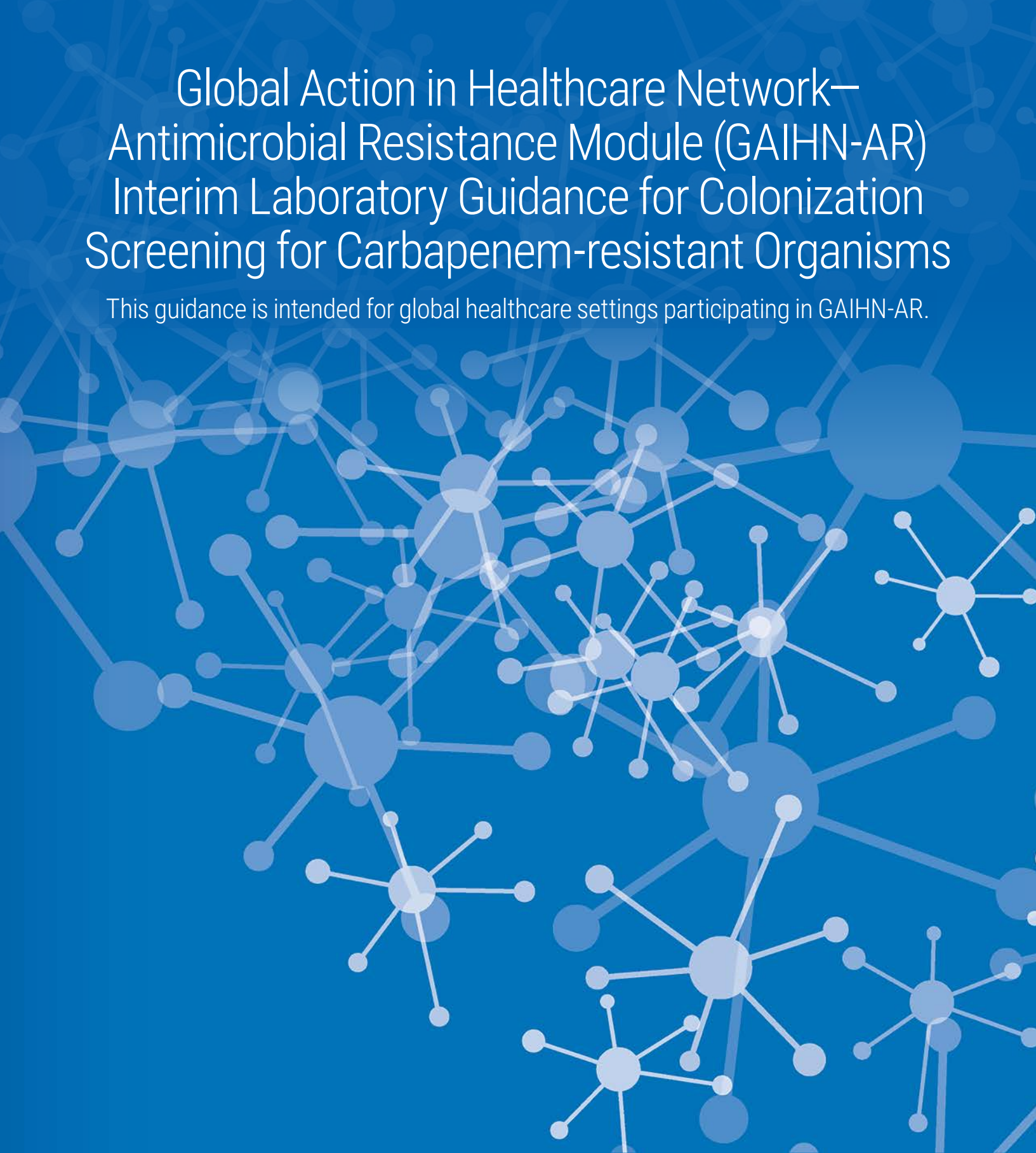
Global Action in Healthcare Network—Antimicrobial Resistance Module (GAIHN-AR) Interim Laboratory Guidance for Colonization Screening for Carbapenem-resistant Organisms

This guidance is intended for global healthcare settings participating in GAIHN-AR.



Version 1, 2024

Centers for Disease Control and Prevention
National Center for Emerging and Zoonotic Infectious Diseases

CS 346591-A

Contents

Glossary

Admission screening: Colonization screening that is conducted upon admission to a healthcare facility (HCF) or unit.

Alert: GAIHN-AR testing results that require immediate notification of infection prevention personnel. Specific alert criteria are defined within the document in the "Communication of Alerts and Actions" section.

Antimicrobial-resistant organisms: Some bacteria and fungi are naturally (intrinsically) resistant to certain antimicrobials. For the purposes of this document, this term refers to bacteria that are resistant to one or more classes of antimicrobials to which they are usually susceptible.

Broad phenotypic carbapenemase production testing: Laboratory testing that detects carbapenemase activity. Examples of phenotypic carbapenemase testing methods include modified carbapenem inactivation method (mCIM), Blue Carba, and Carba NP. These methods cannot identify specific carbapenemase genes/enzymes but may be useful, particularly in areas of low carbapenemase-producing carbapenem-resistant Enterobacterales (CP-CRE) prevalence, to reduce the number of carbapenem-resistant Enterobacterales (CRE) isolates requiring carbapenemase gene or enzyme identification testing and inform infection prevention and control (IPC) actions.

Carbapenem-resistant organisms (CROs): Gram-negative bacteria, such as Enterobacterales, *Pseudomonas aeruginosa*, and *Acinetobacter baumannii*, that test resistant to at least one carbapenem against which they are not intrinsically resistant.

Carbapenemases: Types of beta (β)-lactamase enzymes that can hydrolyze penicillins, cephalosporins, and carbapenem antibiotics. Bacteria that produce carbapenemases can cause difficult-to-treat infections. Carbapenemase genes, which encode these enzymes, are often carried on mobile genetic elements, such as plasmids, and have the potential for rapid spread in healthcare settings.

Carbapenemase-producing carbapenem-resistant Enterobacterales (CP-CRE): Enterobacterales that test resistant to at least one carbapenem agent and produce or carry genes that encode for at least one carbapenemase. CP-CRE are associated with high levels of antimicrobial resistance and difficult-to-treat infections. For more information about CP-CRE, visit https://www.cdc.gov/hai/organisms/cre/technical-info.html.

Carbapenemase-producing organism (CPOs): Organisms that produce or carry a gene that encodes a carbapenemase.

Colonization screening: The use of laboratory testing to determine if a patient is asymptomatically colonized (i.e., a carrier) with antimicrobial-resistant organisms such as CP-CRE to enact appropriate IPC actions during their care to limit transmission to others.

Confirmed novel or non-targeted carbapenemase: A carbapenemase that has never been detected or is not one of the targeted carbapenemases (*Klebsiella pneumoniae* carbapenemase (KPC), New Delhi metallo-β-lactamase (NDM), Verona Integron-encoded metallo-β-lactamase (VIM), Imipenemase metallo-β-lactamase (IMP), and oxacillinase (OXA)-48-like) and is unusual for the healthcare facility. Identification of a novel carbapenemase requires the use of whole genome sequencing (WGS), and non-targeted carbapenemases may be confirmed by PCR or WGS. The epidemiological understanding of novel carbapenemases and some non-targeted carbapenemases is unclear (e.g., populations at risk, modes of transmission, etc.) and will require Tier 1 containment response.

Contact: For the purposes of this document, refers to a patient who is currently or was previously housed in the same unit in the healthcare facility as the index patient.

Contact Precautions: Contact Precautions are actions intended to prevent transmission of infectious agents, including CP-CRE, that are spread by direct or indirect contact with infected or colonized patients or the patients' environment. A single-patient room is preferred for those who require Contact Precautions. In multi-patient rooms, ≥1-meter spatial separation between beds is advised to reduce the opportunities for inadvertent sharing of items between the infected/colonized patient and other patients. When healthcare workers are caring for patients on Contact Precautions, a gown and gloves should be worn for all interactions involving contact with the patient and the patient's environment. The use of dedicated patient equipment is also recommended; however, when this is not possible, shared equipment should be cleaned and disinfected immediately after each use. High-touch surfaces in rooms or areas housing patients on Contact Precautions should be cleaned and disinfected at least twice daily. Additionally, the transport of patients outside of their room on Contact Precautions should be limited to medically necessary purposes.

Containment response: Activities described in GAIHN-AR Interim Guidance for Containment Activities that are implemented in response to detecting a single antimicrobial-resistant threat. While containment can be used for various antimicrobial-resistant organisms, GAIHN-AR currently focuses on implementing a containment response for CP-CRE containing a novel carbapenemase or a rare targeted or non-targeted carbapenemase.

Health care facility (HCF): In this document, refers to the hospital setting.

Index patient: The initial patient infected or colonized with the Tier 1 or Tier 2 [1] organism that led to the initiation of the containment response. If multiple patients were reported before initiation of the containment response, then the patient with the earliest specimen collection date is considered the index patient.

Molecular/enzymatic carbapenemase identification: Laboratory testing methods such as polymerase chain reaction (PCR) or immunochromatography that aim to identify five specific targeted carbapenemase genes/enzymes: KPC, NDM, VIM, IMP, and OXA-48-like.

