Evidence-based Practice Center Rapid Response Protocol

Project Title: Making Healthcare Safer IV: Active Infection Surveillance of *Clostridioides difficile* and Multi-Drug Resistant Organisms: *Methicillin-Resistant Staphylococcus aureus (MRSA), Carbapenem-Resistant Enterobacterales (CRE), Candida auris*

Review Questions

1. What is the frequency and severity of harms associated with healthcare associated infections and asymptomatic colonization due to MRSA, CRE, *C.auris*, and *C.difficile*?

2. What patient safety measures or indicators have been used to examine the harm associated with healthcare associated infections and asymptomatic colonization due to MRSA, CRE, *C.auris*, and *C.difficile*?

3. What infection surveillance PSPs for MRSA, CRE, *C.auris*, and *C.difficile* have been used to prevent or mitigate the harms and in what settings have they been used?

4. What is the rationale for the infection surveillance PSPs for MRSA, CRE, *C.auris*, and *C.difficile* that have been used to prevent or mitigate the harms?

5. What studies have assessed the effectiveness and unintended effects of infection surveillance PSPs for MRSA, CRE, *C.auris*, and *C.difficile* and what new evidence has been published since the search was completed for the Making Healthcare Safer (MHS) III report of 2019?

6. What are common barriers and facilitators to implementing infection surveillance PSPs for MRSA, CRE, *C.auris*, and *C.difficile*?

7. What resources (e.g., cost, staff, time) are required for implementation of infection surveillance PSPs for MRSA, CRE, *C.auris*, and *C.difficile*?

8. What toolkits are available to support implementation of infection surveillance PSPs for MRSA, CRE, *C.auris*, and *C.difficile*?

Context and Domain Being Studied

The Agency for Healthcare Research and Quality (AHRQ) Making Healthcare Safer (MHS) reports consolidate information for healthcare providers, health system administrators, researchers, and government agencies about practices that can improve patient safety across the healthcare system - from hospitals to primary care practices, long-term care facilities, and other healthcare settings. In Spring of 2023, AHRQ launched its fourth iteration of the MHS Report (MHS IV).

Infection surveillance as a PSP was identified as high priority for inclusion in the MHS IV reports using a modified Delphi technique by a Technical Expert Panel (TEP) that met in December 2022. The TEP included 15 experts in patient safety with representatives of governmental agencies, healthcare stakeholders, clinical specialists, experts in patient safety issues, and a patient/consumer perspective. See the Making Healthcare Safer IV Prioritization Report for additional details.[1]

Preventing exposure, colonization, and infection of *Clostridioides difficile* and multi-drug resistant organisms (MDROs) is a critical patient safety and public health priority. In the United States, more than 2.8 million antimicrobial-resistant infections occur each year and more than 35,000 people die as a result.[2] *Clostridioides difficile* and MDRO pathogens, including methicillin-resistant *Staphylococcus aureus* (MRSA), carbapenem-resistant Enterobacterales (CRE) and *Candida auris*, are a particular concern for medically vulnerable persons, resulting in significant patient harm and economic cost.[3] These organisms in particular are the focus of multiple frameworks for mitigating the threat of harm due to healthcare associated infections (HAI) including National Healthcare Safety Network (NHSN) MDRO module[4], the National Action Plan for Combating Antibiotic-resistant Bacteria (CARB) report[5], along with the CDC's Interim Guidance for a Public Health Response to Contain Novel or Targeted Multidrug-resistant Organisms (MDROs).[6] Owing to these organisms' increasing prevalence over time, limited treatment options, limited capability to rapidly detect them, and emergence of novel antimicrobial resistance mechanisms they require multifaceted resource-intense infection prevention and control systems anchored by infection surveillance programs.[4-6] *C. difficile* and MDRO transmission

pathways[7] in healthcare settings may involve transmission between patients, providers, and the environment. Prevention and control of *C. difficile* and MDROs relies upon both traditional infection control approaches, including isolation precautions and hand hygiene, and newer techniques, such as whole genome sequencing, machine learning algorithms, regional MDRO registries and geospatial mapping.[8-10]

Overview of the Patient Safety Practice (PSP)

Surveillance is the cornerstone of any *C. difficile* and MDRO control program, allowing detection of newly emerging pathogens, monitoring epidemiologic trends, and measuring the effectiveness of interventions.[11] Active surveillance cultures (ASC) for *C. difficile* and MDROs involves the collection and culturing of samples to identify asymptomatic colonization on the skin, mucosal surfaces, or gastrointestinal tract of patients. Active surveillance also requires the systematic collection, analysis, and reporting of data to trend organism burden, identify patient and environmental reservoirs, and measure the impact of infection control interventions to mitigate these harms. Recent innovations have resulted in new active surveillance approaches. For example, whole genome sequencing surveillance of targeted organisms has identified reservoirs and routes of healthcare transmission that were not apparent using traditional epidemiologic surveillance methods.[8,12] Similarly, geospatial mapping techniques combined with genomic data have defined transmission patterns and informed infection control strategies within hospitals and across regional healthcare facilities.[13,14] Nevertheless, implementing infection surveillance PSPs presents several challenges for hospitals and health systems, including identifying target populations, selecting methods for obtaining and processing ASC specimens, optimizing the timing and frequency of collecting ASC, and evaluating the effectiveness of using ASC on reducing *C. difficile* and MDRO burden, antimicrobial overuse, healthcare acquired infections (HAI), and cost of care.

