Replacing the Carbapenem-resistant Enterobacteriaceae (Carbapenemase-producing) (CP-CRE) Condition with Carbapenemase-producing Organisms (CPO) in the Laboratory Reportable Conditions List[1] (Title 17, Section 2505, Subsection (e)(2)), effective September 1, 2022

Frequently Asked Questions (FAQ)

What are carbapenemase-producing organisms (CPO)?

- CPO are bacteria that produce carbapenemase enzymes (e.g., KPC, NDM, OXA-48, IMP, VIM).[2] These enzymes inactivate carbapenem antibiotics, such as meropenem. CPO include *Acinetobacter baumannii, Pseudomonas aeruginosa,* and bacteria in the Enterobacterales order such as *Escherichia coli (E. coli)* and *Citrobacter, Enterobacter,* and *Klebsiella* species (spp.).

Why make CPO reportable?

- Since 2019, when carbapenemase-producing *Enterobacter* and *Klebsiella* spp. and *E. coli* became reportable as CP-CRE, other Enterobacterales, *Acinetobacter,* and *Pseudomonas* spp. have become epidemiologically important, and CPO are now nationally notifiable.[3]
- Carbapenemase genes can be transmitted within and between bacterial species on mobile genetic elements, which can lead to rapid spread of CPO in healthcare settings. CPO can be resistant to all classes of antibiotics, causing infections that are difficult to treat and associated with high mortality rates. The Centers for Disease Control and Prevention (CDC) have designated these pathogens an urgent threat to public health.[4]
- Reporting CPO to public health can facilitate timely public health response and epidemiologic surveillance for these organisms.

What laboratory tests can detect carbapenemases?

- Phenotypic tests detect carbapenemase production by bacteria. Molecular tests, including whole genome sequencing (WGS), identify the specific carbapenemase gene, such as bla_{KPC} or bla_{NDM}.[5] Laboratories may perform phenotypic, molecular, or a combination of tests to identify CPO.

Who will report CPO?

- CPO is a **laboratory-reportable condition**, with no clinical criteria included. Laboratories must report via electronic laboratory reporting to the California Reportable Disease Information Exchange (CalREDIE).[1]
- Healthcare providers are not required to report CPO cases, but are still responsible for reporting any outbreaks and unusual infectious disease occurrences.[6] Healthcare providers may be contacted by public health staff during an investigation.

What is reportable?

- Per the updated case definition,[3] laboratories should report the following results for any specimen:
    - Positive phenotypic test (see Table 1) result for carbapenemase production, with or without identification of a specific carbapenemase type
    - Positive molecular test (see Table 1) result detecting a carbapenemase gene[5]
    - Detection of a carbapenemase gene[4] by next-generation sequencing (e.g., whole genome sequencing)
    - Specimen positive for a carbapenemase gene without bacterial species identification, (e.g., Xpert Carba-R rectal swab, other culture-independent diagnostic test)

Table 1. Examples of phenotypic and molecular (genotypic) methods for carbapenemase testing[7]

Phenotypic tests	Molecular tests
Carba NP	BD MAX™ Check-Points CPO
Carbapenem inactivation method (CIM)	BioFire® FilmArray® Blood Culture Identification 2
EDTA-modified CIM (eCIM)	Nucleic acid amplification test (NAAT) (e.g., polymerase chain reaction (PCR))
NG-Test® Carba 5	
Immunochromatography test (ICT)	Streck ARM-D® Kit, β-Lactamase
Metallo-β-lactamase test (e.g., E-test)	Verigene® Gram-Negative Blood Culture Nucleic Acid Test (BC-GN)
Modified carbapenem inactivation method (mCIM)	Whole genome sequencing (WGS)
Modified Hodge test (MHT)[8]	Xpert® Carba-R

Laboratories should wait until all tests (i.e., antimicrobial susceptibility, phenotypic and molecular carbapenemase) are resulted before submitting a report.

How is CPO different from the original CP-CRE condition?

- The CPO condition differs from the original CP-CRE condition in three main ways:
  1. **Expands** reporting from carbapenemase-producing *E. coli, Enterobacter* and *Klebsiella* spp. to all bacteria in the Enterobacterales order, including *Citrobacter, Providencia,* and *Serratia* spp., and other epidemiologically important organisms such as *A. baumannii* and *P. aeruginosa*
  2. **Removes** the requirement to report antimicrobial susceptibility testing (AST) results
  3. **Removes** the requirement to report carbapenem-resistant organisms in isolates for which carbapenemase testing was not obtained

How does this new reporting requirement affect existing local health department carbapenem-resistant organism (including CRE) reporting requirements?

- The updated Title 17 reporting requirements do not change existing local health department reporting requirements (e.g., some jurisdictions might require isolate submission or reporting of all CRE cases). Per California state regulations, CPO is a laboratory-reportable condition. For further clarification, contact the relevant local health department.

Why is carbapenemase testing important?