Non-targeted carbapenemase: A carbapenemase other than KPC, NDM, IMP, VIM and OXA-48-like. Non-targeted carbapenemase genes may be detected by supplemental PCR, if available, or may require WGS.

Non-Tier 1 or 2: Organisms with targeted carbapenemases and antimicrobial susceptibility patterns that are commonly identified in the HCF and for which containment should *not* be routinely used. This tiered system is described in detail in the document "Global Action in Healthcare Network - Antimicrobial Resistance Module (GAIHN-AR) Interim Guidance for Containment Activities."

Pan-resistant organism: In this guidance, a pan-resistant organism is resistant to all relevant antimicrobials tested at the clinical laboratory that serves the healthcare facility. Relevant antimicrobials for CP-CRE are those that have activity against Enterobacterales and are available for treatment in the healthcare facility. Confirmation of pan-resistance and additional characterization by a reference laboratory is recommended for all potentially pan-resistant organisms.

Prevention activities: Continuous and ongoing activities such as infection prevention and control (IPC) assessments, IPC practice monitoring (auditing), and colonization screening such as admission and routine surveillance screening that are used to limit the transmission of antimicrobial-resistant organisms within a facility and, unlike containment, are not deployed specifically in response to the identification of a patient with CP-CRE.

[1] A tiered system (Tier 1, Tier 2, and Non-Tier 1 or 2) was developed to help facilities prioritize which alerts to consider responding to with containment. This tiered system can be found in the document, "Global Action in Healthcare Network -Antimicrobial Resistance Module (GAIHN-AR) Interim Guidance for Containment Activities. "

Priority organisms: Priority CRE organisms for GAIHN-AR include ***Escherichia coli***, ***Klebsiella oxytoca***, ***Klebsiella pneumoniae***, ***Klebsiella*** (**formerly *Enterobacter***) ***aerogenes***, and ***Enterobacter* spp**. (If species cannot be obtained in some of the isolates, use the genus). HCFs may target additional CROs as desired, according to local epidemiology and resources available.

Routine surveillance screening: Colonization screening performed at some predefined and recurrent frequency (e.g., weekly, every 2 weeks, or as determined by local protocol) on the patients currently located in an HCF unit.

Suspected novel or non-targeted carbapenemase: Isolates that test positive for carbapenemase production using a phenotypic test method (e.g., mCIM) but test negative for ALL targeted carbapenemase genes (including at least KPC, NDM, VIM, IMP, and OXA-48-like) may harbor a novel or non-targeted carbapenemase gene. Novel carbapenemase genes are only detectable through WGS.

Targeted carbapenemases: In this document, the carbapenemases of interest for GAIHN-AR include KPC, NDM, VIM, IMP, and OXA-48-like for which ample epidemiological information is currently known. Targeted carbapenemases may also include others that are of local and/or national importance.

Tier 1: Organisms with a confirmed novel or non-targeted carbapenemase that has never or rarely been identified in the HCF and for which a more extensive investigation is needed to define its epidemiology (e.g., routes of transmission). This tiered system and the recommendations for containment actions for Tier 1 are described in detail in the document "Global Action in Healthcare Network - Antimicrobial Resistance Module (GAIHN-AR) Interim Guidance for Containment Activities."

Tier 2: Organisms with a targeted carbapenemase which is never or rarely detected in the HCF. These "targeted" carbapenemases are KPC, NDM, VIM, IMP, and OXA-48-like. Tier 2 organisms may also include organisms with a targeted carbapenemase, which is commonly detected in an HCF and has or develops pan-resistance. The pan-resistance and targeted carbapenemase combination should never or rarely be detected in the HCF. For example, KPC-producing CRE may be common and would not trigger containment, but if a pan-resistant KPC-producing CRE is uncommonly found in the HCF, it should trigger Tier 2 containment. This tiered system and the recommendations for containment actions for Tier 2 are described in detail in the document, "Global Action in Healthcare Network - Antimicrobial Resistance Module (GAIHN-AR) Interim Guidance for Containment Activities."

Acronyms

Acronym	Definition
AR	Antimicrobial Resistance
AST	Antimicrobial Susceptibility Testing
CDC	U.S. Centers for Disease Control and Prevention
CLSI	Clinical and Laboratories Standards Institute
CP-CRE	Carbapenemase-producing Carbapenem-resistant Enterobacterales
EUCAST	European Committee on Antimicrobial Susceptibility Testing
FDA	U.S. Food and Drug Administration
GAIHN-AR	Global Action in Healthcare Network – Antimicrobial Resistance Module
HCF	Healthcare Facility
ICT	Immunochromatography Test
IFU	Instructions for Use
IMI	Imipenem-hydrolyzing β-lactamase
IMP	Imipenemase metallo-β-lactamase
IPC	Infection Prevention and Control
KPC	*Klebsiella pneumoniae* carbapenemase
NDM	New Delhi metallo-β-lactamase
NMC	Non-metallo-carbapenemase
OXA	Oxacillinase
PCR	Polymerase Chain Reaction
POC	Point-of-contact
RT-PCR	Real-time Polymerase Chain Reaction
TAT	Turnaround Time
VIM	Verona Integron-encoded metallo-β-lactamase
WGS	Whole Genome Sequencing

Introduction

The Global Action in Healthcare Network - Antimicrobial Resistance Module (GAIHN-AR) seeks to detect, prevent, and reduce the spread of highly resistant bacterial organisms in non-US healthcare settings and improve patient safety through real-time communication and coordination of laboratory and infection prevention and control (IPC) activities. One such activity is colonization screening. Colonization screening is an infection prevention method using laboratory testing to identify patients who are colonized with antimicrobial-resistant organisms or resistance mechanisms, but who are not exhibiting signs/symptoms of infection. Identifying asymptomatic carriers allows implementation of IPC measures designed to reduce the spread of antimicrobial-resistant threats in healthcare settings. Colonization screening may take place:

- Upon admission to the healthcare facility (HCF) or to a high-risk unit within the HCF (admission screening)
- During regular unit surveillance of all currently admitted patients (routine surveillance screening)
- As part of containment efforts in response to detection of a specific AR threat (contact screening)

Admission and routine surveillance screening support IPC activities such as placing patients on Contact Precautions and monitoring rates of antimicrobial-resistant organism acquisition. IPC considerations for admission and routine surveillance screening for CROs are described in the document "Global Action in Healthcare Network—Antimicrobial Resistance Module (GAIHN-AR) Interim Guidance for Prevention Activities: Colonization Screening."

Contact screening supports containment response activities, which are performed following the detection of Tier 1 or Tier 2 organisms, as described in the document "Global Action in Healthcare Network-Antimicrobial Resistance Module (GAIHN-AR) Interim Guidance for Containment Activities." That document also contains more specific recommendations regarding indications and use of contact screening for a containment response.

This guidance document identifies testing options and details recommended procedures for specimen handling, results communication, and isolate storage related to colonization screening for both GAIHN-AR infection prevention (admission and routine surveillance) and containment (contact) screening activities.

General Considerations

When using this colonization screening guidance, GAIHN-AR laboratories should consider:

- This document recommends options for laboratory testing methods. Methods used by laboratories are not limited to these options; however, alternative testing methods should identify and characterize CP-CRE with similar turnaround times (TATs) and accuracy to those recommended here, and may require in-house verification or validation[2] prior to use.
- Each Network laboratory should designate a laboratory point of contact (POC) to lead laboratory coordination with other laboratories and IPC teams in their GAIHN-AR referral network. This POC should have expertise in antimicrobial resistance (AR) detection and clinical diagnostics. Up-to-date lab POC contact information must be made available to relevant GAIHN-AR partners.

Note: Use of trade names and commercial sources in this document is for identification only and does not imply endorsement by the U.S. Department of Health and Human Services.

[2] Validations and verifications are processes used to confirm the validity and accuracy of laboratory tests and techniques. To support validations and verifications the following templates are available on the GAIHN-AR External SharePoint Drive: Cepheid Gene Xpert verification, mCIM validation, NG-Test Carba 5 verification, RT-PCR validation. Additionally, well characterized isolates from the CDC & FDA Antimicrobial Resistance Isolate Bank that correspond to the templates are available to GAIHN-AR partners.

Priority Organisms and Targeted Carbapenemases

Priority organisms for GAIHN-AR include carbapenemase-producing carbapenem-resistant Enterobacterales (CP-CRE), specifically ***Escherichia coli***, ***Klebsiella pneumoniae***, ***Klebsiella oxytoca***, ***Klebsiella*** (**formerly *Enterobacter*) *aerogenes***, and ***Enterobacter* spp**. (If species cannot be identified in some of the isolates, categorize by genus.) Carbapenemases targeted for GAIHN-AR detection are KPC, NDM, VIM, IMP, OXA-48-like. However, GAIHN-AR also aims to detect additional non-targeted carbapenemases, with particular focus on suspected and confirmed novel[3] carbapenemases. If a country's priorities include antimicrobial-resistant organisms or carbapenemases other than those targeted by GAIHN-AR, these priorities may be added to their country-specific GAIHN-AR protocols.

GAIHN-AR laboratories will detect the AR bacterial threats listed above from two sources: clinical culture and colonization screening. This guidance focuses on detection of CP-CRE from colonization screening.

