. Unfortunately, the fidelity of the intervention (including screening, +/- isolation, +/- decolonization) was infrequently reported in the literature included in this comparative effectiveness review. Thus, the results of studies that did not report intervention fidelity at all should not considered better or more accurate than studies that reported low intervention fidelity. We have changed that text describing the results of the Leonhardt study to indicate that there was no statistically significant decrease in MRSA screening. One potential reason that this study did not achieve statistical significance is its small sample size. We do not exclude the Huskins and Harbarth studies. Comments critical of these studies reflect their limitations for applicability but not study quality. We add the correct reference for the paper by Rodriguez-Bano and colleagues.

Commentator & Affiliation	Section	Comment	Response
		Leonhardt, et al., (2011, PMID 21768764) was listed as not showing a decrease in MRSA infections when the study actually found a decrease in MRSA infections from 0.27% to 0.15% comparing Universal Screening vs. Targeted Screening or a decrease of 44.4%. The main reason this study did not reach significance was because the experimental group was from a small hospital (167 beds) and the study's N was too small. Of additional interest is the study of Rodriguez-Bano, et al., (2010, PMID 19845694). I believe this is a wrong reference since it does not deal with surveillance. The correct reference should be Rodriguez-Bano, et al., (2010, PMID 20524852). This article observed a significant decrease in both MRSA acquisition (P < 0.001) and bacteremia (p < 0.01). "The MRSA bacteremia rate decreased by 80%, whereas the rate of bacteremia due to methicillin-susceptible S. aureus did not change."	
Reviewer #1 (TEP)	Results	Results: I would consider a table that helps clarify the criteria that led to the determination of study quality for the 15 SOE papers (ie, what are the criteria and which were met or not met.	We have clarified the methods used to determine strength of evidence. In the Results chapter, each Key Question has a strength of evidence section that has been revised to give clarity to the key domains of risk of bias, consistency, directness and precision. In addition, we have added a table as appendix G that depicts the criteria that led to determination of study quality.
Reviewer #2 (TEP)	Results	Results: I think the results sections were presented and organized well with the exception of the strength of evidence synthesis described above.	None required.
Reviewer #2 (TEP)	Results	Results: I don't think it is inappropriate to downgrade study findings on a transmission outcome just because it is an intermediate outcome (Question 1). If the authors of the report feel this is not a clinically relevant outcome then don't include it in the final report. If they do feel it is a clinically relevant outcome then I would remove wording in the strength of evidence assessment sections that imply that this is not a clinically relevant outcome.	As noted in the analytic framework, we considered MRSA transmission to be an intermediate (and therefore indirect) outcome. This is also noted in the SOE tables. However, when determining the SOE, we did not downgrade for indirectness.

Commentator & Affiliation	Section	Comment	Response
Reviewer #2 (TEP)	Results	Results: The whole structure of Question 4 was a bit confusing to me. I still do not have a good sense of what expanded versus targeted screening means nor were the intervention/target population for this question well described. How is this question different from what was described for Questions 3a/b/c? This question requires much greater clarity in both the methods and results sections of the report.	KQ 4 evaluates broader screening strategies compared to more limited screening strategies. The screening strategies used were defined by study authors and are included in the results section of the comparative effectiveness review. For example, a broader screening strategy might be screening of patients and health care workers in wards with documented MRSA transmission, and surveillance of all patients admitted from other hospitals or from long-term care facilities and all readmitted patients previously colonized with MRSA compared to a more limited screening strategy of screening of all paitents admitted from other hospitals or long-term care facilities and all readmitted patients. We have clarified this in the PICOTs section and the Results chapter.
Reviewer #7 (Public; Schoomaker)	Results	Results: Were the following studies: Bode NEJM 2010 or Konvalinka Journal of Hospital Infection 2006, considered for inclusion to address key question 3B? If so, why were they excluded? If the argument for excluding these studies is that all patients were screened before randomization, then the STAR*ICU study should be excluded because control patients were screened in that study as well.	As these are not studies of screening compared to no screening or of expanded screening compared to limited screening, they were excluded from this comparative effectiveness review.
Reviewer #7 (Public; Schoomaker)	Results	Results: Why is the Muder study included in Key Question 3B but not Key Question 3A?	The Muder study has been added to KQ 3A.
Reviewer #7 (Public; Schoomaker)	Results	Results: In the results sections of the executive summary (and to a lesser extent the full manuscript) too much emphasis is placed on screening and not enough emphasis is placed on what is done with the screening results (interventions). As the authors describe in the background and limitations, screening alone does not prevent infections. Rather, isolation and/or decolonization after screening prevent infections. The interventions should be included in Table ES-1 of the executive summary. Additionally, this information should be included in the summary strength of evidence tables in the main manuscript.	The interventions are described in text form and are included in the results section. However, due to space limitations, they are not included in Table ES-1.

Commentator & Affiliation	Section	Comment	Response
Reviewer #4 (Peer)	Results	Results: The results section is detailed and excellent, provides easy to read tables with appropriate information about the studies. I do not think the authors left important studies out, though I have minor comments below: For Key Question 1, one point that perhaps should be emphasized about the Jain study is the fact that the reduction in MRSA transmission (acquisition) was far less than the reduction in MRSA infections. Indeed, a recently published modeling study by Gurieva, Bootsma and Bonten argues convincingly that only 2-6% of the observed MRSA infection reduction in this quasi study could have been due to interruption of MRSA transmission. The remainder, presumably, would be related to secular trends, unmonitored decolonization attempts, and bundled interventions to reduce infections generally (e.g. CLABSI, VAP). Similarly, in the Robiscek study I believe 60% of more of detected MRSA carriers had decolonization attempted. Again, this harkens back to the distinction between preventing transmission and preventing infection among those already colonized.	These potential confounders and secular trends are important and are addressed both in the introduction and in the results sections. For example, in the Introduction we state, "While the decrease in the incidence of MRSA infection may be due to efforts to screen for MRSA-carriage, it may also be due to secular trends (such as efforts to improve patient safety) and to confounders (such as efforts to improve the appropriate use of antibiotics and to decrease health care-associated infections in general, including catheter-associated bloodstream infection, ventilator-associated pneumonia and surgical site infection)."
Reviewer #4 (Peer)	Results	Results: For Key Question 3, I don't agree that the cluster-randomized trial of Huskins, et al, should be graded the same quality (good) as the quasi study by Robiscek. I believe it more accurate to say that the Robiscek study was of fair quality, based primarily on the quasi design, and on other characteristics outlined on page 16 ("some but not all important outcomes are considered"). If one recommendation of this review is for investigators and funding agencies to perform high-quality cluster-randomized trials rather than quasi studies, grading the two approaches similarly does not help convince. I'm also slightly puzzled by the judgment that the Huang study is of poor quality compared with the Robiscek study-my reading of the two studies in the past has led me to ascribe more weight to the Huang study.	We have clarified the methods used to determine study quality and provide more detail about the specific ratings of Huskins, Robiscek and Huang. In the results chapter we note, "Of the studies that used statistical methods to attempt to control for confounders or secular trends, the Robicsek17 and Huskins24 studies were judged to be of good quality overall because they presented baseline characteristics for intervention and control groups, conducted appropriate analyses (tested for trend, addressed autocorrelation and controlled for at least one confounder) and reported on an important (health care-associated) outcome." We have added a table with full details of the rationale for quality assessment ratings to the Methods section. We believe that both randomized trials and observational studies have the potential to provide valid data on the effectiveness of MRSA screening.
Reviewer #4 (Peer)	Results	Results: For Key Question 3B, is there any utility in referencing RCTs that address S. aureus generally, rather than only MRSA? For example, the Bode study from the Netherlands that convincingly demonstrated a reduction in S. aureus SSI after a screening/decolonization intervention? Although not including MRSA colonized patients, it seems that this broader approach (to screen for all S. aureus) has the potential to trump or to encompass an MRSA-only strategy, rendering this question of less relevance.	This CER addressed screening for MRSA-carriage rather than screening for MRSA overall