- Carbapenemase testing results can help guide treatment options.
  - Updated antimicrobial prescribing guidelines recommend different agents for infections caused by carbapenem-resistant organisms depending on their carbapenemase type.[9] Carbapenemase testing can be particularly important for isolates identified from sterile sites (e.g., bloodstream), indicating infections that require antimicrobial therapy.
  - Understanding the local epidemiology of CPO can help guide empiric antimicrobial treatment guidelines. For example, empiric antimicrobial choices might differ in a region or facility where NDM-producing organisms are more common than KPC-producing organisms.
- Carbapenemase testing can help identify patients with CPO and enable implementation of appropriate infection prevention and control (IPC) activities.
  - Detection of more than one patient with the same carbapenemase (e.g., NDM) might indicate a transmission event, and rapid initiation of IPC measures can prevent further spread.
  - Knowledge of a patient's carbapenemase status can inform patient and staff cohorting strategies.

    - Screening high-risk patients for carbapenemases can help prevent spread within a facility. For example, an acute care hospital may screen all new admissions with healthcare exposure abroad in the previous year, or those from a facility with a known outbreak.[10]
- Testing for specific carbapenemases can identify uncommon or epidemiologically significant CPO, e.g., NDM-producing CRAB.
- The Clinical and Laboratory Standards Institute (CLSI) recommends carbapenemase testing when clinical laboratories have not implemented the most updated CLSI carbapenem breakpoints for Gram-negative organisms.[7]

What if carbapenemase testing is not available at my laboratory?

- CDPH encourages all clinical laboratories to develop carbapenemase testing in-house, or access testing at a reference or public health laboratory. See the CDPH Algorithm for Prioritizing Carbapenemase Testing (www.cdph.ca.gov/Programs/CHCQ/HAI/CDPH%20Document%20Library/CPTestingPrioritizationAlgorithm.pdf) if resources are limited.
- Free carbapenemase testing services at some public health laboratories are available to all California healthcare facilities.
    - Submit carbapenem-resistant organisms to your local public health laboratory to access local, state, and regional carbapenemase testing resources.[11]
    - Facilities can participate in the Targeted Surveillance Program and routinely submit all CRAB to the regional public health lab for carbapenemase testing.[12]

Where can I find additional resources?

- See the CDPH website on CPO for Public Health and Healthcare Providers (www.cdph.ca.gov/Programs/CHCQ/HAI/Pages/CRE_InfectionPreventionStrategies.aspx).

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[1] CDPH Reportable Diseases and Conditions (www.cdph.ca.gov/Programs/CID/DCDC/Pages/Reportable-Disease-and-Conditions.aspx)

[2] KPC=*Klebsiella pneumoniae* carbapenemase, NDM=New Delhi metallo-β-lactamase, VIM=Verona integron-encoded metallo-β-lactamase, IMP=imipenemase metallo-β-lactamase, OXA=oxacillinase

[3] Council of State and Territorial Epidemiologists CPO Position Statement (PDF) (cdn.ymaws.com/www.cste.org/resource/resmgr/ps/ps2022/22-ID-04_CPO.pdf)

[4] CDC 2019 AR Threats Report (PDF) (www.cdc.gov/drugresistance/pdf/threats-report/2019-ar-threats-report-508.pdf)

[5] Common carbapenemase genes include: *bla*$_{KPC}$, *bla*$_{NDM}$, *bla*$_{VIM}$, *bla*$_{IMP}$, *bla*$_{OXA-48}$; other carbapenemase genes include but are not limited to: *bla*$_{GES}$, *bla*$_{SIM}$, *bla*$_{GIM}$, *bla*$_{SPM}$, other OXA genes, etc.

[6] CDPH All-Facilities Letter 19-18 (PDF) (www.cdph.ca.gov/Programs/CHCQ/LCP/CDPH%20Document%20Library/AFL-19-18.pdf)

[7] CLSI: When Should Clinical Microbiology Laboratories Perform Carbapenemase Detection Tests? (PDF) (clsi.org/media/2046/burning-question-when-should-clinical-microbiology-laboratories-perform-carbapenemase-detection-tests.pdf)

[8] The Modified Hodge test is no longer included in CSLI guidelines, and should only be used in conjunction with other phenotypic or molecular tests for carbapenemases. See CLSI M100 guidelines (clsi.org/all-free-resources/).

[9] Infectious Diseases Society for America Antimicrobial Resistant Treatment Guidance: Gram-Negative Bacterial Infections (PDF) (www.idsociety.org/globalassets/idsa/practice-guidelines/amr-guidance/idsa-amr-guidance.pdf)

[10] CDPH CPO Screening Decision Tree (PDF) (www.cdph.ca.gov/Programs/CHCQ/HAI/CDPH%20Document%20Library/Tier2_Pathogen_Screening_Decision_Tree_Oct202 0.pdf)

[11] Please use CDPH Microbial Diseases Laboratory (MDL) form 'Antimicrobial Susceptibility Testing-AST' to submit carbapenem-resistant organism isolates for further testing. See the FAQ Sheet for the most updated submission form and instructions on the MDL website (www.cdph.ca.gov/Programs/CID/DCDC/Pages/MDLSubmissionInstructionsandForms.aspx). Some local public health laboratories also provide carbapenemase testing services; please contact your local health department.

[12] AR Lab Network Targeted Surveillance Flyer (PDF) (www.cdph.ca.gov/Programs/CHCQ/HAI/CDPH%20Document%20Library/CDPH_ARLN_TargetedSurveillanceDescription_052521.pdf)