Decisions about workflows, methods, and when to perform broad phenotypic carbapenemase production testing and/or carbapenemase identification for laboratory activities should always consider the IPC HCF Team goals for the activity. Please note some key differences in this guidance as compared to the guidance for testing of clinical culture isolates.

In the guidance document, "Global Action in Healthcare Network – Antimicrobial Resistance Module (GAIHN-AR) Interim Laboratory Guidance for Clinical Culture of Carbapenem-resistant Enterobacterales":

- Clinical culture isolates require both broad phenotypic carbapenemase production testing and carbapenemase identification for all targeted carbapenemases to support:
  - Understanding of the carbapenemase epidemiology in the healthcare facility to inform containment Tiers
  - Launching containment response for at least Tier 1 carbapenemases (confirmed novel or non-targeted carbapenemases)

Differently, in this guidance:

- The IPC goals of colonization screening may not require both broad phenotypic carbapenemase production and carbapenemase identification. An exception to this would be contact screening for Tier 1 (confirmed novel or non-targeted carbapenemase) containment response.
- For admission, routine surveillance, and Tier 2 containment response colonization screening activities:
  - Sites may choose to perform either broad phenotypic carbapenemase production testing or carbapenemase identification based on the IPC goals of the activity.
  - For sites that have sufficient resources and choose to perform both broad phenotypic carbapenemase production testing and carbapenemase identification, guidance is included within this document.

For more guidance on IPC goals regarding colonization screening for prevention, refer to, "Global Action in Healthcare Network - Antimicrobial Resistance Module (GAIHN-AR) Interim Guidance for Prevention Activities: Colonization Screening."

[3] Isolates that test positive for carbapenemase production using a phenotypic test method, e.g., mCIM, but test negative for ALL targeted carbapenemases, may harbor a novel or non-targeted carbapenemase gene.

Communication of Alerts and Actions

GAIHN-AR testing results that should trigger immediate review by infection prevention personnel are known as **alerts**. For isolates meeting alert criteria (see Table 1 immediately below), laboratories should immediately notify healthcare facility IPC teams, thereby facilitating immediate IPC action, such as implementation of Contact Precautions and possible initiation of containment activities. For isolates meeting alert criteria, a tiered system (Tier 1, Tier 2, and Non-Tier 1 or 2) was developed to help facilities prioritize which alerts to consider responding to with containment. This tiered system is described in detail in the document, "Global Action in Healthcare Network - Antimicrobial Resistance Module (GAIHN-AR) Interim Guidance for Containment Activities."

Hospitals and reference laboratories may use or adapt their own established data systems to communicate alerts within their hospital and to the national level (if indicated) according to their local protocols. Hospitals or countries that do not have an integrated laboratory and IPC data or communication system in place should work internally and with their implementing partner as needed to create a system for communication of alerts. Ideally, local data systems would automatically notify IPC when testing results (e.g., CP-CRE) meeting alert criteria are entered in a reporting database.

Table 1. Colonization Screening Test Alert Criteria and Actions

Footnotes for this table immediately follow.

Alert Criteria	Inclusion Criteria	Organisms[1]	Actions
Carbapenemase Producing	Positive for carbapenemase production by phenotypic method	At minimum: *E. coli*, *Klebsiella pneumoniae*, *Klebsiella oxytoca*, *Klebsiella aerogenes*, or *Enterobacter* spp.	Within 24 hours: ■ Notify IPC ■ Record date and time of IPC notification If consistent with IPC goals of the colonization screening activity: ■ For contact screening, gene or enzyme testing is required ■ For admission and routine surveillance screening, gene or enzyme testing may be requested

CONTINUED

Alert Criteria	Inclusion Criteria	Organisms[1]	Actions
Targeted[2] carbapenemase gene or enzyme detected (at least: IMP, KPC, NDM, VIM, or OXA-48-like)[3] (Tier 2)	Positive for a targeted carbapenemase gene or enzyme using PCR or Immunochromatography (ICT) tests	If targeted carbapenemase gene or enzyme is identified prior to organism identification, proceed to actions before organism identification results are available. For culture-based testing workflows at minimum: *E. coli*, *Klebsiella pneumoniae*, *Klebsiella oxytoca*, *Klebsiella aerogenes*, *Enterobacter* spp.	Within 24 hours: ■ Notify IPC ■ Record date and time of IPC notification If organism contains targeted carbapenemase that is considered Tier 2 by the healthcare facility: ■ Consult with IPC to determine how to proceed with additional screening. Contact screening may be initiated if capacity is available[4]
Suspected novel or non-targeted carbapenemase[6]	Positive broad phenotypic carbapenemase production test (e.g., mCIM) but negative for ALL targeted carbapenemase genes or enzymes	At minimum: *E. coli*, *Klebsiella pneumoniae*, *Klebsiella oxytoca*, *Klebsiella aerogenes*, *Enterobacter* spp.[5]	Within 24 hours: ■ Notify IPC ■ Record date and time of IPC notification ■ **If resources allow:** Send isolate to country-level reference laboratory or other Network-level laboratory for applicable confirmatory or supplemental testing, including WGS if warranted If laboratory and IPC teams determine there is high concern this isolate represents Tier 1 carbapenemase prior to WGS results: ■ Consult with IPC to determine how to proceed with additional screening. Contact screening is recommended and should be initiated or continued if capacity is available[4]

CONTINUED

Alert Criteria	Inclusion Criteria	Organisms[1]	Actions
Confirmed novel or non-targeted carbapenemase[6] (Tier 1)	Novel or non-targeted carbapenemase confirmed by supplemental PCR or WGS	At minimum: *E. coli*, *Klebsiella pneumoniae*, *Klebsiella oxytoca*, *Klebsiella aerogenes*, *Enterobacter* spp.	Within 24 hours: ■ Notify IPC and all appropriate hospital administration and public health authorities ■ Record date and time of IPC notification ■ Notify CDC and share isolate(s) and WGS data, as allowed by local regulations If organism contains a carbapenemase gene that is defined as Tier 1: ■ Consult with IPC to determine how to proceed with additional screening. Contact screening is recommended or should be continued if capacity is available

[1] GAIHN-AR's activities are currently focused on carbapenemase-producing carbapenem-resistant Enterobacterales (CP-CRE), but a facility may choose to expand alerts to include other carbapenemase-producing organisms. Additionally, depending upon prevalence and resources, some facilities may choose to alert on CRE that either have not yet been tested for carbapenemase production/mechanism or are non-carbapenemase-producing.

[2] Targeted carbapenemase genes/enzymes MUST include KPC, NDM, VIM, IMP, OXA-48-like. May also include other carbapenemases of local and/or national importance.

[3] Facilities may make epidemiology-based decisions to exclude alerts for certain GAIHN-AR targeted carbapenemases detected, depending on the prevalence of those carbapenemases.

[4] For more guidance on the response tiers these alerts refer to, "Global Action in Healthcare Network Antimicrobial Resistance Module (GAIHN-AR) Interim Guidance for Containment Activities".

[5] If AST results are available, consider excluding *Enterobacter* spp. isolates that are carbapenem, cefotaxime, ceftriaxone, and ceftazidime intermediate/resistant but cefepime susceptible. This AST profile is consistent with high levels of AmpC beta-lactamase(s) combined with porin mutation and is associated with false-positive phenotypic carbapenemase production test results.

[6] For admission, routine surveillance, and Tier 2 containment response colonization screening activities, laboratories are not required to perform both broad phenotypic carbapenemase production testing **and** carbapenemase identification. However, suspect and confirmed novel or non-targeted carbapenemase categories are included here to account for any laboratories performing the full testing menu, in which case a suspect or confirmed novel or non-targeted carbapenemase could be detected.

Laboratory Testing Workflows and Methods

This guidance recommends options for culture-based and molecular colonization screening testing methods. Methods used by GAIHN-AR laboratories are not limited to these options; however, alternative testing methods should identify and characterize CP-CRE with similar TATs and accuracy to those recommended here. All methods selected should be properly verified/validated[4] for use in each laboratory. For carbapenemase identification methods, this includes confirmation that regionally circulating variants are detectable using the method of choice. The verification/validation process provides objective evidence that the method will meet the laboratory's acceptance criteria and intended use. Laboratories are responsible for understanding limitations associated with selected test methods and should always refer to current manufacturer instructions for use (IFU) for the most up-to-date information. Deviation from the manufacturer's IFU will require validation, a more comprehensive process than verification.

Recommended testing methods for organism identification, antimicrobial susceptibility testing (AST), broad phenotypic carbapenemase production testing, and carbapenemase identification can be found in the "Global Action in Healthcare Network—Antimicrobial Resistance (GAIHN-AR) Interim Laboratory Guidance for Clinical Culture of Carbapenem-resistant Enterobacterales."

Colonization Screening Workflows and Testing Method Considerations

Colonization screening may be conducted using culture-based (isolate) methods or molecular (testing primary specimen) methods. **Decisions about when to use culture-based or direct molecular methods and what testing to include in a laboratory's colonization screening workflow should be decided in collaboration with IPC to ensure the testing supports the IPC goals of the colonization screening activity and considers cost, TAT, and local CRE/CP-CRE prevalence[5].** For further guidance on IPC goals regarding colonization screening, refer to "Global Action in Healthcare Network—Antimicrobial Resistance Module (GAIHN-AR) Interim Guidance for Prevention Activities: Colonization Screening."