Commentator & Affiliation	Section	Comment	Response
Reviewer #5 (Peer)	Results	Results: The detail presented in the results section is appropriate. I think the authors do an outstanding job of describing the studies included in the review. I dont have any further comment regarding the key messages and the results as they are presented (please see comment above). The tables are comprehensive and allow the reader to easily compare and contrast the studies available on the topic. I was not able to find additional studies the authors should include that would alter their results. The only other general comment I would have regarding the results is that the paper comes across a bit "negative" essentially stating there are no studies that provide "good enough" evidence to recommend anything regarding the topic. This might be frustrating for some readers from institutions without specific IC/ID expertise trying to make decisions about screening for MRSA.	The conclusion of this comparative effectiveness review is that there is low strength of evidence that universal screening of hospital patients decreases MRSA infection. However, there is insufficient evidence on other outcomes of universal MRSA screening, including morbidity, mortality, harms and resource utilization. There is also insufficient evidence on any outcomes of MRSA screening in other settings. We realize that for some, this conclusion may seem "negative."
Reviewer #6 (Peer)	Results/ES	Results Executive Summary: The results are clear and well-described in the text and tables.	None required.
Reviewer #6 (Peer)	Results/ES	Results Executive Summary: [page ES-12, lines 21-24] When more than 1 study addresses a Key Question, the strength of evidence ratings appears to be a sort of "average" across all of the studies addressing that question. This yields some almost nonsensical results. For example, for Key Question 3A, the table indicates that the strength of evidence for MRSA acquisition is considered to have a moderate (or medium) risk of bias, even though a randomized controlled trial (Huskins [21]) is included in this assessment. In contrast, the table indicates the strength of evidence for MRSA infection, which includes only 1 quasi-experimental, non-controlled study (Robiscek [15]), is considered to have a low risk of bias. Consequently, it appears that the poor quality studies have "pulled" the strength of evidence for MRSA acquisition downward, despite the fact this outcome was addressed in a cluster-randomized trial. How does this make sense? The overall grade for the strength of evidence then is then classified as "insufficient." What would it take to regard the strength of evidence as "sufficient?" Two cluster-randomized trials?	We have clarified the methodology, including the assignment of strength of evidence. In particular, we have clarified the decision rules used to determine the SOE. Please see the tables depicting the Strength of Evidence Rating Domains, the Strength of Evidence Categories and Rules, and the Summary of Outcomes Measures and SOE. Bodies of evidence consisting of at least one good quality RCT are at low risk of bias. Bodies of evidence consisting of at least one fair quality RCT or one observational study of good quality and one additional study of good or fair quality are of medium risk of bias. Bodies of evidence that do not meet the requirements for low or medium risk of bias are of high risk of bias. Using the decision rules, for KQ 3A, we now clarify the risk of bias for the group of studies that evaluated MRSA acquisition as low (as the body of evidence includes one good quality RCT) and the risk of bias for the group of studies that evaluated MRSA infection as high (as the body of evidence that evaluated this outcome included only quasi-experimental studies, only one of which was of good quality).

Commentator & Affiliation	Section	Comment	Response
Reviewer #6 (Peer)	Results/ES	Results Executive Summary: [page ES-14, lines 34-40] Why is a study by Huang et al, which reported data on MRSA acquisition, not included in the studies reviewed in Key Question 3C (Huang SS, et al. J Infect Dis 2007;195:330-8)?	This study was not included because it is did not evaluate screening for MRSA carriage compared to no screening, or expanded screening for MRSA carriage compared to limited screening.
Reviewer #8 (Peer)	Results	Results: Page 26. At the bottom of the page, the report states that health care-associated MRSA acquisition is an indirect outcome measure. Since transmission of MRSA results in acquisition of the organism by a susceptible host from a healthcare worker's hands, directly from a colonized or infected healthcare worker, or in fewer instances from a contaminated inanimate object, why is acquisition considered an indirect outcome? Acquisition is, in fact, the best measure of transmission of MRSA. MRSA infection is an indirect outcome that results from acquisition of the organism, followed by inadequate or breached host defenses that allow for tissue invasion by the organism.	As noted in the analytic framework, health care-associated MRSA acquisition is an intermediate outcome, rather than a health outcome and is therefore indirect. The analytic framework was reviewed and vetted by the Key Informants and TEP and was posted for comment We have clarified the methodology used to grade the strength of evidence.
Reviewer #8 (Peer)	Results	Results: Page 29, Table 4. KQ2. Why wasn't a "down arrow" placed next to NS in the column labeled Statistical Result for the study by Leonhardt et al? A review of the Leonhardt paper revealed that the intervention resulted in a non-significant reduction in the rate of hospital-acquired MRSA infection rate from 0.27% to 0.15%.	We have added a "down arrow" in this column.
Reviewer #8 (Peer)	Results	Results: Page 32, Table 6. KQ3A. Why were the studies by Gould, Blumberg and Souweine excluded from the table? The Executive Summary (page ES-10) cites these 3 studies as addressing KQ3A. Also, what is meant by the statement that the Gould study was rated as fair quality because it did not report on a "purely health care-associated outcome"? Do you mean that they did not distinguish between patients who may have been colonized or infected on admission from those who developed nosocomially-acquired MRSA colonization or infection? If so, consider re-wording the statement on Page 32.	Screening for MRSA-carriage is most proximately expected to affect health care-associated outcomes. We have clarified the KQs and the Methods section to note that the focus of this CER is on health care-associated outcomes. Studies that did not report health care-associated outcomes separately from MRSA infections including both health care-associated and community-acquired cases were not included in the SOE. Therefore, the Gould study was not included in this table. The Blumberg and Souweine studies were non-CCS studies and therefore, were not included in the SOE analyses or in the table. We have clarified the methodology used to determine study quality. Greater detail about rating of individual study quality has been added to each Key Question, with new tables describing key aspects of all studies that attempted to control for secular trends and confounding.
Reviewer #8 (Peer)	Results	Results: I strongly disagree with the classification of the Huskins study as one of Good quality. I agree that the Huskins study has a number of strong features, including its cluster-randomized study design, analysis of a number of confounding variables and potential secular trends, analysis of ICU-level	The methodology used to determine study quality for this CER (US Preventative Services Task Force method) did not include an assessment of the testing turnaround time and the management

