Screening Implementation Guide

Implementation of Carbapenemase-Producing Organism Colonization Screening

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Contents

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Introduction

Antimicrobial-resistant (AR) pathogens are responsible for more than 2.8 million infections and 35,000 deaths annually.* Many of these infections occur in a healthcare setting, such as long-term care facilities and skilled nursing facilities.** These environments present unique challenges with AR pathogens spreading through contaminated surfaces, devices and patient transfers.

Carbapenemase-producing organisms (CPOs), particularly those carrying KPC, NDM, IMP, VIM or OXA-48 carbapenemases, are among those AR pathogens that pose a significant risk. Mobile genetic elements can facilitate resistance transfer between bacteria, including carbapenemase genes. This enhances the spread of CPOs and their threat to patients. Additionally, a patient can be asymptomatically colonized with a CPO but can still spread the pathogen. Therefore, timely detection and identification of CPOs in colonized patients are crucial for containment.

Colonization screening (also commonly referred to as surveillance testing in many settings) aims to identify asymptomatic carriers of CPOs for targeted infection control and contain the spread within a facility; it is not intended to identify clinical cases of infection for treatment purposes. Screening can be conducted upon admission or via point prevalence surveys. Because of the importance of containing spread, timely testing and coordination between partners is of utmost importance.

This document offers guidance for laboratories seeking to implement CPO colonization screening and provides a variety of aspects to consider when implementing testing. The guidance is not only directed at clinical laboratories working to establish CPO colonization screening capabilities, but may also benefit those public health laboratories not yet performing this testing function and considering implementation. Regional laboratories in the AR Lab Network, created by the US Centers for Disease Control and Prevention (CDC), have conducted colonization screening for facilities since its inception and can serve as a point of contact for any additional guidance needed.

Using This Guide

This document is intended to provide general guidance to laboratories interested in performing CPO colonization screening. Interested laboratories should be able to:

- **Develop an optimal workflow selection based on laboratory personnel proficiency, available instrumentation and anticipated turnaround time, ensuring practicality and timely receipt of results to guide infection control practices.**
- **Conduct resource assessment and procurement for chosen screening approach.**
- **Implement a collaborative communication strategy with relevant partners, including public health departments.**

* CDC. Antibiotic Resistance Threats in the United States, 2019. Atlanta, GA: US Department of Health and Human Services, CDC; 2019. Available from: www.cdc.gov/antimicrobial-resistance/media/pdfs/2019-ar-threats-report-508.pdf

** Weiner-Lastinger LM, Abner S, Edwards JR, Kallen AJ, Karlsson M, Magill SS, et al. Antimicrobial-resistant pathogens associated with adult healthcare-associated infections: Summary of data reported to the National Healthcare Safety Network, 2015–2017. Infection Control & Hospital Epidemiology. 2020;41(1):1–18. doi:10.1017/ice.2019.296

Glossary

Below are definitions for key terminology in this document:

Colonization

The presence of a pathogenic organism in or on a person's body without signs or symptoms of infection. Colonized individuals are at increased risk of becoming infected, and can unknowingly spread pathogens to others in shared settings.

Colonization Screening

Performing testing on specimens that are collected for the purposes of detecting colonization of a specific pathogen in or on a specific person. This is also commonly referred to as "surveillance testing" in many settings.

Carbapenemase Producing Organisms

These bacteria have developed carbapenem resistance through the production of enzymes that inactivate carbapenems and other β-lactam antibiotics. Carbapenemase enzymes can be classified into groups under the Ambler classification system (class A, B, C or D). The carbapenemases can be encoded by either chromosomal or plasmid-mediated genes. Resistant organisms carrying the carbapenemases in Table 1 pose a significant risk to the efficacy of antimicrobial treatment.

Laboratory-developed Test (LDT)

A test developed wholly—or in part—by the performing laboratory. This may include use of analyte specific reagents or adoption of another laboratory's LDT or non-cleared or approved test.