Culture-based methods require culture of the rectal swab, perirectal swab, or other specimen source validated for colonization screening, to detect priority CRE. TAT is typically 48-72 hours from time of collection and costs may be lower than direct molecular methods. Laboratory testing for priority CRE isolates identified from admission or routine surveillance screening for prevention should at minimum include broad phenotypic carbapenemase production or carbapenemase gene or enzyme identification; however, some HCFs may choose to do both. Carbapenemase identification is ideal but not required for admission or routine surveillance screening, and may be performed depending on laboratory capabilities, resources available, and facility IPC goals. However, if performing contact screening for containment, laboratories must have the capacity for carbapenemase identification. **Note that for contact screening involving a suspected novel or non-targeted carbapenemase undetectable by on-site molecular methods, a culture-based test method and laboratory capacity for broad phenotypic carbapenemase production is required.**

Direct molecular methods such as Cepheid GeneXpert® Carba-R test the primary specimen, usually a rectal or perirectal swab extract or enriched broth, to detect and identify the presence of specific carbapenemases. The advantage of molecular methods is the rapid TAT: patients colonized with a targeted carbapenemase can be identified as quickly as an hour after swab collection, allowing IPC activities to rapidly take place. Therefore, during containment responses, a molecular method is encouraged because a rapid TAT can support efforts

[4] Validations and verifications are processes used to confirm the validity and accuracy of laboratory tests and techniques. To support validations and verifications the following templates are available on the GAIHN-AR External SharePoint Drive: Cepheid Gene Xpert verification, mCIM validation, NG-Test Carba 5 verification, RT-PCR validation. Additionally, well characterized isolates from the CDC & FDA Antimicrobial Resistance Isolate Bank that correspond to the templates are available to GAIHN-AR partners.

[5] For further guidance on IPC goals regarding colonization screening refer to, "Global Action in Healthcare Network - Antimicrobial Resistance Module (GAIHN-AR) Interim Guidance for Prevention Activities: Colonization Screening."

to quickly contain spread. If a molecular method is not available at the facility, specimens may be shipped to a designated Network reference laboratory if comparable TAT can be achieved. However, it is important to note that molecular methods cannot identify the specific organism(s) carrying the targeted carbapenemase(s). If a carbapenemase gene is detected during a containment response, then a paired swab should ideally be cultured for positive patients to recover the carbapenemase-producing isolate and characterize the organism containing the gene(s) detected (see section "Direct Molecular Method Suggested Workflow"). The isolate containing the carbapenemase may be a GAIHN-AR non-targeted organism, e.g., *Pseudomonas aeruginosa*, or *Acinetobacter baumannii*. **Note that molecular methods cannot be used for contact screening involving a suspected novel or non-targeted carbapenemase undetectable by molecular methods.**

Culture-based (Isolate) Method Suggested Workflows:

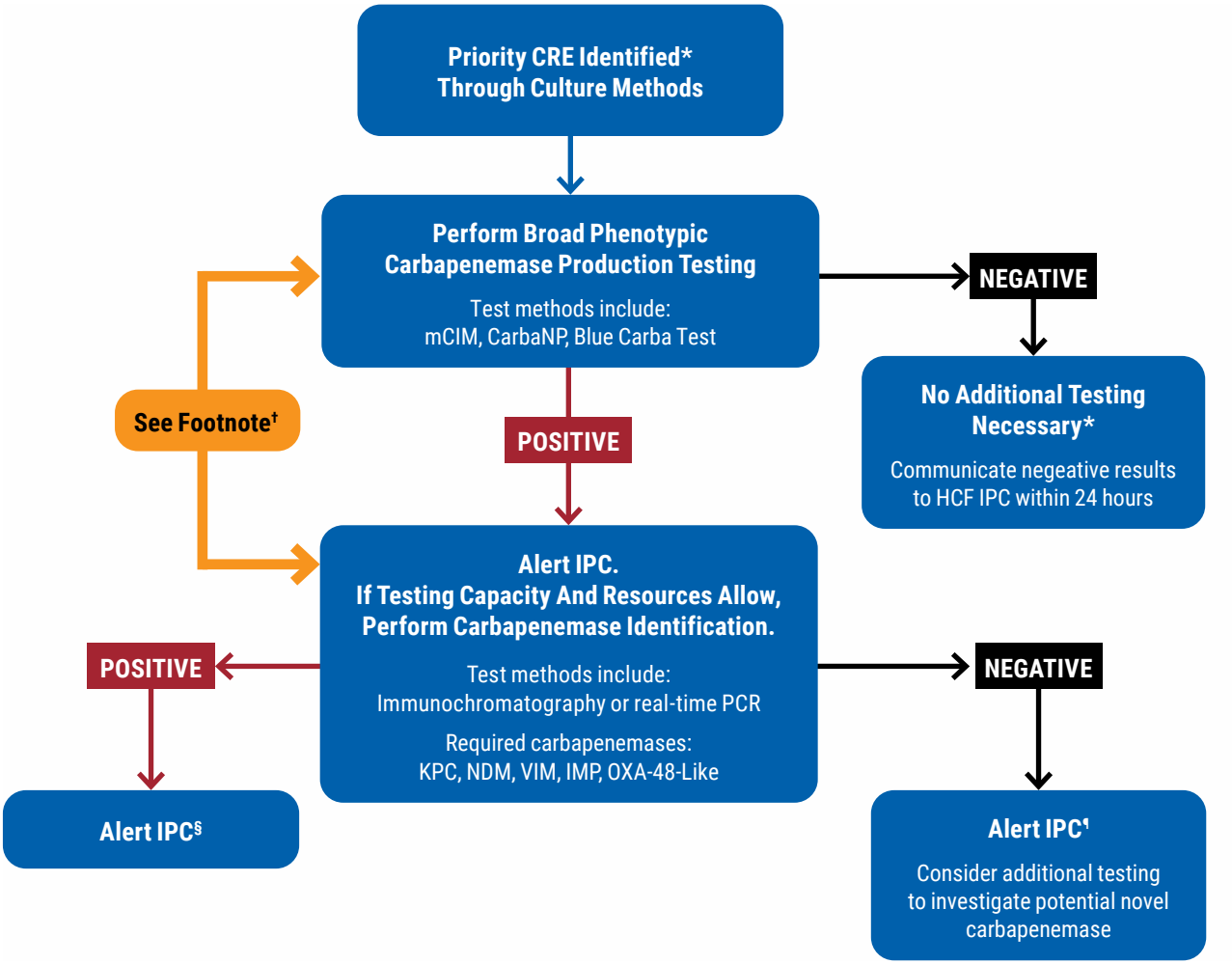
Many culture-based methods for colonization screening are available. GAIHN-AR partners, including CDC, may assist with selection of an appropriate method upon request. Regardless of method selected, workup should follow the workflows suggested below, based on screening type, in Figure 1, Figure 2, and Figure 3.

- Primary culture methods should utilize reagents (e.g., disks, agars, and/or broths) that select for carbapenem-resistant Gram-negative organisms and have been verified/validated[6] by the laboratory to perform as expected. Suspicious colonies should be sub-cultured to non-selective media and definitively identified.
- All CRE isolates should be characterized using phenotypic carbapenemase production testing and/or carbapenemase identification.
  - Carbapenemase identification is required for contact screening during containment.
    - If performing a Tier 1 containment response, carbapenemase identification **and** broad phenotypic carbapenemase production testing must be performed.
  - Carbapenemase identification for admission and routine screening is ideal but not required when carbapenemase identification resources are limited or when it is not necessary for the IPC goals of a facility.

[6] Validations and verifications are processes used to confirm the validity and accuracy of laboratory tests and techniques. To support validations and verifications the following templates are available on the GAIHN-AR External SharePoint Drive: Cepheid GeneXpert verification, mCIM validation, NG-Test Carba 5 verification, RT-PCR validation. Additionally, well characterized isolates from the CDC & FDA Antimicrobial Resistance Isolate Bank that correspond to the templates are available to GAIHN-AR partners.

Figure 1: Suggested Workflow for Culture-based (Isolate) Admission and Routine Surveillance Screening

Footnotes for this flow diagram immediately follow. For accessible explanation with footnotes go to Appendix A.



* Depending upon prevalence and resources, some facilities may choose to alert on CRE that either have not yet been tested for carbapenemase production/mechanism or are carbapenemase-producing negative.