Commentator & Affiliation	Section	Comment	Response
		and patient-level variables and Cox proportional-hazard models. However, a number of hospital epidemiologists with considerable experience with MRSA (and I include myself in this group) feel that the study had a "fatal flaw". Namely, the fact that the average delay in reporting the results of screening cultures was 5.2 days. In fact, for patients who were MRSA-positive the average delay was 5.6 days. Moreover, the mean interval between reporting of screening results and initiation of contact precautions was 0.7 days. As a result, the average delay between obtaining screening cultures and implementing contact precautions was ~6.3 days for MRSA-positive patients and ~6 days for VRE-positive patients. Such delays do not reflect the manner in which MRSA screening cultures are employed in most health-care facilities. As a result, for patients with ICU length of stay of > 3 days, 59% of ICU days occurred before the results of screening cultures were reported. These aspects of the study significantly reduced the likelihood that the intervention would show any benefit in reducing MRSA acquisitions and infection, and puts the major conclusion of the study into question. The study also had a number of other deficiencies which likely contributed to the poor results obtained. Importantly, 55% of patients admitted to the ICUs had lengths of stay of less than three days, and were not included in the analysis. Since it is likely that approximately 10 to 12% of these patients were also colonized with MRSA on admission, such patients could easily have contributed to transmission of MRSA in the ICUs and to the lack of apparent effectiveness of MRSA screening. The fact that compliance with glove use for contact with patients and hand hygiene after contact were only marginally higher in the intervention ICUs than in control ICUs represent additional weaknesses of the study. As alluded to in the Introduction of the Comparative Effectiveness Review, screening would only be expected to be beneficial if health-care workers comply at a fairly high rate with other elements of the prevention bundle, including hand hygiene and contact precautions, which was not the case in Huskins trial. The study fails to take into account several other confounding variables including colonization pressure, the level of environmental contamination, the adequacy of environmental cleaning, and the potential for transmission from colonized or infected healthcare workers. Another potential weakness of the study is that the investigators did not differentiate between acquisition of MRSA (colonization) versus infection as the primary outcome measure. Transmission of pathogens such as MRSA is best measured by the rate of acquisition of the pathogen by susceptible hosts. The progression from acquisition (colonization) to infection cannot be influenced by screening procedures, but is due to host factors that permit invasion (infection) by the pathogen to occur. Failure to specifically measure acquisition is a potential weakness of the study. Based on the above	of patients awaiting the results of screening tests. As a result, this confounder did not impact study quality, though it does affect applicability. Similarly, the methodology used to determine study quality for this CER (US Preventative Services Task Force method) did not include an assessment of whether or not a study measured adherence to potential confounders such as hand hygiene or threshold values for adherence to these potential confounders. As a result, these confounders did not impact study quality, though they do affect applicability

Commentator & Affiliation	Section	Comment	Response
		weaknesses, I believe the quality of the Huskins trial should be rated at best as a Fair, or maybe even Poor.	
Reviewer #8 (Peer)	Results	The study by Harbarth (ref. 29) also has a number of weaknesses that detract from the strength of the evidence provided by the trial. For example, nosocomial acquisition of MRSA was expressed as the rate of new MRSA cases detected by clinical cultures. As shown by Thompson et al. (Ann Intern Med 1982;97:309), and as alluded to in the Introduction of the Comparative Effectiveness review, clinical cultures fail to detect a substantial proportion of patients who are colonized with MRSA. Failure to include acquisition of MRSA as a measure of the effectiveness of the intervention is a weakness of the study by Harbarth. Although adherence of healthcare workers to contact precautions and hand hygiene policies was included as a confounding variable, the methods used to measure compliance were far from ideal. For example, adherence to contact precautions was rated as low if there was no contact precautions sign and protective equipment at the entrance of a room. This would suggest little if any compliance of healthcare workers entering such rooms. Importantly, the presence of a contact precautions signs and personal protective equipment at the entrance of a room is not considered by any experts as a true measure of compliance of health care workers in donning gloves and putting on counts prior to room entry. Therefore any information about compliance of health care workers with contact precautions in the Harbarth study is subject to considerable question. Furthermore, measurement of the use of alcohol-based hand rubs was used as a surrogate marker for hand hygiene adherence. No observational data regarding the actual compliance of health care workers with recommended hand hygiene policies was reported in the study. Although a number of other studies have shown a positive association between the frequency of alcohol-based hand rubs and hand hygiene compliance, other studies have found little or no correlation between the two measures (Boyce JM Infect Control Hosp Epidemiol 2011;32:1016). In the Harbarth study, it is also worth noting that the use of alcohol-based hand rubs during the intervention periods was not significantly higher than during control periods. In a way, this suggests that hand hygiene practices did not confound the results related to MRSA screening. However one might have expected a higher frequency of hand hygiene during the intervention periods, when screening would have detected additional patients with MRSA who would have remained in contact precautions. As a result of the above elements of the study design, one cannot be confident that adherence to contact precautions and hand hygiene were convincingly eliminated as confounding variables. Another important weakness of the Harbarth study was the fact that 40 of the 93 patients who developed a nosocomial MRSA infection during the intervention periods had a previous history of MRSA or were found to be	We have clarified the methodology used to determine study quality. We have added more detail regarding our assessment of the Harbarth study. In the results section we write, “The Harbarth study34 was a prospective, interventional cohort study with crossover design. This study was judged to be of good quality overall because it presented baseline characteristics for the intervention and control groups, conducted appropriate analyses (tested for trend, addressed autocorrelation and controlled for at least one confounder) and reported on an important (health care-associated) outcome.” More detail about the quality rating for this study is presented in the table that describes study quality in detail.

Commentator & Affiliation	Section	Comment	Response
		colonized at the time of admission. Infections in the 40 patients could not have been prevented by screening. It seems like these infections should have been excluded because, although they most likely represented nosocomial MRSA infections, these infections did not result from acquisition of the organism in the study units during the intervention periods. Another weakness alluded to by Harbarth and colleagues was the fact that 41% of patients who developed MRSA surgical site infections during intervention periods were either colonized or infected prior to surgery, and as a result of third of the patients who were MRSA carriers did not receive anti-MRSA preoperative prophylaxis at the time they are surgical procedure. Furthermore, 59% of the surgical patients received < 1 day of decolonization therapy prior to their procedure, which may have adversely affected the incidence of MRSA surgical site infections. Based on the weaknesses cited above, the quality of the Harbarth study should be considered as Fair, rather than Good.	
Reviewer #10 (Peer)	Results	Results: Results section contains a large amount of detail; the tables help to make this more manageable. The studies are well described and key messages are clear, including the limitations of existing studies.	None required.
Reviewer #10 (Peer)	Results	Results: Page numbers below refer to document and not pdf. Typo p. 50, line 49: “confounders rather that” should be “confounders rather than.”	We have corrected this typo.
Reviewer #10 (Peer)	Results	Results: Page numbers below refer to document and not pdf. Typo p. 64, line 23: “versus compared to” should be either “versus” or “compared to.”	We have corrected this typo.
Reviewer #10 (Peer)	Results	Results: Page numbers below refer to document and not pdf. References, p. 132, line 20 lists “Excluded: Animal Study” but this study was done in hospitalized patients.” Title appears incorrect.	We have corrected this error.
Reviewer #10 (Peer)	Results	Results: Page numbers below refer to document and not pdf. Missing blank line between references 194 and 195 on p. 146, line 35.	We have corrected this error.
Reviewer #10 (Peer)	Results	Results: Overall, literature review appears very thorough.	None required.
Reviewer #11 (Peer)	Results	Results: The authors go to great lengths to present all of the details of their analysis. Each article included in their analysis is discussed in detail, with a description of the quality of the study, its outcomes, and its various limitations. The results are organized well into the various key questions, and the results of the analysis are easily determined (which is helped by the fact that the results are, essentially, the same throughout for each key question).	None required.