Mobile Genetic Elements

DNA elements, such as plasmids, that promote intra- or intercellular DNA mobility. These elements may be transmitted within and between bacterial species and can facilitate the acquisition and dissemination of resistance genes. Carbapenemase genes are often located on plasmids, enhancing their spread.

Validation Study

The process used to establish performance characteristics, with objective evidence, that an LDT or modified US Food and Drug Administration (FDA)-cleared or approved test method or instrument system delivers reliable results for the intended application.

Value Analysis Team

An interdisciplinary group of clinical and non-clinical team members whose function is to use a systematic, objective, evidence-based process to evaluate products and services that meet or exceed requirements of performance, quality, safety and cost effectiveness.

Verification Study

The one-time process by which a laboratory determines that an unmodified FDA-cleared or approved test performs according to the manufacturer's specifications when used as directed.

Table 1. Resistant organisms carrying the following carbapenemases pose a significant risk to the efficacy of antimicrobial treatment:

Carbapenemase	Abbreviation	Ambler Class
***Klebsiella pneumoniae* carbapenemase**	KPC	Class A
Imipenemase metallo-β-lactamase	IMP	Class B
Verona integron-encoded metallo-β-lactamase	VIM	Class B
New Delhi metallo-β-lactamase	NDM	Class B
Oxacillinase group β-lactamase-48	OXA-48	Class D

Considerations for Implementing Screening of CPO Pathogens

Technology and Expertise

This section outlines potential methods laboratories can adopt for conducting CPO colonization screening. When conducting screening, laboratories may opt for either molecular methods or a culture-dependent workflow. Each approach has its own advantages and constraints. Considerations in workflow selection should include the competency of laboratory personnel, required instrumentation, specimen type and anticipated turnaround time. It is crucial to note that the purpose of colonization screening is to prevent transmission and will influence patient movement per infection control protocols. Therefore, it is essential to choose an approach that is both practical and emphasizes the timely receipt of results.

When performing colonization testing for CPOs, the primary specimen is typically a rectal swab, although other specimen sources can include but are not limited to sputum and wounds. This choice should be directed by the epidemiology of a potential outbreak or transmission event in a facility. The verification or validation of the assay in use is also a factor when choosing specimen type and source for testing. See **Table 2** for more information about molecular and culture-dependent testing.

Additional Technology and Expertise Resources

Additional examples of molecular or culture-dependent test methods include:

- Carbapenemase Testing for CRO: A Primer for Clinical and Public Health Laboratories (**California Department of Public Health**)
- Commercial assays for the detection of acquired carbapenemases (**UK Health Security Agency**)

The resources included here and in Table 2 are not meant to be an exhaustive list. Laboratories are responsible for performing the research to select the appropriate test methods for their needs.

For more information about verification vs. validation, please see APHL's Verification and Validation Toolkit, which provides a general summary of the differences.