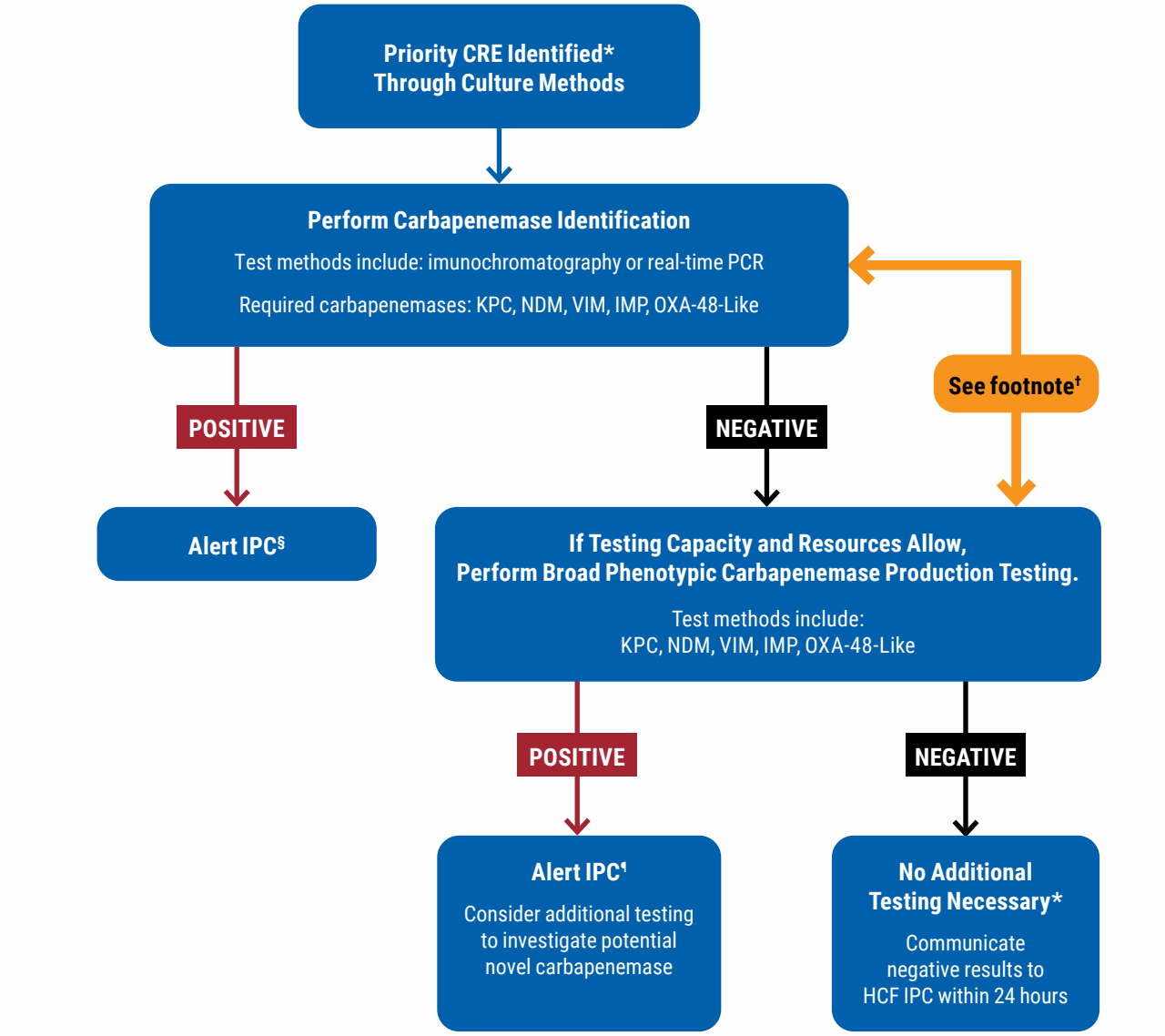
† In settings with low CP-CRE prevalence it may be most cost effective to perform broad phenotypic carbapenemase production testing prior to carbapenemase identification, if performing both, as shown in this workflow. However, in settings with high CP-CRE prevalence, it may be more cost-effective to perform carbapenemase gene identification prior to broad phenotypic carbapenemase production testing if performing both. Also note for admission and routine screening, laboratories are not required to perform broad phenotypic carbapenemase production testing AND carbapenemase identification; however, in this workflow both are included to account for any laboratories performing the full testing menu. If only performing carbapenemase gene or enzyme detection, laboratories may skip broad phenotypic carbapenemase production testing in this workflow.

§ Carbapenemases triggering alerts may vary depending on epidemiology within facility.

¶ When alerting IPC about *Enterobacter* spp. that are positive for carbapenemase production but negative for carbapenemase genes or enzymes, exclude *Enterobacter* spp. that are carbapenem, cefotaxime, ceftriaxone, and ceftazidime intermediate/resistant but cefepime susceptible. This AST profile is consistent with high levels of AmpC β-lactamase(s) combined with porin mutation and has been associated with false-positive phenotypic carbapenemase production test results. Include isolates that are resistant to carbapenem(s) but susceptible to cefotaxime, ceftriaxone, and ceftazidime. This AST profile can be indicative of the presence of a non-metallo-carbapenemase (NMC) or imipenem-hydrolyzing β-lactamase (IMI) carbapenemase.

Figure 2: Suggested Workflow for Culture-based (Isolate) Contact Screening during Tier 2 Containment Response

Footnotes for this flow diagram immediately follow. For accessible explanation with footnotes go to Appendix A.



* Depending upon prevalence and resources, some facilities may choose to alert on CRE that either have not yet been tested for carbapenemase production/mechanism or are carbapenemase-producing negative.

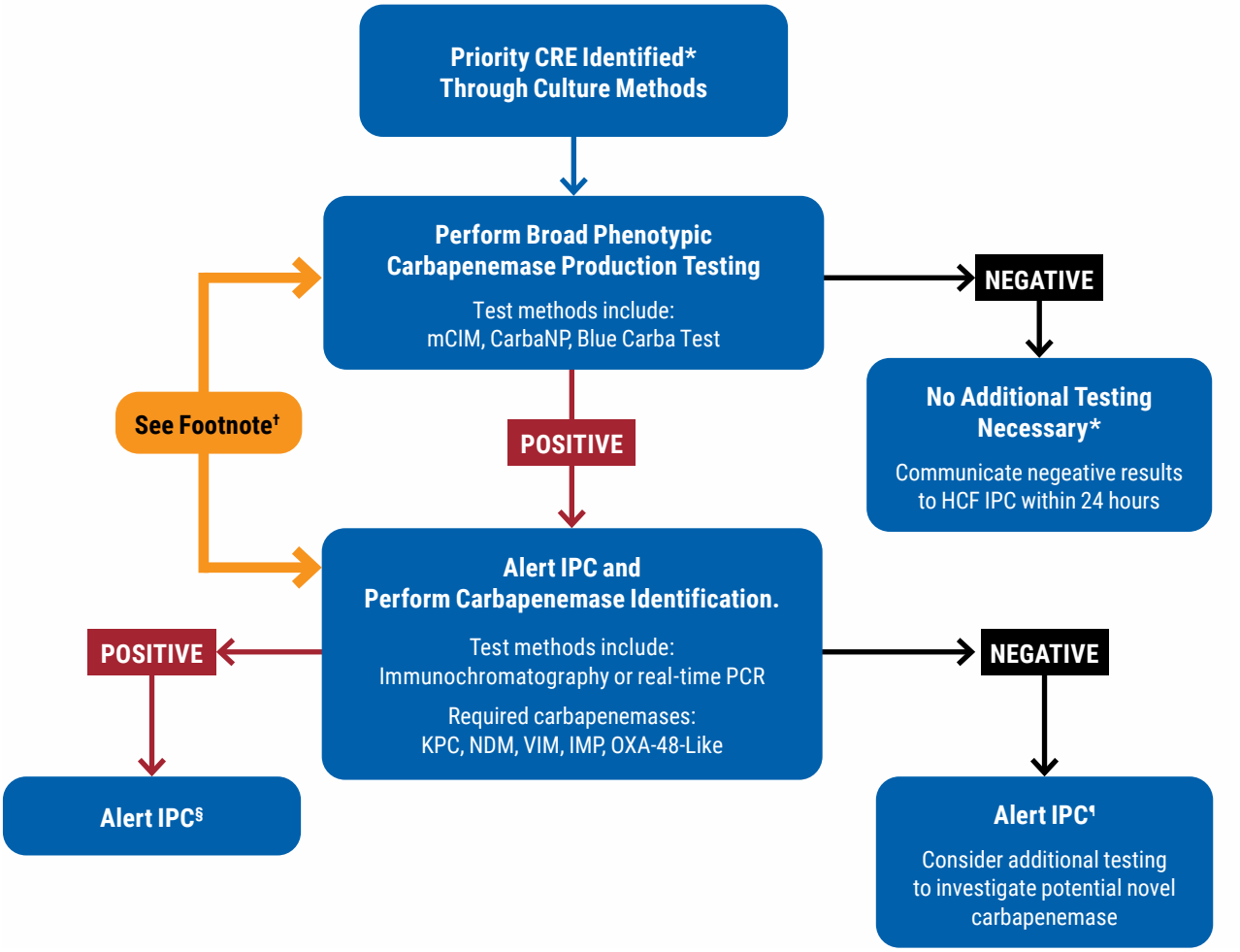
† Laboratories can perform broad phenotypic carbapenemase production prior to carbapenemase identification if that is preferred due to resource constraints or low CP-CRE prevalence. However, when performing contact screening for a Tier 2 response, carbapenemase identification testing is required while but broad phenotypic carbapenemase production testing is optional.

§ Carbapenemases triggering alerts may vary depending on epidemiology within facility.