Commentator & Affiliation	Section	Comment	Response
Reviewer #11 (Peer)	Results	Results: The Figures and Tables are adequate with some of the limitations mentioned already above. In addition, there are a few minor points to consider: (1) some of the values used in Table ES-1 for the B column are not defined in the abbreviations list (L for low, M for medium) when others (H for high) are; and (2) it seems odd to me that values of Y and N are used in Table ES-1 for the C, D, and P columns, when the values used for these in the corresponding tables in the full manuscript (eg, Table 3 on Page 29) are different (eg, direct/indirect, precise/imprecise, and consistent/inconsistent). It would seem to me to make sense to be consistent in how this information is presented.	(1) We have added definitions of "L" and "M" for Table ES-1. (2) We have altered the language used to ensure consistency in the presentation of strength of evidence.
Reviewer #11 (Peer)	Results	Results: Another minor point is that the discussion of the Jain article from NEJM is somewhat confusing. There are multiple references to the "control group" in the Jain study (pages 26 and 27 in the full manuscript), but it was designed as a before-after study. If the "before" population is being referred to as the control group, it would be better to state this more clearly. Some of the subsequent statements about the differences between "intervention" and "control" groups (eg, page 27, lines 13-26) seem odd, particularly the practices followed for MRSA-positive patients in each group. Also, in this same paragraph on page 27, the Jain article is incorrectly referenced (it should be reference 39, but in one place it is reference 28, which is the Robicsek study).	For consistency of presentation, for the Jain study and other included studies that utilized a before/after study design, we refer to the "before" population as the "control group." We corrected the reference to reflect the Jain paper rather than the Robicsek paper. (Jain R, Kralovic SM, Evans ME, et al. Veterans Affairs initiative to prevent methicillin-resistant Staphylococcus aureus infections. N Engl J Med. 2011 Apr 14;364(15):1419-30. PMID: 21488764.)
Reviewer #12 (Peer)	Results	Results: Page ES-14, line 21-22; page 32, line 3-4: As mentioned in the General Comments section, it seems that lack of statistical significance is being used as the determinant of both consistency and precision. Based on the definitions of the terms provided in the original source document, I would interpret these findings to be consistent but imprecise.	We have clarified that statistical significance is being used as the determinant of precision, but not of consistency.
Reviewer #12 (Peer)	Results	Results: Page ES-18, line 17-19; page 53, line 19-20: This comment is similar to that in the previous comment. Are these findings not consistent but imprecise?	We have clarified that the direction of the point estimates are used to determine consistency and statistical significance used to determine precision.
Reviewer #12 (Peer)	Results	Results: Page ES-20, line 19; page 62, line 37: Shouldn't the consistency here be described as "unknown" since only one CCS study was available for inclusion?	We have corrected this error.
Reviewer #12 (Peer)	Results	Results: Page 22, Figure 4, "Full Text Review" box: In its current format, it is difficult to quickly understand the data presented here. The small boxes list all studies as both included and excluded. I think the point that the authors are trying to make is that all studies that were included after the title and abstract review process were subsequently excluded at the full text review. However, the equivalent alignment of "included" and "excluded" suggests that these are mutually exclusive categories, rather than serial assessment of the same study. Perhaps reformatting would allow this to be more apparent to the reader.	We have added an arrow to indicate that these studies were included in the full text review and then subsequently excluded.

Commentator & Affiliation	Section	Comment	Response
Reviewer #12 (Peer)	Results	Results: Page 27, line 21: The wrong reference number is given to the Jain study. The correct reference number is 39.	We have corrected this reference.
Reviewer #12 (Peer)	Results	Results: Page 31, line 40: Typographical error: "…nor was the difference in difference (p=0.34)." Please clarify.	We have corrected this typo.
Reviewer #12 (Peer)	Results	Results: Page 33, Table 6, line 32: There appears to be inconsistent use of terminology here. Why is this result described as "significant ↓" when others with statistically significant decreases are described as "SS ↓"?	We have changed the terminology to "SS" followed by a downward arrow.
Reviewer #12 (Peer)	Results	Results: Page 33, line 49: The authors state that the Gould study was of fair quality and it is discussed several times in the subsequent paragraphs. However, this study is not listed in Table 6 and it is also not included in any of the subsequent sections that address the specific outcomes under this Key Question. Why has this study been excluded for the Table and the assessments of strength of evidence?	We have clarified in the Methods chapter that screening for MRSA-carriage is most proximately expected to affect health care-associated MRSA acquisition/infection. Therefore, health care-associated outcomes are the outcomes of interest. As the Gould study did not report a health care-associated outcome, it was not included in the strength of evidence analysis.
Reviewer #12 (Peer)	Results	Results: Page 36, line 33-35: The authors state that the Huang study recommended no action for MRSA-positive patients in the control group. As far as I can tell, this is not actually stated in the published article describing this study. My understanding is that contact precautions were used in the control group.	We have clarified that the Huang study did not specify if any action was taken for MRSA-positive patients in the control group.
Reviewer #12 (Peer)	Results	Results: Page 37, line 9-10: The authors incorrectly state that in the Boyce study, no intervention was recommended for MRSA-positive patients in the control period. The published paper actually states that ongoing acquisition was occurring "despite" a policy of contact precautions for patients known to be colonized or infected.	We have corrected this error.
Reviewer #12 (Peer)	Results	Results: Page 50, Table 10; throughout the text for Key Question 3C; throughout the text for Key Question 4: The wrong citation is provided for the Rodriguez-Bano study. The correct citation is: Infect Control Hosp Epidemiol 2010;31(8): 786.	We have corrected this citation.
Reviewer #12 (Peer)	Results	Results: Page 50, Table 10, line 29-30; Page 55, line 8-10: The Rodriguez-Bano study is reported as having found a non-significant result but there was a significant decrease in incidence detected after the introduction of active surveillance. Since there was a significant reduction, doesn't this changed the assessment of the strength of evidence since all 3 CCS studies found statistically significant decreases? In other words, aren't the findings actually consistent?	The consistency of the findings is unknown because only one CCS study addressed each outcome of interest.