Table 2. **Molecular vs Culture-dependent Testing for CPOs**

	Molecular Testing	Culture-dependent Testing
Purpose	To detect a carbapenemase gene(s) present **in a primary specimen**.	To **detect organisms** that contain a carbapenemase gene(s) from a primary specimen. This method may be used: • When molecular tests do not detect certain targeted carbapenemases or if a laboratory cannot utilize a specific specimen type. • To obtain a pure isolate for further characterization.
Specimen Source and Type	• Primary specimen is typically a **rectal swab**. • Other specimen sources can include but are not limited to **sputum specimens** and **wound swabs**. Specific specimen and swab types may be required depending on assay verified or validated.	• Primary specimen is typically a **rectal swab**. • Other specimen sources can include but are not limited to **sputum specimens** and **wound swabs**.
Potential Approaches	**FDA-cleared/approved Assays:** • Examples include Cepheid Carba-R and BD MAX Checkpoints CPO • FDA 510(k) database allows users to search for FDA-cleared devices (see **"Appendix: Using Product Codes to Search the FDA 510(k) Database," on page 14** for additional database information). • Laboratories must refer to the Instructions for Use for more information and limitations. **Laboratory-developed Tests (LDTs):** Polymerase chain reaction (PCR) methods for detection of specified carbapenemase genes and variants.	Potential workflows for culture-dependent colonization screening involve several steps aimed at isolating and identifying organisms containing carbapenemase genes from primary specimen. The exact workflow and algorithms can vary between laboratories. Below are examples of test methods a laboratory can incorporate into their workflow. **Isolation and identification of an organism from primary specimen**: • Broth enrichment. • Selective media (e.g., CHROMagars). • Differentiating media (e.g., MacConkey). • Selection with antibiotics (e.g., use of a carbapenem disk). • Laboratory's standard method for species identification (e.g., matrix-assisted laser desorption/ionization time-of-flight [MALDI-TOF]). **Phenotypic detection of carbapenemase production**: • Lateral flow assays (e.g., Hardy NG-Carba-5). • Modified carbapenem inactivation method (mCIM). **LDTs for molecular detection**: Real-time PCR methods for carbapenemase identification in isolates after culture recovery using analyte specific reagents (e.g., Streck kits) or other methods.
Time from Test Start to End	**A few hours**; this time may not include pre-analytical or accessioning steps (e.g., extraction).	Dependent on the methods; entire workflow may take between **two to five days**.
Result	Carbapenemase gene detection.	Dependent on the methods, the result will be: • Organism identification. • Carbapenemase production detected or not detected. • Detection of a carbapenemase gene.

	Molecular Testing	Culture-dependent Testing
Method Considerations	• The detection of carbapenemase genes is restricted to the targets and gene variants that the manufacturer claims in their Instructions for Use. • Automated systems can be more costly but are less hands-on and do not require in-depth subject matter expertise. • LDTs can be tailored to detect certain variants and utilize specific specimen types/sources. • Further culture workup is necessary to procure an isolate for additional characterization.	• Time and resource intensive. • Requires expertise in microbiology methods.
Implementation Considerations	• Commercial assays may require investment in proprietary equipment and software. • FDA-cleared tests require a verification study. • If pursuing an LDT, expertise in developing in-house molecular methods is necessary and potentially extensive validation studies are required.	• Expertise in developing in-house or lab-developed culture methods may be necessary. • Potentially extensive validation studies are required.

Additional Characterization Testing

Based on the test results, there may be a need for additional testing and characterization. Collaboration with an AR Lab Network laboratory can facilitate this process. The AR Lab Network has the resources and expertise required for this additional testing and can offer their support to clinical labs who need additional resources. This collaboration between clinical and public health laboratories will also ensure proper public health action can be taken and data collected to better inform the AR national landscape. It is important to have processes in place to address additional testing and isolate submission to the public health laboratory if needed.

The following are suggested considerations for additional testing:

- Connect with your public health laboratory to work together to establish the best processes to facilitate communication and results sharing. Additional testing may include organism identification via MALDI-TOF, antibiotic susceptibility testing, or next-generation sequencing (NGS).
- It is important to communicate with and understand any additional testing that may be requested by infection preventionists (IPs) and healthcare-associated infection (HAI) epidemiologists investigating the outbreak, such as the need to determine relatedness of isolates from different patients through NGS methods.

Equipment and Materials

Commercial instrumentation and ancillary equipment may be required depending on which test method(s) is selected. The following should be considered to ensure that all resources are available to perform the testing.

- **Test Method Selection:** Value analysis team, or similar committee.
- **Cost Per Sample:** This can vary widely; the following will impact the cost per test and determine sustainability of testing strategy:
  - Volume of specimens to be tested
  - Repeat testing
  - Training and competency of staff
  - Quality control (QC) requirements
  - Testing workflow and algorithms
  - Staff time
- **Testing Instrument:** When making the initial purchase of laboratory testing instrument, consider:
  - What instrumentation can be used for test method selected? Can it be used for other purposes when not used for screening? Is there adequate space for the instrument?
  - Is there funding for new instrumentation?
  - Instrument service contract (after expiration of initial warranty)
- **Supporting Equipment:** Could include but is not limited to:
  - Heating block
  - Centrifuge
  - Pipettors
  - Incubators
  - Extraction instrument
  - Thermal cyclers
- **Testing Materials:** Testing materials, based on volume, which could include but are not limited to:
  - Reagents
  - Supplies
  - Consumables
  - Selective media
  - Molecular reagents and kits
  - Plastic consumables
- **Materials for Collecting, Packaging and Shipping Specimens:**
  - Specific swabs (e.g., Copan dual swabs, Eswabs, etc.)
  - Packaging and shipping materials
  - Packaging and shipping training and certification
  - Shipping costs