¶ When alerting IPC about *Enterobacter* spp. that are positive for carbapenemase production but negative for carbapenemase genes or enzymes, exclude *Enterobacter* spp. that are carbapenem, cefotaxime, ceftriaxone, and ceftazidime intermediate/resistant but cefepime susceptible. This AST profile is consistent with high levels of AmpC β-lactamase(s) combined with porin mutation and has been associated with false-positive phenotypic carbapenemase production test results. Include isolates that are resistant to carbapenem(s) but susceptible to cefotaxime, ceftriaxone, and ceftazidime. This AST profile can be indicative of the presence of a NMC or IMI carbapenemase.

Figure 3: Suggested Workflow for Culture-based (Isolate) Contact Screening during Tier 1 Containment Response

Footnotes for this flow diagram immediately follow. For accessible explanation with footnotes go to Appendix A.



* Depending upon prevalence and resources, some facilities may choose to alert on CRE that either have not yet been tested for carbapenemase production/mechanism or are carbapenemase-producing negative.

† In settings with low CP-CRE prevalence it may be most cost effective to perform broad phenotypic carbapenemase production testing prior to carbapenemase identification if performing both, as shown in this workflow. However, in settings with high CP-CRE prevalence, it may be more cost-effective to perform carbapenemase identification prior to broad phenotypic carbapenemase production testing if performing both. If performing contact screening for a Tier 1 response, broad carbapenemase production testing AND carbapenemase identification are required.

§ Carbapenemases triggering alerts may vary depending on epidemiology within facility.

¶ When alerting IPC about *Enterobacter* spp. that are positive for carbapenemase-production but negative for carbapenemase genes or enzymes, exclude *Enterobacter* spp. that are carbapenem, cefotaxime, ceftriaxone, and ceftazidime intermediate/resistant but cefepime susceptible. This AST profile is consistent with high levels of AmpC β-lactamase(s) combined with porin mutation and has been associated with false-positive phenotypic carbapenemase production test results. Include isolates that are resistant to carbapenem(s) but susceptible to cefotaxime, ceftriaxone, and ceftazidime. This AST profile can be indicative of the presence of a NMC or IMI carbapenemase.

Direct (Molecular) Method Suggested Workflow:

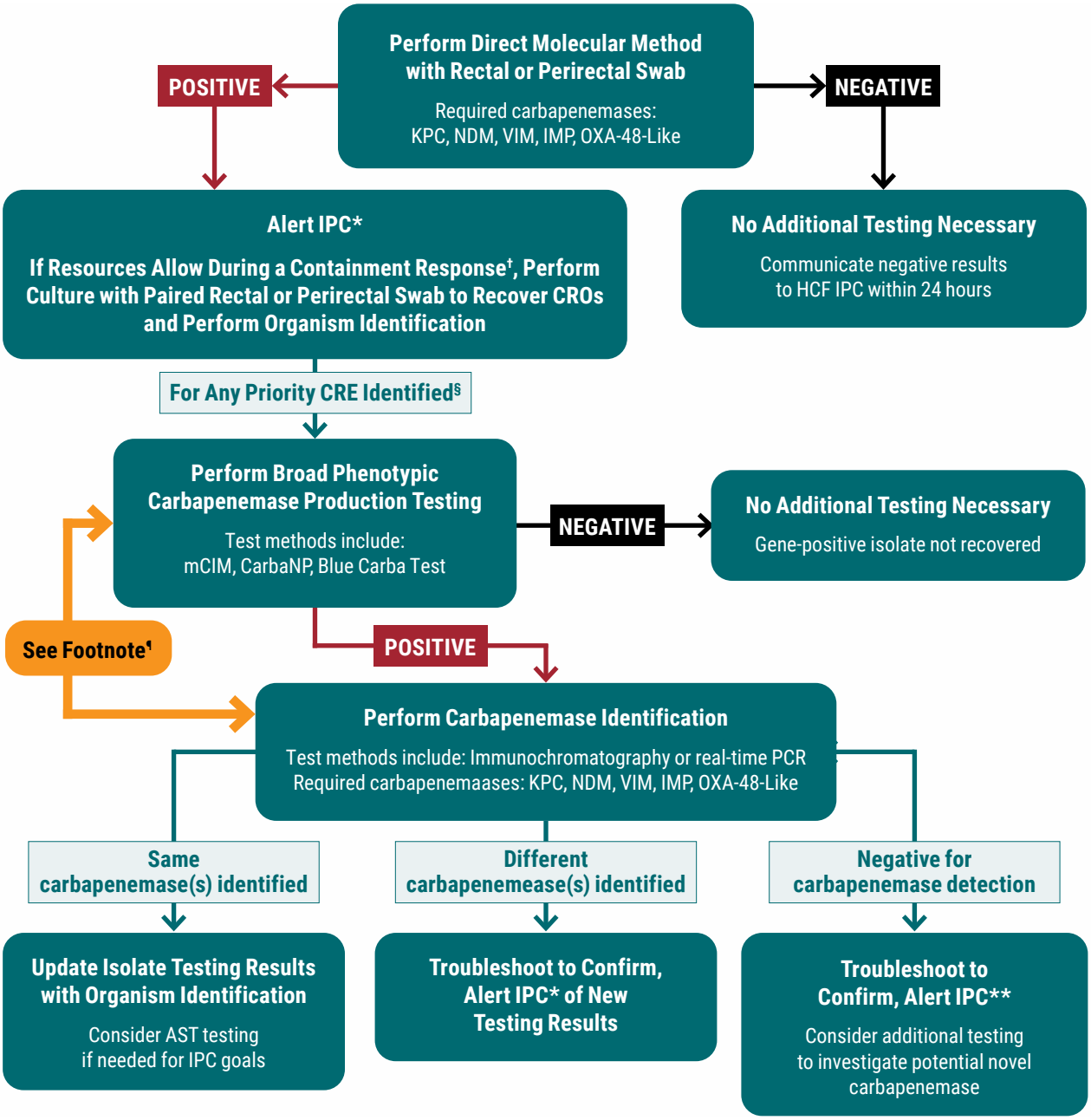
Direct molecular methods for colonization screening, such as Cepheid GeneXpert® Carba-R or BD Max™, are used for detection of carbapenemase genes directly from validated specimens, like rectal or perirectal swabs. Refer to the direct method workflow described in Figure 4.

- Molecular methods cannot identify the genus or species of the organism(s) containing the carbapenemase gene(s). Therefore, when using a molecular method for colonization screening, two rectal or perirectal swabs must be collected so that the second paired swab is available for culture to recover, identify, and characterize the organism(s) carrying the carbapenemase gene(s) detected using molecular methods.
- If using direct molecular method in a containment response ensure the gene or variant identified through culture-based characterization (i.e., ICT) is detectable using the direct molecular method (i.e., Cepheid or BD Max), or if detectability is unknown, confer with implementing partner or CDC.
- Culture of all carbapenemase-positive swabs is preferable during a containment response[7]. If a laboratory lacks the resources to culture all positive swabs, then swabs should be cultured when knowing the organism may influence the IPC response. For example, when:
  - The swab is positive for a gene that differs from the index patient to determine if a new containment response should be initiated. Exceptions may be made for genes considered endemic in the HCF.
  - Requested by IPC due to ongoing transmission despite increased IPC efforts.
- Characterization of isolates cultured from direct molecular method-positive swabs should include organism identification and confirmatory carbapenemase identification using molecular or ICT methods for all carbapenem-resistant organisms. Consider characterization of isolates with AST if needed for IPC or epidemiological goals. This may include non-priority organisms, such as *Pseudomonas aeruginosa* and *Acinetobacter baumanni*i.
- Considerations for Cepheid GeneXpert® Carba-R:
  - Genes detectable by the Cepheid GeneXpert® Carba-R assay include bla_{KPC}, bla_{NDM}, $bla_{OXA\text{-}48\text{-}like}$, bla_{VIM}, and bla_{IMP}.
    - Note: Cepheid Xpert® Carba-R does not detect all bla_{IMP} variants including IMP-7, IMP-13, or IMP-14 gene sequences. Upon request, CDC can share its data on bla_{IMP} variant detection by Cepheid.
- Considerations for BD Max™ CPO assay:
  - Genes detectable by the BD Max™ CPO assay include bla_{KPC}, bla_{NDM}, $bla_{OXA\text{-}48\text{-}like}$, bla_{VIM}, and bla_{IMP}.
  - As of May 2024, the BD Max™ CPO assay does **not** differentiate between bla_{VIM} and bla_{IMP} genes. For swabs that test positive for bla_{VIM}/bla_{IMP}, it is required that specimens be cultured to recover, identify, and characterize the bla_{VIM}/bla_{IMP} isolate(s) and differentiate between bla_{VIM} and bla_{IMP} genes resulted on the machine using an alternative carbapenemase gene or enzyme identification method. Please consider the additional time and resources necessary to perform this differentiation if using the BD Max™ CPO assay.

[7] If the gene or variant identified in the index case is not detectable by the direct molecular method in use (i.e., included among those reported as detectable *in vitro*), or if detectability is unknown, the use of a direct molecular method is not recommended.

Figure 4: Suggested Workflow for Direct (Molecular) Method Testing

Footnotes for this flow diagram immediately follow. For accessible explanation with footnotes go to Appendix A.



* Carbapenemases triggering alerts may vary depending on epidemiology within facility.

† Note that direct molecular methods **cannot** be used for contact screening or a containment response involving a suspected novel or non-targeted carbapenemase undetectable by molecular methods.