Commentator & Affiliation	Section	Comment	Response
Reviewer #7 (Public; Persing)	Results	Study Quality We would like to stress that in addition to study design being a key determinant of judging whether a study is of "high" quality, compliance with the intervention must also be considered. As pointed out in the CER, the Agency acknowledges that differences exist in technologies used in the intervention (i.e., turnaround time; (1) In the Harbarth study only 43% of carriers received appropriate antibiotics prior to their surgery (2) The Huskins study was well designed, but was not properly implemented and test results were not received for five days – after many patients were discharged and certainly after ample opportunity for patient to patient transmission). This fact, combined with low compliance with the infection control intervention most likely led to findings of "no impact" of the program. (3) Hardy et. al. (2010) used a prospective cross over study design and demonstrated that the reduction in MRSA acquisition in surgical wards was statistically less likely in patients that were screened using rapid methods compared to culture. The study controlled for potentially confounding variables yet was not included in the current CER (See Hardy K, et. al., Clin Microbiol. Infect. 2010 Apr;16(4):333-9).	We have clarified the methodology used to determine study quality. However, the fidelity of the intervention (including screening, +/- isolation, +/- decolonization) is not included in the assessment of study quality. In addition, fidelity of the intervention was infrequently reported in the literature included in this comparative effectiveness review. Thus, the results of studies that did not report intervention fidelity at all should not considered better or more accurate than studies that reported low intervention fidelity. In the Discussion section, we acknowledge the importance of capturing this metric in future studies. The Hardy study was not included as it the study is not a randomized controlled trial (RCT) or quasi-experimental study (QEX) comparing either: 1) screening (by either culture or PCR) vs no screening; 2) universal (all patients admitted to a hospital) vs targeted screening OR 3) more limited targeted screening vs expanded targeted screening.
Reviewer #7 (Public; Rodriguez-Bano)	Results	We are authors of the reference provided as number 45 in page ES-26 and as number 66 in page 78 (Rodriguez-Bano J, Lopez-Prieto MD, Portillo MM, et al. Epidemiology and clinical features of community-acquired, healthcare-associated and nosocomial bloodstream infections in tertiary-care and community hospitals. Clin Microbiol Infect. 2010 Sep;16(9):1408-13. PMID: 19845694), but I'm afraid it is wrong. The correct one is another one from our group: Rodríguez-Baño J, García L, Ramírez E, Lupión C, Muniain MA, Velasco C, Gálvez J, del Toro MD, Millán AB, López-Cerero L, Pascual A. Long-term control of endemic hospital-wide methicillin-resistant Staphylococcus aureus (MRSA): the impact of targeted active surveillance for MRSA in patients and healthcare workers. Infect Control Hosp Epidemiol. 2010 Aug;31(8):786-95. PMID: 20524852.	We have corrected this citation.

Commentator & Affiliation	Section	Comment	Response
Reviewer #7 (Public; Rodriguez-Bano)	Results	Table 10, page 49. I am not sure that the results of our study (Rodriguez-Bano) were adequately interpreted. After the intervention that included targeted screening, there was not a significant change in the rate immediately after the intervention (beta 4), but a clearly significant change in the trend (beta 5). This should not be interpreted as that the rate did not changed (it did, please see figure 1 and table 1 in the article!) but as that the change took some time to occur. As regards bacteremia, the reduction was so fast that it was significant even immediately after the intervention (beta 4).	Both trend and level are important in interpreting the results of this study. We have changed the text to read, "The Rodriguez-Bano study51 showed reductions in the incidence and trend of health care-associated MRSA infection or colonization with expanded screening compared to limited screening. Though the reduction in trend was statistically significant (change in trend after the third intervention 0.047; 95 percent CI: 0.035-0.059, p<0.001), the reduction in incidence was not (change in incidence after the third intervention 0.077 [NS; 95 percent CI: -0.012 to 0.165]).51"
Reviewer #7 (Public; Rodriguez-Bano)	Results	Screening for MRSA is not a finalist measure in itself. It is only performed as a means to early identify carriers so that transmission from them can be prevented by additional measures. Thus, a key issue in interpreting the studies investigating the impact of screening for MRSA is the adherence to these additional measures (usually, contact precautions and environmental cleaning). In any study, adherence to contact precautions must be assessed (or activities performed aimed at promoting such adherence) whenever active screening is not associated with a reduction in MRSA transmission or in rate of MRSA infection before concluding that screening has no impact.	None required.
Reviewer #7 (Public; Kavanagh)	Results	Tables: I recommend the following changes which I believe will improve the report. 1) Table 6, uses "NSS" for the abbreviation for not statistically significant. To be consistent "NS" should be used. 2) The studies of Habarth, et al., (2008, PMID 18334690 and Huskins, et al. 2011, PMID 1000373) should be eliminated from the data analysis along with being deleted from Tables 1, 6, 8, and 10. 3) Table 4 should list the study of Loenhardt, et al. as "NS" with a downward arrow. 4) Table 10 need to be corrected to list the results of Rodrigues-Bano, et al. to be significant and showing a decrease (downward arrow) in MRSA bacteremia and acquisition. The inclusion of the Data from Rodrigues-Bano in table 12 should be questioned since each intervention was added onto the other. Intervention C involved surveillance for MRSA in hospital units that had transmission, as Intervention D involved previously colonized or patients transferred from another facility. Thus, these are for the most part two different populations, and since this baseline did not change, it could be inferred that the more limited intervention (D) may not be as effective as the unit level intervention (C).	1. We chose to use NSS (rather than NS) throughout the manuscript. 2. Based on their quality ratings and reported outcomes, the studies by Harbarth and Huskins have been included in the data analysis and the tables. 3. We have listed the Leonhardt study as "NS" with a downward arrow. The Rodriguez-Bano study evaluated screening a limited patient population (targeted screening) vs screening a broader patient population (expanded screening). As the Rodriguez-Bano presents data that addresses this key question, it continues to be included in the analysis.