Establishing and Sustaining Testing

When establishing a new assay, it is important to consider specific quality and safety aspects, such as performing a risk assessment and deciding whether it is necessary to do a validation or verification. Additionally, plans to do an individualized quality control plan (IQCP) are important to consider. Getting your LIS ready for the new assay, and making sure that proficiency testing is available are also important pieces to establishing and sustaining the new test.

- **Risk Assessment:**
  - When implementing a new assay, a risk assessment should be performed prior to implementation of method, per the laboratories established policies, procedures and local regulations for applicable hazards.
  - For the method(s) selected, both chemical and biological risks should be considered, per the Instructions for Use.
  - Detailed guidance on hazard identification, management, mitigation and safety practices is available in the Biosafety in Microbiological and Biomedical Laboratories (BMBL) 6th Edition.
  - General considerations and descriptions of the steps of a risk assessment can be found on the CDC's biosafety resources page: Biological Risk Assessment: General Considerations for Laboratories.
- **Validation or Verification:**
  - Testing kits or other materials for verification or validation
  - Staff time
  - Isolates and specimens
    - CDC & FDA AR Isolate Bank
    - Contact your state PHL, who may be able to provide isolates or residual specimens
    - Utilization of contrived specimens may be necessary
- **IQCP:**
  - CDC's Step-By-Step Guide for Developing an IQCP
  - IQCP Risk Assessment
  - IQCP Data Collection and associated costs
- **Laboratory Information System (LIS) Needs:**
  - Interfacing instrument to LIS
  - Building new test in LIS
  - Validation of new test LIS
  - Adding new test to electronic test ordering and reporting process
- **Proficiency Testing:** Availability of proficiency testing programs or establishing an alternate assessment. Examples of proficiency testing programs include:
  - Wisconsin State Laboratory of Hygiene Proficiency Testing Program
  - College of American Pathologists Proficiency Testing Program
  - American Proficiency Institute

Test Volume and Clinical Needs

Before implementing CPO screening, it is important to engage all partners to discuss testing strategies, especially public health HAI experts that can provide specific guidance. It is essential to have a plan for which patients will get screened that aligns with the laboratory's testing capacity. Understanding the local and regional epidemiology of specific carbapenemases is also essential.

These discussions and the resulting plan should be informed by the guidance provided in two key CDC resources for prevention and containment:

- Public Health Strategies to Prevent the Spread of Novel or Targeted Multidrug-resistant Organisms (MDROs)
- Interim Guidance for a Public Health Response to Contain Novel or Targeted MDROs

Test volumes will be impacted by the testing strategies used, the size of the patient population and the laboratory capacity. It is essential that testing strategies are developed in conjunction with the Infection Control team, using guidance available from CDC and consultation from public health HAI coordinators and laboratory subject matter experts. The following items should be considered when implementing a testing strategy:

- **Testing Strategies:**
  - It is important to detect CPOs in individual patients to mitigate and prevent transmission to others.
  - Consider colonization screening of contacts to a CPO positive patient. This can include:
    - Roommates.
    - Patients who are on the same floor or unit.
    - Patients who have shared clinical and non-clinical spaces.
    - Patients served by the same nursing staff or clinical team.
    - Patients associated with a similar medical device or procedure.
  - Facilities in areas with high burdens of CPO may want to consider more extensive screening strategies, such as:
    - Testing patients on intake (known as admission screening):
      - All new intakes.
      - Those that have transferred from high-risk settings, such as:
        - Long-term care facilities or ventilated skilled nursing facilities.
        - Facilities in areas with high rates of CPOs.
        - Facilities known to have active transmission or colonization.
    - Screening patients prior to higher risk procedure, such as endoscopy.
  - Facilities that have experienced outbreaks or have ongoing transmission could consider routine surveillance to inform patient cohorting. This can include:
    - Screening every patient in the facility once during an outbreak.
    - Regularly screening in a particular wing or floor.
    - Environmental testing.