§ For GAIHN-AR, culture and further characterization is requested for priority organisms only. However, organisms recovered may include non-priority organisms such as *Pseudomonas aeruginosa* and *Acinetobacter baumannii*. Depending upon prevalence and resources, facilities may choose to perform further characterization of non-priority carbapenem-resistant organisms.

¶ Performing contact screening for a Tier 2 response, carbapenemase identification testing is required while broad phenotypic carbapenemase production testing is optional. Laboratories can perform broad phenotypic carbapenemase production prior to carbapenemase identification if that is preferred due to resources or CP-CRE prevalence. If only performing carbapenemase identification, laboratories may skip broad phenotypic carbapenemase production testing in this workflow.

** When alerting IPC about *Enterobacter* spp. that are positive for carbapenemase-production but negative for carbapenemase genes or enzymes, exclude *Enterobacter* spp. that are carbapenem, cefotaxime, ceftriaxone, and ceftazidime intermediate/resistant but cefepime susceptible. This AST profile is consistent with high levels of AmpC β-lactamase(s) combined with porin mutation and has been associated with false-positive phenotypic carbapenemase production test results. Include isolates that are resistant to carbapenem(s) but susceptible to cefotaxime, ceftriaxone, and ceftazidime. This AST profile can be indicative of the presence of a NMC or IMI carbapenemase.

Specimen Collection and Transport

To select the most appropriate test method and workflow and provide correct guidance around the proper timing of collection and collection device, it is important for the laboratory to know whether specimens were collected for admission screening, routine surveillance screening, or contact screening. Prior to initiating specimen collection for colonization screening, IPC teams should consult with the clinical laboratory to determine if testing can be performed locally or if assistance is needed from a supporting GAIHN-AR reference laboratory (e.g., due to insufficient human or material resources at the clinical laboratory).

It is important to confirm in advance which laboratory will perform testing to ensure:

1. Specimen collection devices are compatible with the testing method used by that laboratory
2. The testing method is appropriate for the specific organism, carbapenemase, or phenotype targeted
3. To arrange for timely specimen transport, if needed, and testing

Once the testing laboratory and proper specimen collection devices are confirmed, healthcare facilities may collect rectal swabs, perirectal swabs, or another specimen source validated for admission, routine surveillance, or in the event of a containment response, contact screening.

Testing should be initiated within one day of receiving specimens. Testing results meeting alert criteria (see "Communication of Alerts and Actions" section) should be reported back to the submitting healthcare facility within 24 hours of obtaining test results.

Technical Notes:

- Rectal swabs should be collected by trained clinical staff following established protocols. Testing laboratories are responsible for providing clinical staff with the appropriate type of swabs for the test method to be used, clear guidance around appropriate specimen collection, labeling, handling, and storage, and timing requirements from specimen collection to laboratory submission. If the specimen needs to be shipped, laboratories should provide clear guidance around specimen transport, storage requirements, and shipping instructions.
- For appropriate communication with IPC, it is important for the laboratory to record whether specimens were collected for admission screening, routine surveillance screening, or contact screening.
- When using the Cepheid GeneXpert® Carba-R assay, use of the manufacturer-validated Cepheid dual-swab collection device (Cepheid part number 900-0370) is strongly recommended. Other swabs may not be compatible with the Carba-R assay and require validation to establish performance characteristics prior to use.

Recording Laboratory Results

Laboratories should record testing results for all priority CRE isolates tested for GAIHN-AR, including both CP-CRE and non-CP-CRE. Ideally, laboratories will incorporate all core and supplemental GAIHN-AR test results into their existing electronic laboratory information system used for diagnostic clinical culture or referral isolate workup. Doing so will minimize duplicate data entry, enable real-time data use, and facilitate future data extraction, analysis, and reporting. If adapting the laboratory information system to accommodate GAIHN-AR test methods is not possible, an alternative electronic system that creates an isolate-level line list including all core and supplemental test results is strongly recommended. If additional antimicrobials are tested, laboratories should also include these results when communicating testing results to the submitter and to CDC.

Reporting Laboratory Data

As a global network that aims to be on the forefront of detecting emerging AR in healthcare, sharing and analysis of isolate/specimen-level data, WGS data, and isolates is essential.

CDC requests that sites share:

- Isolates and WGS data from Tier 1 responses. Select isolates from Tier 2 responses may also be requested. We recommend sharing WGS data via an accessible repository (e.g., the GAIHN-AR BioProject: ID 962934—BioProject—NCBI (nih.gov), a component of the CDC International HAI/AR Seq NCBI Umbrella Project).
- De-identified isolate-level data for all GAIHN-AR CRE priority organisms tested, at least every six months, including results generated by:
  - Organism identification
  - AST
  - Phenotypic carbapenemase production testing
  - Carbapenemase identification
  - WGS, if performed

CDC recognizes that some sites may have barriers to sharing isolates and certain isolate-level data. CDC will work with partners and countries to establish any necessary data use agreements and to adapt processes as is feasible to help them meet these requirements.

GAIHN-AR sites will also be required to report GAIHN-AR indicators to implementing partners and CDC every 6 months. Some of the indicator data requested relies on summarized laboratory testing results. Indicator data will be used to:

- Monitor progress and impact of GAIHN-AR activities over time
- Support quality improvement efforts for laboratory, IPC, and communication
- Identify and advocate for Network resources
- Provide feedback and recommendation reports to each site

More information about requirements and use for data and isolates shared to CDC can be found in the document, "Global Action in Healthcare Network—Antimicrobial Resistance Module (GAIHN-AR) Core Principles."

Data Retention and Isolate Storage

Laboratories should maintain a database of test results and retain the results for a minimum of 2 years or according to local or national regulations, whichever is longer.

All CP-CRE isolates should be retained by either the clinical or reference laboratory at -70°C for a minimum of 2 years. If -70°C storage capacity is limited, prioritize retention as follows:

1. Isolates with a confirmed novel or non-targeted carbapenemase
2. CP-CRE that are not susceptible to the newest[8] antimicrobials for treating infections caused by CP-CRE
3. Pan-resistant CP-CRE
4. Isolates with >1 targeted carbapenemase
5. Other carbapenemase-producing/-positive isolates. Additional retention criteria based on specific genes and/or organism-gene combinations will depend on local and national epidemiology. Contact CDC for assistance determining retention priorities if needed.

[8] Will vary by country based on availability; examples include but are not limited to: ceftazidime-avibactam, ceftolozane-tazobactam, meropenem-vaborbactam, imipenem-relebactam, aztreonam-avibactam, cefiderocol, etc.

If sending an isolate to their reference laboratory, clinical laboratories should store CP-CRE isolates at -20°C or -70°C at least until the reference lab has completed testing, resolved any discrepancies, and confirmed isolates will be retained for a minimum of 2 years.

Laboratories performing WGS should back-up WGS data locally and deposit WGS data meeting the required quality standards in a recommended accessible repository (e.g., the GAIHN-AR BioProject: ID 962934—BioProject—NCBI (nih.gov), a component of the CDC International HAI/AR Seq NCBI Umbrella Project), with minimum levels of metadata to protect patient privacy.

Laboratory Quality Considerations

- **Quality Control:** Quality control for organism identification, AST, phenotypic carbapenemase production testing, and molecular or enzymatic carbapenemase identification, and WGS should be performed according to manufacturer recommendations or in compliance with national regulatory standards. Generated WGS data should meet quality standards per CDC guidance for HAI/AR isolates.
- **Assay Verification or Validation:** Upon request, CDC can assist laboratories with implementation of select testing methods by providing isolates from the CDC & FDA Antimicrobial Resistance Isolate Bank, verification and validation templates, and expertise in methods and results interpretation.
- **Proficiency Testing:** All Network laboratories should participate in routine surveillance bacteriology PT for organism identification, AST, phenotypic carbapenemase production testing, and molecular or enzymatic carbapenemase identification, as applicable to their specific test menu. Laboratories should work with their implementing partner and other in-country or Network laboratories as needed to create a proficiency testing plan.
- **External Quality Assessment:** GAIHN-AR will support EQA for Cepheid GeneXpert® Carba-R for Network reference laboratories.
- **Standard Operating Procedures:** Laboratories should develop and implement standard operating procedures for all sample collections, processing, test methods, equipment use, and result interpretation, recording, and reporting.
- **Training and Competency Assessment:** Laboratory personnel should be trained on all laboratory methods they perform. Laboratories should conduct annual or biannual competency assessments.
- **Document and Record Quality Control Data:** Laboratories should record quality control data such as equipment maintenance performed, equipment temperature monitoring, personnel training and competencies completed. This documentation should be kept according to the laboratory policy.

References

1. CLSI. *Performance Standards for Antimicrobial Susceptibility Testing*. 33rd ed. CLSI supplement M100. Clinical and Laboratory Standards Institute; 2023.
2. CLSI. *CLSI Subcommittee on Antimicrobial Susceptibility Testing CLSI AST News Update*. Vol 2, Issue 1. Clinical and Laboratory Standards Institute; Jun 2017.
3. EUCAST. *EUCAST guidelines for detection of resistance mechanisms and specific resistances of clinical and/or epidemiological importance*. Version 2.0. European Committee on Antimicrobial Susceptibility testing. Jul 2017.
4. Cepheid. *GeneXpert Carba-R Instructions for Use*. Rev G. July 2020.
5. BD. *BD MaxTM CPO Instructions for Use*. Revision 02. July 2022.