Commentator & Affiliation	Section	Comment	Response
Reviewer #1 (TEP)	Discussion/ Conclusion	Discussion/ Conclusion: In multiple places in the discussion portion the lack of data on harms of MRSA screening is mentioned (eg, last paragraph of page 71, conclusion, etc). I think the authors should be cautious here as this appears to have been assessed only among studies that were first identified based on their evaluation of an MRSA control measure. In order to assess the harms in a systematic way they would need to approach the question in a different way that might have identified additional literature (e.g., look for studies that look at harms regardless of MRSA evaluation).	We have clarified that the included studies provided insufficient data about the harms of screening compared to the harms of no screening/limited screening.
Reviewer #1 (TEP)	Discussion/ Conclusion	Discussion/ Conclusion: Page 104, the authors state that these findings are inconsistent with the CDC/HICPAC MDRO guidelines. However, I think that this is inaccurate. This systematic review using VERY stringent criteria (ie, presenting a very conservative estimate of the evidence) suggested there was not enough evidence to show that MRSA screening reduces a number of outcomes. This is very different than showing they did not have an affect. The HICPAC recs were specifically tiered so that things that are less well supported provided as second tier interventions. This would seem to be very consistent with the findings of this report.	Because this CER did not find sufficient evidence to support or refute screening for MRSA-carriage, it is neither able to support nor refute the recommendation to screen for MRSA-carriage. We have modified the language in the Discussion to state, "Based on the conclusions reached in the current review of specific key questions regarding MRSA screening, the applicability of these findings and the strength of the available evidence do not appear to readily support or refute the recommendations adopted by the CDC HICPAC or in the earlier SHEA Guidelines. That MRSA screening has been adopted as a mandatory practice through legislative action in some jurisdictions is also not easily supported or refuted by the findings of the present review."
Reviewer #2 (TEP)	Discussion/ Conclusion	Discussion/ Conclusion: Very well written, summarizes the results very well and provides direction for further work in this content area.	None required.
Reviewer #3 (Peer)	Discussion/ Conclusion	Discussion/ Conclusion: It may be beneficial to have a next steps section that describes current studies that may contribute to this literature. For example, Dr. Susan Huang's large AHRQ funded REDUCE MRSA cluster-randomized trial on screening has recently ended and the results are currently being analyzed.	We reviewed clinical trials.gov and found no additional studies for inclusion in this CER. The body of evidence identified by the MRSA CER consistently overwhelmingly of observational studies. Because ongoing observational studies need not be registered in clinicaltrials.gov, it is difficult to systematically identify all studies underway that might ultimately contribute to this literature. Therefore, we have chosen not to include a discussion of this topic in the discussion/conclusion.

Commentator & Affiliation	Section	Comment	Response
Reviewer #3 (Peer	Discussion/ Conclusion	Discussion/ Conclusion: Although this systematic literature review did not find high quality studies that assessed harms associated with contact precautions, a recent systematic literature review of observational studies assessed this association.(Morgan DJ, Diekema DJ, Sepkowitz K, Perencevich EN. Adverse outcomes associated with Contact Precautions: a review of the literature. Am J Infect Control. 2009 Mar;37(2):85-93) That review should be referenced here.	This CER evaluated the harms of screening for MRSA-carriage compared to the harms of not screening for MRSA-carriage. In addition, it evaluated the harms of screening selected populations for MRSA-carriage compared to the harms of not screening, and the harms of screening limited populations compared to the harms of screening expanded populations. An evaluation of the harms of screening (without a comparison of the harms of not screening) was outside of the scope of this review.
Reviewer #3 (Peer)	Discussion/ Conclusion	Discussion/ Conclusion: Typo on page 64 (101) lines 22 and 23, “universal versus compared to screening of selected patient populations” should either say versus or compared to. Typo page 70 (107) line 9, “may also me due” should be “may also be due.”	We have corrected these typos.
Reviewer #4 (Peer)	Discussion/ Conclusion	Discussion/ Conclusion: Excellent. The implications of the findings are clearly stated, the limitations adequately described, and I don’t believe that important literature was omitted. There are at least a couple important studies with results coming soon that may impact these questions (the REDUCE MRSA trial at HCA hospitals, PI Susan Huang, and the ICU BUGG study, PI Anthony Harris), but that can’t be helped.	None required.
Reviewer #4 (Peer)	Discussion/ Conclusion	Discussion/ Conclusion: I believe the authors should consider allocating even more space and attention to suggesting what future investigators need to do to remedy the current situation (of having so little good-quality evidence). The two biggest problems I see with current literature, and to which the authors refer, are (1) the lack of attention to the decolonization intervention that often occurs after screening reveals MRSA carriage. Future studies simply must take a more careful approach to this aspect of the screening intervention; and (2) the complete lack of attention given to the potential harms of screening (patient safety issues, resource utilization, etc.).	The discussion section addresses future research needs. These future research needs will be addressed comprehensively in a subsequent document.

Commentator & Affiliation	Section	Comment	Response
Reviewer #5 (Peer)	Discussion/ Conclusion	Discussion/ Conclusion: The limitations of the review and the studies included in the review are discussed very well. Due to the limitations of the studies, as concluded by the authors, there really is no major implication of the findings of this report other than to clearly identify the gap in appropriately conducted research trials. A very important component of this section includes the discussion regarding compliance with measures in these studies (not reported in majority). The discussion seems to contradict itself by stating that the available evidence doesnt readily support the CDC guidelines (page 67) but then states that if hospital leadership feels further control of MRSA is desired then they advise use of the CDC gudielines (page 72). Its a little confusing.	We have clarified that there is insufficient evidence to support or refute screening for MRSA carriage. We note that, "However, even in the absence of these data, hospital leaders may feel compelled to make a determination regarding the appropriateness of MRSA screening based on the other factors described at the beginning of this section. More specifically, if MRSA infection is affecting a large number of patients and the resultant infections are severe and even life threatening, infection prevention experts and hospital leadership may feel the potential benefits of screening outweigh the risks, even in light of the limited available evidence to deploy a screening program." In other words, some circumstances may require hospitals to make decisions, even when the evidence is insufficient to guide these decisions.
Reviewer #5 (Peer)	Discussion/ Conclusion	Discussion/ Conclusion: The authors clearly state what future research is needed and how it should be conducted to be considered high quality. Hopefully this will be a focus for funding agencies.	None required.
Reviewer #6 (Peer)	Discussion/ Conclusion	Discussion/ Conclusion Executive Summary: 15. Beyond the assessment of study quality, readers will benefit from a comprehensive and insightful discussion of the particular strengths and limitations of the key studies, such as those rated as "good," either in the Results or the Discussion. These studies get lost in the large number of studies included in the review, most of which are "poor" quality studies.	For each KQ, we have included a discussion of the rationale for the quality rating of each study in the Results section. In addition, we have provided a table summarizing the results of each study
Reviewer #6 (Peer)	Discussion/ Conclusion	Discussion/ Conclusion Executive Summary: [page ES-22, lines 35-43] The lack of a formal assessment of agreement between reviewers should be acknowledged as a limitation.	We have clarified the study methodology, especially the assessment of agreement between reviewers. We note, "Quality of the abstracted studies was assessed by at least two independent reviewers, and the final quality rating was assigned by consensus adjudication."

Commentator & Affiliation	Section	Comment	Response
Reviewer #6 (Peer)	Discussion/ Conclusion	Discussion/ Conclusion Executive Summary: [page ES-23, lines 15-24] Since one of the conclusions is that the field would benefit from more high-quality, cluster-randomized trials, it would be more informative to acknowledge relevant cluster randomized trials that are complete (www.clinicaltrials.gov; NCT00980980, NCT00976638) or underway (NCT01318213). Results from the two complete studies may be available later in 2012. A brief summary of the questions addressed by these trials would be helpful. This would also alleviate the somewhat depressing impression that there is "insufficient" evidence across the board, despite the large number of studies.	We reviewed clinical trials.gov and found no additional studies for inclusion in this CER. Because it is difficult to systematically identify all studies underway that might ultimately contribute to this literature, we have chosen not to include a discussion of this topic in the discussion/conclusion. Based on the literature identified by this CER, many ongoing studies are likely to be observational studies that need not be registered in clinicaltrials.gov.
Reviewer #8 (Peer)	Discussion/ Conclusion	Discussion/ Conclusion: Page 64. In the Strength of Evidence section, I think undue weight was given to the study by Huskins, which for reasons I have outlined above, had serious flaws which are likely to have affected its results and conclusions.	We have clarified the methodology used to determine study quality and strength of evidence.