In MHS III, active surveillance was examined as a PSP within the larger topic of MDROs. Available evidence addressed surveillance for MRSA, CRE, vancomycin-resistant Enterococci (VRE), and general gram-negative bacteria. A separate chapter dedicated to *C. difficile* infection also reviewed surveillance strategies specific to that organism. The report also noted a lack of consensus regarding surveillance for *C. auris*.

In the prioritization process, the Making Healthcare Safer IV TEP noted that the infection surveillance PSP and testing topics in MHS III would be subsumed by this rapid response owing to

few new studies estimated to be eligible and likely overlapping with prior findings. Our rapid response subsumes entirely types of infection surveillance PSPs covered in MHS III but narrows to specific, critical MDROs and *C. difficile* which are most burdensome on patient safety. Additionally, owing to the overlapping findings of the *C.difficile* testing chapter in MHS III, our rapid response will also subsume the *C.difficile* surveillance and testing topics as it relates to active surveillance, along with screening and testing in asymptomatic patients. Owing to the limited time and funding allocated to this update on infection surveillance PSP, along with publication of updated CDC guidelines for *C.difficile* testing in 2017, there has been an acceleration in publications evaluating *C.difficile* testing and diagnostic stewardship interventions in symptomatic patients that is beyond the scope of our rapid response.[15,16]

Purpose of the Review

The overall purpose of this rapid response is to summarize the most relevant and recent literature on PSPs focused on infection surveillance and how these PSPs can be implemented.

Methodologic Approach

For this rapid response, strategic adjustments will be made to streamline traditional systematic review processes and deliver an evidence product in the allotted time. We will follow adjustments and streamlining processes proposed by the AHRQ Evidence-based Practice Center (EPC) Program. Adjustments include being as specific as possible about the questions, limiting the number of databases searched, modifying search strategies to focus on finding the most valuable studies (i.e., being flexible on sensitivity to increase the specificity of the search), and restricting the search to studies published recently (since 2019 when the search was done for the MHS III report) in English and performed in the United States, and having each study assessed by a single reviewer. The EPC team will have a randomly selected 10% sample of excluded references checked by a second reviewer at the title and abstract screening stage.

We will consider all PSPs specific to active infection surveillance, screening, and testing in asymptomatic patients for MRSA, CRE, *C.auris*, and *C.difficile* that focus on healthcare associated infections or colonization.

We will search for recent high quality systematic reviews and will rely primarily on the content of any such systematic review that is found. We will not perform an independent assessment of

original studies cited in any such systematic review.

We will ask our content experts to answer Review Questions 1 and 2 by citing selected references that best answer the questions, in addition to findings identified in Review Question 5 relevant to Review Questions 1 and 2, without conducting a systematic search for all evidence on the targeted harms and related patient safety measures or indicators.

We will ask our content experts to answer Review Question 3 and 4 by citing selected references, including infection surveillance PSPs used and explanations of the rationale presented in the studies we find for Review Question 5.

For Review Questions 6 and 7, we will focus on the barriers, facilitators, and required resources reported in the studies we find for Review Question 5.

For Review Question 8, we will identify publicly available patient safety toolkits developed by AHRQ or other organizations that could help to support implementation of the PSPs. To accomplish that task, we will review AHRQ's Patient Safety Network (PSNet) (https:/psnet.ahrq.gov) and AHRQ's listing of patient safety related toolkits (see https://www.ahrq.gov/tools/index.html?search_api_views_fulltext=&field_toolkit_topics=14170&sort_by=title&sort_order=ASC) and we will include any toolkits mentioned in the studies we find for Review Question 5. We will identify toolkits without assessing or endorsing them.

Eligibility Criteria for Studies of Effectiveness

We will search for original studies and systematic reviews on the review questions according to the inclusion and exclusion criteria presented in Table 1.