Appendix A: Explanations for Accessibility for Figures 1–4

Footnotes for each figure discretion immediately follow the figure descriptions.

Figure 1. Suggested Workflow for Culture-based (Isolate) Admission and Routine Surveillance Screening:

A flow chart describing workflow suggestions for admission and routine surveillance screening with priority CRE identified through culture-based methods. If a priority CRE is identified* through culture methods, perform broad phenotypic carbapenemase production testing using mCIM, CarbaNP, or Blue Carba test†. If results are negative, no additional testing is necessary; communicate negative results to HCF IPC within 24 hours*. If results are positive, alert IPC and if testing capacity and resources allow, perform carbapenemase identification using immunochromatography or real-time PCR. If KPC, NDM, VIM, IMP, or OXA-48-like carbapenemases are identified, alert IPC . If these carbapenemases are not identified, alert IPC¶ and consider additional testing needed to investigate a potential novel carbapenemase. (Return to Figure 1)

* Depending upon prevalence and resources, some facilities may choose to alert on CRE that either have not yet been tested for carbapenemase production/mechanism or are carbapenemase-producing negative.

† In settings with low CP-CRE prevalence it may be most cost effective to perform broad phenotypic carbapenemase production testing prior to carbapenemase identification, if performing both, as shown in this workflow. However, in settings with high CP-CRE prevalence, it may be more cost-effective to perform carbapenemase gene identification prior to broad phenotypic carbapenemase production testing if performing both. Also note for admission and routine screening, laboratories are not required to perform broad phenotypic carbapenemase production testing AND carbapenemase identification; however, in this workflow both are included to account for any laboratories performing the full testing menu. If only performing carbapenemase gene or enzyme detection, laboratories may skip broad phenotypic carbapenemase production testing in this workflow.

§ Carbapenemases triggering alerts may vary depending on epidemiology within facility.

¶ When alerting IPC about *Enterobacter* spp. that is positive for carbapenemase production but negative for carbapenemase genes or enzymes, exclude *Enterobacter* spp. that are carbapenem, cefotaxime, ceftriaxone, and ceftazidime intermediate/resistant but cefepime susceptible. This AST profile is consistent with high levels of AmpC β-lactamase(s) combined with porin mutation and has been associated with false-positive phenotypic carbapenemase production test results. Include isolates that are resistant to carbapenem(s) but susceptible to cefotaxime, ceftriaxone, and ceftazidime. This AST profile can be indicative of the presence of a NMC or IMI carbapenemase.

Figure 2. Suggested Workflow for Culture-based (Isolate) Contact Screening during Tier 2 Containment Response:

A flow chart describing workflow suggestions for contact screening during a Tier 2 containment response with priority CRE identified through culture-based methods. If priority CRE is identified* through culture methods, perform carbapenemase identification using immunochromatography or real-time PCR†. If KPC, NDM, VIM, IMP, or OXA-48-like carbapenemases are identified, alert IPC§. If these carbapenemases are not identified, and if testing capacity and resources allow, perform broad phenotypic carbapenemase production testing using mCIM, CarbaNP, or Blue Carba test. If results are positive, alert IPC¶ and consider additional testing needed to investigate a potential novel carbapenemase. If results are negative, no additional testing is necessary; communicate negative results to HCF IPC within 24 hours. (Return to Figure 2)

* Depending upon prevalence and resources, some facilities may choose to alert on CRE that either have not yet been tested for carbapenemase production/mechanism or are carbapenemase-producing negative.

† Laboratories can perform broad phenotypic carbapenemase production prior to carbapenemase identification if that is preferred due to resource constraints or low CP-CRE prevalence. However, when performing contact screening for a Tier 2 response, carbapenemase identification testing is required while but broad phenotypic carbapenemase production testing is optional.

§ Carbapenemases triggering alerts may vary depending on epidemiology within facility.

¶ When alerting IPC about *Enterobacter* spp. that is positive for carbapenemase production but negative for carbapenemase genes or enzymes, exclude *Enterobacter* spp. that are carbapenem, cefotaxime, ceftriaxone, and ceftazidime intermediate/resistant but cefepime susceptible. This AST profile is consistent with high levels of AmpC β-lactamase(s) combined with porin mutation and has been associated with false-positive phenotypic carbapenemase production test results. Include isolates that are resistant to carbapenem(s) but susceptible to cefotaxime, ceftriaxone, and ceftazidime. This AST profile can be indicative of the presence of a NMC or IMI carbapenemase.

Figure 3. Suggested Workflow for Culture-based (Isolate) Contact Screening during Tier 1 Containment Response:

A flow chart describing workflow suggestions for contact screening during Tier 1 containment response with priority CRE identified through culture-based methods. If priority CRE is identified* through culture methods, perform broad phenotypic carbapenemase production testing using mCIM, CarbaNP, or Blue Carba test†. If results are negative, no additional testing is necessary*; communicate negative results to HCF IPC within 24 hours. If results are positive, alert IPC and perform carbapenemase identification using immunochromatography or real-time PCR. If KPC, NDM, VIM, IMP, or OXA-48-like carbapenemases are identified, alert IPC§. If these carbapenemases are not identified, alert IPC¶ and consider additional testing needed to investigate a potential novel carbapenemase. (Return to Figure 3)

* Depending upon prevalence and resources, some facilities may choose to alert on CRE that either have not yet been tested for carbapenemase production/mechanism or are carbapenemase-producing negative.

† In settings with low CP-CRE prevalence it may be most cost effective to perform broad phenotypic carbapenemase production testing prior to carbapenemase identification if performing both, as shown in this workflow. However, in settings with high CP-CRE prevalence, it may be more cost-effective to perform carbapenemase identification prior to broad phenotypic carbapenemase production testing if performing both. If performing contact screening for a Tier 1 response, broad carbapenemase production testing AND carbapenemase identification are required.

§ Carbapenemases triggering alerts may vary depending on epidemiology within facility.

¶ When alerting IPC about *Enterobacter* spp. that is positive for carbapenemase-production but negative for carbapenemase genes or enzymes, exclude *Enterobacter* spp. that are carbapenem, cefotaxime, ceftriaxone, and ceftazidime intermediate/resistant but cefepime susceptible. This AST profile is consistent with high levels of AmpC β-lactamase(s) combined with porin mutation and has been associated with false-positive phenotypic carbapenemase production test results. Include isolates that are resistant to carbapenem(s) but susceptible to cefotaxime, ceftriaxone, and ceftazidime. This AST profile can be indicative of the presence of a NMC or IMI carbapenemase.

Figure 4. Suggested Workflow for Direct (Molecular) Testing:

A flow chart describing workflow suggestions for identifying priority CRE through direct molecular testing with rectal or perirectal swabs. Perform direct (molecular) method testing using a rectal or perirectal swab. If results are negative, no additional testing is necessary; communicate negative results to HCF IPC within 24 hours. If KPC, NDM, VIM, IMP, or OXA-48-like carbapenemases are identified, alert IPC*. If resources allow during a containment response†, perform culture with paired rectal or perirectal swab to recover CROs and perform organism identification. For any priority CRE identified§, perform broad phenotypic carbapenemase production testing using mCIM, CarbaNP, or Blue Carba test¶. If results are negative, no additional testing is necessary; the gene-positive isolate was not recovered. If results are positive, perform carbapenemase identification using immunochromatography or real-time PCR. If the same carbapenemases are identified, update isolate testing results with organism identification and consider AST testing if needed for IPC goals. If different carbapenemases are identified, troubleshoot to confirm, and alert IPC* of new testing results. If carbapenemase detection is negative, troubleshoot to confirm and alert IPC** and consider additional testing to investigate potential novel carbapenemase. (Return to Figure 4)

* Carbapenemases triggering alerts may vary depending on epidemiology within facility.

† Note that direct molecular methods **cannot** be used for contact screening or a containment response involving a suspected novel or non-targeted carbapenemase undetectable by molecular methods.

§ For GAIHN-AR, culture and further characterization is requested for priority organisms only. However, organisms recovered may include non-priority organisms such as Pseudomonas aeruginosa and Acinetobacter baumannii. Depending upon prevalence and resources, facilities may choose to perform further characterization of non-priority carbapenem-resistant organisms.

¶ Performing contact screening for a Tier 2 response, carbapenemase identification testing is required while broad phenotypic carbapenemase production testing is optional. Laboratories can perform broad phenotypic carbapenemase production prior to carbapenemase identification if that is preferred due to resources or CP-CRE prevalence. If only performing carbapenemase identification, laboratories may skip broad phenotypic carbapenemase production testing in this workflow.

** When alerting IPC about *Enterobacter* spp. that is positive for carbapenemase-production but negative for carbapenemase genes or enzymes, exclude *Enterobacter* spp. that are carbapenem, cefotaxime, ceftriaxone, and ceftazidime intermediate/resistant but cefepime susceptible. This AST profile is consistent with high levels of AmpC β-lactamase(s) combined with porin mutation and has been associated with false-positive phenotypic carbapenemase production test results. Include isolates that are resistant to carbapenem(s) but susceptible to cefotaxime, ceftriaxone, and ceftazidime. This AST profile can be indicative of the presence of NMC or IMI carbapenemase.