Commentator & Affiliation	Section	Comment	Response
Reviewer #8 (Peer)	Discussion/ Conclusion	Discussion/ Conclusion: I take issue with your overall conclusion, based on very restrictive criteria, that the studies you have reviewed provide insufficient evidence of any benefit of MRSA screening. Using your criteria, you found that 13 (87%) of 15 CCS studies reported a reduction in MRSA (11 significant and 2 non-significant), and 29 (100%) of 29 non-CCS studies reported a reduction in MRSA (24 significant and 5 non-significant) as a result of implementing MRSA screening. Only 2 studies (judged as Good quality by the reviewers, but considered of lesser quality in my opinion) showed non-significant increases in MRSA as a result of screening (a counter-intuitive result). What is the statistical likelihood that 42 of 44 studies would show some reduction in MRSA colonization or infection strictly by chance alone, when in fact there was no beneficial effect of MRSA screening? I have been under the impression that when study after study yields the same finding or trend, that the consistency of findings contributes to the overall validity of the data. Although many of the studies cited in the review are of suboptimal quality, the consistency with which they found MRSA screening beneficial is noteworthy, and should not be ignored. In an eloquent lecture on the state of the world's health, given at the 2003 Interscience Conference on Antimicrobial Agents and Chemotherapy (ICAAC) by the Director General of the World Health Organization, Dr. Gro Harlem Brundtland stated (I paraphrase) that the key to control of transmissible diseases is early detection and prompt institution of control measures. There is no reason to believe that this general tenant should not apply to MRSA as it does to other transmissible pathogens. MRSA screening, as mentioned by the reviewers of the Comparative Effectiveness Review, is the early detection method by which colonized patients, who represent the major reservoir from which MRSA is transmitted, can be identified so that other elements of a MRSA prevention bundle may be promptly implemented. I agree with the desirability of conducting further studies of the benefits of MRSA prevention bundles. Additional studies on potential adverse effects on patients of MRSA screening are unlikely to identify significant risks of placing a culture or PCR swab into the anterior nares of patients. Concerns over the use of MRSA bundles have dealt primarily with other elements of a prevention bundle, such as placing patients in private rooms and in contact precautions, which often results in fewer visits to the patient by healthcare workers. Such effects on patients should not be construed as an adverse effect of screening, but rather the effects of subsequent prevention measures.	The evidence base for this CER consisted overwhelmingly of observational studies, most of which employed a before/after study design. Because the rate of MRSA infection has been decreasing since approximately 2005, studies that do not adequately control for secular trend are at high risk of bias. Similarly, because interventions designed to decrease health care-associated infections (such as hand hygiene campaigns, identification of patients with a history of multidrug resistant organisms so that isolation can be established upon admission, etc.) are expected to decrease the rate of health care-associated MRSA infection, studies that do not adequately control for these confounders are at high risk of bias. Thus, despite the reduction in MRSA acquisition/infection seen in many of the studies, the observational nature of the studies as well as the risk of bias of the studies as a group often contributed to the insufficient strength of evidence. We have clarified the methodology used to determine study quality and strength of evidence. In addition, we have clarified that uncontrolled confounders and trends may contribute to the findings, especially of the non-CCS studies. Because the downstream effects of harms (e.g., isolation, decolonization/eradication) may cause harm, understanding the comparative harms of screening for MRSA carriage is important.

Commentator & Affiliation	Section	Comment	Response
Reviewer #10 (Peer)	Discussion/ Conclusion	Discussion/ Conclusion: Major findings are clearly stated in the text of the discussion beginning on p. 101. Strength of evidence is acknowledged to be insufficient to draw many conclusions in the report. However, the literature is well summarized and clearly outlines areas of need for future research, including in study design, populations, outcomes and describing details of interventions.	None required.
Reviewer #10 (Peer)	Discussion/ Conclusion	Discussion/ Conclusion: Limitations are well summarized by type and portion of report beginning on p. 109. These are critically important if any conclusions can be drawn from this work, so worth the space that it takes up in the report. Would consider adding in more about the concern for development of mupirocin or chlorhexidine resistance under interventions on p. 73.	We have discussed this concern as a potential harm of screening for MRSA carriage.
Reviewer #11 (Peer)	Discussion/ Conclusion	Discussion/ Conclusion: The authors did a nice job summarizing their study and their findings and discussing these findings in the context of the existing knowledge about MRSA screening. The implications are well stated and the limitations of their work are adequately covered. Still, as mentioned above, the main limitation (the lack of information provided in the articles concerning decolonization practices, other simultaneous HAI reduction campaigns, and adherence data) almost seem to render the immense work that went into this manuscript pointless. The fact that there were two previous reviews in this area (the McGinigle article from CID and the Tacconelli article from Lancet ID) from 2008 and 2009 might lessen the impact of this work to a certain extent, but the comprehensiveness of this manuscript and the inclusion of newer studies (in particular, the Jain article from NEJM) should establish this as the defining review study in the field, despite the fact that little can be gained from the literature reviewed.	None required.
Reviewer #12 (Peer)	Discussion/ Conclusion	Discussion/ Conclusion: ES-21, line 15; page 67, line 29-30: There appears to be a misinterpretation of the 2003 SHEA Guidelines. The guidelines actually recommend surveillance among patients at high-risk for carriage and more extensive surveillance if a high prevalence is found. It is then stated that those strategies should be implemented throughout the system. It does not state that all patients throughout the system must be screened.	We have reviewed these guidelines to ensure they have been described accurately. The 2003 SHEA Guidelines recommend the following: "I. Active Surveillance Cultures to Identify the Reservoir for Spread 1. Implement a program of active surveillance cultures and contact precautions to control the spread of epidemiologically significant antibiotic-resistant pathogens known to be spreading in the healthcare system via direct and indirect contact. (IA) 2. Surveillance cultures are indicated at the time of hospital admission for patients at high risk for carriage of MRSA, VRE, or both. (IB) 3. Periodic (e.g., weekly) surveillance cultures are indicated for patients remaining in the hospital at