Table 1. Inclusion and Exclusion Criteria

Study Parameter	Inclusion criteria	Exclusion criteria
Population	Adult and pediatric patients	
Intervention	Any surveillance or infection control testing, asymptomatic screening conducted for evaluation of the following organisms: • *C. difficile* • *S. aureus* (MRSA) • *C. auris* • carbapenem-resistant	• Diagnostic testing outside of outbreak surveillance testing • Multicomponent interventions in which the isolated effect of surveillance cannot be evaluated • Testing stewardship interventions • No microbial organism of

Study Parameter	Inclusion criteria	Exclusion criteria
	Enterobacterales (CRE)	interest evaluated • Pre-clinical interventions
Comparator	Usual practice or other type of PSP	• No concurrent or historical comparison group • No clear description of intervention
Outcome	**Safety** Adverse events and incidents of harm **Quality of care measures** • Healthcare associated infections due to organism of interest • Colonization due to organism of interest **Utilization of health care services** (focusing on the main utilization measure reported in the study) **Implementation** • Barriers and facilitators • Resources (cost, staff, time)	• No outcome of interest • Studies only assessing test performance
Timing	Original studies published since 2019	Published before 2019
Setting	Inpatient and emergency department settings, nursing, and rehabilitation facilities	Ambulatory, community, or other outpatient settings
Type of studies	Original studies (Randomized controlled trials or observational studies with a comparison group, including pre-post studies), systematic reviews, published since 2019, the year of the search done for the MHS III report on this topic	Guidelines, narrative reviews, scoping reviews, editorials, commentaries, and abstracts

IOM = Institute of Medicine; MHS = Making Healthcare Safer

Literature Searches for Studies of Effectiveness

We will search PubMed and the Cochrane Library for systematic reviews published since 2019, the year of the search completed for the MHS III report on this topic, that address the rapid

response questions. If no recent high quality systematic reviews are identified, we will conduct searches of PubMed for primary studies.

To efficiently identify articles that meet the eligibility criteria, we will distribute citations from the literature search to team members, with plans to have the title and abstract of each citation reviewed by a single team member. A second team member will check a 10% sample of citations to verify that important studies were not excluded after the review of titles and abstracts.

Description of Included Studies

To efficiently describe eligible studies, the full text of each potentially eligible article will be reviewed by a single team member to confirm eligibility and prepare a summary of the study, including author, year, study design, number of study participants, and main findings relevant to each of the rapid response questions. Since Review Question 5 calls for identification of studies on the effectiveness of infection surveillance PSPs for MRSA, CRE, *C. auris*, and *C. difficile*, we will describe the objectives and basic characteristics of those studies without conducting a detailed analysis of their findings. We will ask a second team member to check a randomly selected 10% sample of the excluded citations at full text screening to verify that important studies were not excluded and confirm the accuracy of extracted data.

To describe eligible systematic reviews, a single team member will prepare a summary including the author, year, number of studies by study design, and main findings relevant to each of the rapid response questions.

For Review Question 8, we will list the source of each relevant toolkit along with a 1-2 sentence description. We will not endorse any specific toolkit.

Risk of Bias (Quality) Assessment

For studies that address Review Question 5 about the effectiveness of infection surveillance PSPs for MRSA, CRE, *C.auris*, and *C.difficile*, the primary reviewer will use the Cochrane Collaboration's tool for assessing the risk of bias of randomized controlled trials (RCTs) or the ROBINS-I tool for assessing the Risk Of Bias In Non-randomized Studies - of Interventions.[17,18] When assessing RCTs, we will use the 7 items in the Cochrane Collaboration's tool that cover the domains of selection bias, performance bias, detection bias, attrition bias, reporting bias, and

other bias.[17] When assessing non-randomized studies, we will use specific items in the ROBINS-I tool that assess bias due to confounding, bias in selection of participants into the study, bias in classification of interventions, bias due to deviations from intended interventions, bias due to missing data, bias in measurement of outcomes, and bias in selection of the reported results.[18] The risk of bias assessments will focus on the main outcome of interest in each study.

If we identify a recent eligible systematic review, the primary reviewer will use the criteria developed by the United States Preventive Services Task Force Methods Workgroup for assessing the quality of systematic reviews.[19]

- **Good** - Recent relevant review with comprehensive sources and search strategies; explicit and relevant selection criteria; standard appraisal of included studies; and valid conclusions.
- **Fair** - Recent relevant review that is not clearly biased but lacks comprehensive sources and search strategies.
- **Poor** - Outdated, irrelevant, or biased review without systematic search for studies, explicit selection criteria, or standard appraisal of studies.

The Task Leader will review the risk of bias assessments and any disagreements will be resolved through discussion with the team.

EPC Team Disclosures

EPC core team members must disclose any financial conflicts of interest greater than $1,000 and any other relevant business or professional conflicts of interest. Related financial conflicts of interest that cumulatively total greater than $1,000 will usually disqualify EPC core team investigators from participation in the review.

Role of the Funder

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the report should not be construed as endorsement by AHRQ or the U.S. Department of Health and Human Services.

Format and Content of Report

The report will follow the most recent template approved by AHRQ at the time of approval of the protocol.

References

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