- **Laboratory Capacity**
  - Work with IPs to determine when the different testing strategies could be used.
  - Clearly outline the maximum number of tests that can be performed in a day and the turnaround time possible. Assess the following:
    - Availability of media and reagents needed for screening.
    - Level of staffing available to do the screening.
    - Instrumentation availability and capacity.
  - Develop testing capacity to meet the needs during the different scenarios.

Communication

It is essential to have open communication, including timely communication of results, with all entities that need the information to respond. This includes internal IP team, local or state public health HAI epidemiologists and laboratory, and potentially CDC.

The following items should be considered when developing communication plans.

- **Public Health Communication:**
  - It is important to establish effective communication with public health laboratories and epidemiologists who specialize in HAIs. This includes determining the important points of contact and discussing the processes for sharing results.
  - HAI epidemiologists can assist by providing guidance on testing strategies and specimen collection and sources.
  - Public health laboratory scientists can provide guidance on follow-up testing upon receipt of a positive result.
- **Internal Communication:**
  - It is essential to consider collaborating with partners in hospital and long-term care facilities, including IPs, antibiotic stewardship team, infectious disease clinicians, directors of nursing and facility clinicians. The knowledge on methods used for swabbing during colonization may differ among staff and facilities.
  - To educate staff, facilities should consider providing collection guides and FAQs on obtaining verbal consent, which are all available from public health partners.
- **Results Reporting:**
  - Prompt and timely reporting of results is crucial to implementing targeted infection control measures.
  - Prior to commencing any colonization screening activities, discussions about reporting should occur and may involve LIS personnel.
  - Follow your state healthcare reporting requirements. The public health department can provide guidance and further information on notifiable disease requirements if needed.

Regulatory

Depending on the laboratory setting and type of accreditation held, regulatory requirements for CPO colonization screening may differ from those for diagnostic testing. Factors to consider when determining requirements for colonization screening implementation include but may not be limited to:

- Listing the test on the laboratory's test menu
- Personnel with authority to order testing
- Method utilized (FDA cleared vs. LDT)
- Test verification/validation, proficiency testing and QC requirements
- Personnel performing testing (certification/licensure requirements)
- Reporting results (to patients' electronic health record, infection prevention, public health and/or beyond) and information technology considerations to manage reporting
- Record keeping
- Billing and reimbursement
- Any institutional review board considerations for human subject research.

During the planning stages for colonization screening, the person responsible should review any requirements that would apply to colonization screening as defined in their laboratory's accreditation manual and healthcare facility's policy manuals. The decisions for how to proceed should be made following discussions with the laboratory director, IPs and any other collaborators within the institution. In addition, the team responsible for test implementation (to include the facility's IP) should contact the facility's local or state public health department to obtain any additional guidance for the type of surveillance being implemented and instructions for reporting results to public health authorities.

Conclusion

Implementing CPO colonization screening is an essential component of infection control strategies within healthcare settings to combat the rising threat of AR pathogens. This document outlines important considerations for laboratories interested in implementing CPO colonization screening. By adhering to the recommendations provided and engaging in collaborative efforts with public health epidemiologists, laboratorians and other partners, laboratories can contribute significantly to the containment of AR pathogens and safeguarding public health.

Looking ahead, continuous vigilance, adaptability and adherence to best practices will remain essential in effectively addressing the challenges posed by AR.