Commentator & Affiliation	Section	Comment	Response
			high risk for carriage of MRSA, VRE, or both because of ward location, antibiotic therapy, underlying disease, duration of stay, or all four. (IA) 4. In facilities found to have a high prevalence on initial sampling, a facility-wide culture survey is indicated to identify all colonized patients and allow implementation of contact precautions. (IB) 5. Because transmission occurs throughout the healthcare system, these measures should be implemented in all types of healthcare facilities throughout the system. (IB) 6. The frequency of active surveillance cultures should be based on the prevalence of the pathogen and risk factors for colonization. For example, more frequent cultures are needed in a facility where 50% of all S. aureus isolates are MRSA than in one where less than 1% of all S. aureus isolates are MRSA. (IB) 7. The goal of this program should be to identify every colonized patient, so that all colonized patients are cared for in contact (or cohort) isolation to minimize spread to other patients. (IB)." Our interpretation of the SHEA Guidelines is that screening is recommended upon hospital admission for persons at high risk of MRSA, at intervals throughout the hospital stay for persons at high risk of MRSA, and for all patients in all types of facilities throughout the healthcare system (and perhaps at intervals throughout the hospital stay) in healthcare systems with a high prevalence of MRSA. Thus, the SHEA Guidelines advocate mandatory screening of persons at high risk for MRSA and those seen in all types of facilities in healthcare systems with a high prevalence of MRSA. Although this conflicts with the reviewers' interpretation we feel this interpretation of the SHEA Guidelines is accurate.
Reviewer #12 (Peer)	Discussion/ Conclusion	Discussion/ Conclusion: Page 67, lines 34-37: Similar to the previous comment, the 2003 SHEA Guidelines did not advocate for "mandatory" screening. They recommended screening among patients at high risk and	We have reviewed these guidelines to ensure they have been described accurately. The 2003 SHEA Guidelines state the following:

Commentator & Affiliation	Section	Comment	Response
		allowed for individual hospital assessment/determination of high-risk populations.	"I. Active Surveillance Cultures to Identify the Reservoir for Spread 1. Implement a program of active surveillance cultures and contact precautions to control the spread of epidemiologically significant antibiotic-resistant pathogens known to be spreading in the healthcare system via direct and indirect contact. (IA) 2. Surveillance cultures are indicated at the time of hospital admission for patients at high risk for carriage of MRSA, VRE, or both. (IB) 3. Periodic (e.g., weekly) surveillance cultures are indicated for patients remaining in the hospital at high risk for carriage of MRSA, VRE, or both because of ward location, antibiotic therapy, underlying disease, duration of stay, or all four. (IA) 4. In facilities found to have a high prevalence on initial sampling, a facility-wide culture survey is indicated to identify all colonized patients and allow implementation of contact precautions. (IB) 5. Because transmission occurs throughout the healthcare system, these measures should be implemented in all types of healthcare facilities throughout the system. (IB) 6. The frequency of active surveillance cultures should be based on the prevalence of the pathogen and risk factors for colonization. For example, more frequent cultures are needed in a facility where 50% of all S. aureus isolates are MRSA than in one where less than 1% of all S. aureus isolates are MRSA. (IB) 7. The goal of this program should be to identify every colonized patient, so that all colonized patients are cared for in contact (or cohort) isolation to minimize spread to other patients. (IB). Our interpretation of the SHEA Guidelines is that screening is recommended upon hospital admission for persons at high risk of MRSA, at intervals throughout the hospital stay for persons at high risk of MRSA, and for all patients in all types of facilities throughout the healthcare

Commentator & Affiliation	Section	Comment	Response
			system (and perhaps at intervals throughout the hospital stay) in healthcare systems with a high prevalence of MRSA. Thus, the SHEA Guidelines advocate mandatory screening of persons at high risk for MRSA and those seen in all types of facilities in healthcare systems with a high prevalence of MRSA. Although this conflicts with the reviewers' interpretation we feel this interpretation of the SHEA Guidelines is accurate.
Reviewer #2 (TEP)	Clarity/ Usability	Clarity and Usability: I think the report -- although long -- is clear and most relevant information is included.	None required.
Reviewer #1 (TEP)	Clarity/ Usability	Clarity and Usability: Ordering of report sections (see comments above).	None required.
Reviewer #3 (Peer)	Clarity/ Usability	Clarity and Usability: The report is very organized and the main points are clearly presented. I hope policy makes read this manuscript before mandating universal screening for MRSA.	None required.
Reviewer #4 (Peer)	Clarity/ Usability	Clarity and Usability: The report is well structured and organized, and the main points are clearly presented. The conclusions are important to policy and practice, as they may help pursuade policy makers not to proceed with resource intensive and potentially harmful interventions that are not adequately supported by existing literature.	None required.
Reviewer #5 (Peer)	Clarity/ Usability	Clarity and Usability: The report is well structured and organized. It is easy to follow and extract the information being presented. Due to the conclusions of the limitations of the available literature on the topic using the criteria for review, I dont feel it will dramatically alter current practice. The authors clearly state they do not feel mandatory policies should be developed regarding routine MRSA screening based on the available evidence.	None required.
Reviewer #6 (Peer)	Clarity/ Usability	Clarity and Usability: The report is well-structured and organized and the main points are clear. However, the the assessment that the strength of evidence is "insufficient" for all of the Key Questions will limit the utility of the findings.	None required.
Reviewer #8 (Peer)	Clarity/ Usability	Clarity and Usability: The report is well-structured and organized and the main points are clearly presented. I am very concerned that the reviewers' conclusion that there is insufficient evidence regarding the effectiveness of MRSA screening in any specific setting may be construed by healthcare administrators as evidence that screening has been proven to have no benefit, which is not the case. I suggest that the authors add the qualifying statement similar to one used in the executive summary (page ES-22) to the conclusion section: Where MRSA infection affects a large number of patients, the resultant infections are severe, and other infection control strategies have been unable to check the spread of infection, the deployment of a screening program may be sensible.	We have clarified that there is insufficient evidence to recommend for or against screening for MRSA carriage.

Commentator & Affiliation	Section	Comment	Response
Reviewer #10 (Peer)	Clarity/ Usability	Clarity and Usability: The report is comprehensive and well structured. The main points are clearly presented, but the material is dense; tables do help to guide the reader through to the conclusions. I would consider clarification of some figures and tables as outlined above. The section on implications for clinical and policy decision making (beginning on p. 108) is well written and clearly outlines the problems with the current US approach. Conclusions are limited due to the design of the underlying studies but clearly show that the evidence base has too many gaps at present to lead to national decision making. The definition of remaining questions and outlining important needed areas of research as done in this report may help to provide support for needed future work.	None required (addressed in discussion of tables and figures).
Reviewer #11 (Peer)	Clarity/ Usability	Clarity and Usability: The manuscript is extremely well organized and structured, based around the four key questions about the subject that are identified early on. The writing is excellent and the main points of the work are clearly stated and presented; of course, this is helped by the fact that the results are essentially the same for all of the key questions. The main conclusion of the work -- that there is insufficient evidence to support the routine implementation of screening for MRSA carriage, is well described and supported, and confirms at least some of the previous work in this area. Finally, since this work was written and designed to inform and support policymaking, it succeeds in providing a comprehensive summary of the evidence that can be used for decision-making purposes at the administrative level.	None required.
Reviewer #12 (Peer)	Clarity/ Usability	Clarity and Usability: The report is well structured and organized. There are few opportunities to improve the clarity of certain sections of the report. These have been described in the preceding comments.	None required (addressed in prior comments above).
Reviewer #12 (Peer)	Clarity/ Usability	Clarity and Usability: The conclusions of the report are limited by the available data which prevents the conclusions from substantially informing policy and practice. The systematic study describing the lack of strong evidence is perhaps more informative for policy than for practice.	None required.