Resources

Below are the resources referenced in this document:

- **510(k) Premarket Database** (FDA), available from: www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfpmn/pmn.cfm
- **AR Information** (FDA), available from: www.fda.gov/emergency-preparedness-and-response/mcm-issues/antimicrobial-resistance-information-fda
- **AR Isolate Bank** (CDC & FDA), available from: www.cdc.gov/antimicrobial-resistance/php/public-health-strategy/
- **AR Lab Network**, available from: www.cdc.gov/antimicrobial-resistance-laboratory-networks/php/about/domestic.html
- **AR Pathogens Associated With Adult Healthcare-associated Infections: Summary of Data Reported to the National Healthcare Safety Network, 2015–2017**, available from: www.cambridge.org/core/journals/infection-control-and-hospital-epidemiology/article/antimicrobialresistant-pathogens-associated-with-adult-healthcareassociated-infections-summary-of-data-reported-to-the-national-healthcare-safety-network-20152017/8172ED836D43D153047F480781E420C1
- **AR Threats Report**, 2019 (CDC), available from: www.cdc.gov/antimicrobial-resistance/media/pdfs/2019-ar-threats-report-508.pdf
- **Biosafety in Microbiological and Biomedical Laboratories (BMBL) 6th Edition**, available from: www.cdc.gov/labs/bmbl/
- **Biological Risk Assessment: General Considerations for Laboratories Commercial Assays for the Detection of Acquired Carbapenemases** (UK Health Security Agency), available from: www.cdc.gov/safelabs/resources-tools/bio-risk-assessment.html
- **Carbapenemase Testing for CRO: A Primer for Clinical and Public Health Laboratories** (California Department of Public Health), available from: www.cdph.ca.gov/Programs/CHCQ/HAI/CDPH Document Library/CRO_PrimerTests_for_Carbapenemases.pdf
- **Individualized Quality Control Plan** (CDC), available from: www.cdc.gov/labquality/iqcp.html
- **Interim Guidance for a Public Health Response to Contain Novel or Targeted MDROs** (CDC), available from: www.cdc.gov/healthcare-associated-infections/media/pdfs/Health-Response-Contain-MDRO-H.pdf
- **Public Health Strategies to Prevent the Spread of Novel and Targeted MDROs** (CDC), available from: www.cdc.gov/healthcare-associated-infections/media/pdfs/Health-Response-Prevent-MDRO-508.pdf
- Proficiency Testing:
  - **American Proficiency Institute**, available from: api-pt.com/
  - **College of American Pathologists Proficiency Testing Program**, available from: www.cap.org/laboratory-improvement/proficiency-testing
  - **Wisconsin State Laboratory of Hygiene Proficiency Testing Program**, available from: wslhpt.org/
- **Test Method Verification and Validation Toolkit** (APHL), available from: www.aphl.org/toolkits/Pages/Verification-Validation-Toolkit.aspx

Appendix: Using Product Codes to Search the FDA 510(k) Database

The FDA 510(k) database allows users to search for FDA-cleared devices. The database is extensive and may be challenging to navigate unless searches are limited to a specific type of device or assay. One way to do this is to narrow the search by entering specific three-letter product codes into the "Product Code" field in the database search.

The FDA has provided information to help enable identification of product codes for AR-related in vitro diagnostic devices:

- Codes associated with AR pathogen testing can be found in the Center for Devices and Radiological Health Product Classification database by searching for the terms "susceptibility," "antimicrobial" or "resistance" in the "device" section.
- A selection of product codes noted by the FDA as associated with AR-related device approvals include: JTN, JWY, LON, LTT, LRG, LTW, PEN, PAM and POC.
- Phenotypic antimicrobial susceptibility test (AST) devices and molecular testing devices are included in these product codes.

Additional examples of relevant product codes:

- Product code "PMY" will yield search results for System, Nucleic Acid Amplification Test, DNA, Carbapenem Non-Susceptible Gram-Negative Organism.
- Product code "POC" will yield search results for System, Nucleic Acid Amplification Test, DNA, Antimicrobial Resistance Marker, Direct Specimen.
- Product code "PTJ" will yield search results for Phenotypic Test Kit, Non-Susceptible/Elevated Mic Organisms, Cultured Isolates.

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