Carbapenemase-producing Organisms (CPOs): CDPH Laboratory and Epidemiology Updates

via Webinar

May 14, 2024

Healthcare-Associated Infections (HAI) Program
Microbial Diseases Laboratory (MDL)
California Department of Public Health

Objectives

- Provide updates on carbapenemase testing services available through the regional Antimicrobial Resistance (AR) Laboratory Network laboratory, MDL, and local public health laboratories
- Review California CPO epidemiology
- Describe how to access public health carbapenemase testing services

Quick Refresher: Carbapenem-resistant Organisms (CROs)

- Gram-negative bacteria, commonly Enterobacterales (CRE), *Acinetobacter baumannii* (CRAB), *Pseudomonas aeruginosa* (CRPA)

- Non-carbapenemase-producing
  - Resistant due to the presence of porin loss, efflux pumps, etc.

    OR

Quick Refresher: Carbapenem-resistant Organisms (CROs)

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- *Non-carbapenemase-producing*
  - *Resistant due to the presence of porin loss, efflux pumps, etc.*

  OR

- **Carbapenemase-producing**
  - Carbapenemase enzymes often plasmid-mediated; transmissible between species
  - Can spread rapidly among patients especially in the environment or via the hands and clothing of healthcare workers
  - Lab reportable as of September 2022 Title 17 update

Carbapenemase-producing Organisms (CPOs)

- Carbapenemase enzymes fall into three main categories
  - Class A carbapenemases (e.g., KPC, GES)
  - Class B metallo-β-lactamases (e.g., NDM, VIM, IMP)
  - Class D oxacillinases (e.g., OXA-48, OXA-23)

GES=Guiana extended-spectrum, KPC=*Klebsiella pneumoniae* carbapenemase, IMP=imipenemase, NDM=New Delhi metallo-beta-lactamase, OXA=oxacillinase, VIM=Verona-integron metallo-beta-lactamase

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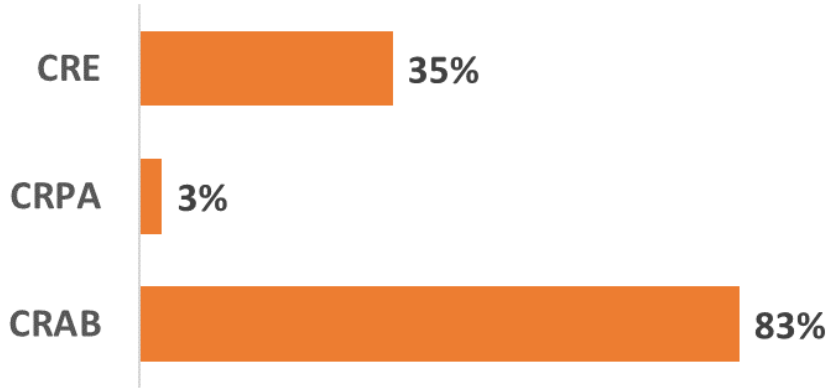
  - *Class D oxacillinases (e.g., OXA-48, OXA-23)*

- Proportion of CROs that produce carbapenemases varies by organism



Source: CDC Antibiotic Resistance & Patient Safety Portal AR Lab Network (arpsp.cdc.gov/)

Carbapenemase Testing

- Two primary methods to detect CPOs
  - **Phenotypic** tests identify carbapenemase production (CP) (CP+ or CP-)
    - Some can determine specific carbapenemase type or Ambler class
  - **Molecular** tests detect genes that encode for carbapenemase enzymes
  - Public health labs perform both types of testing

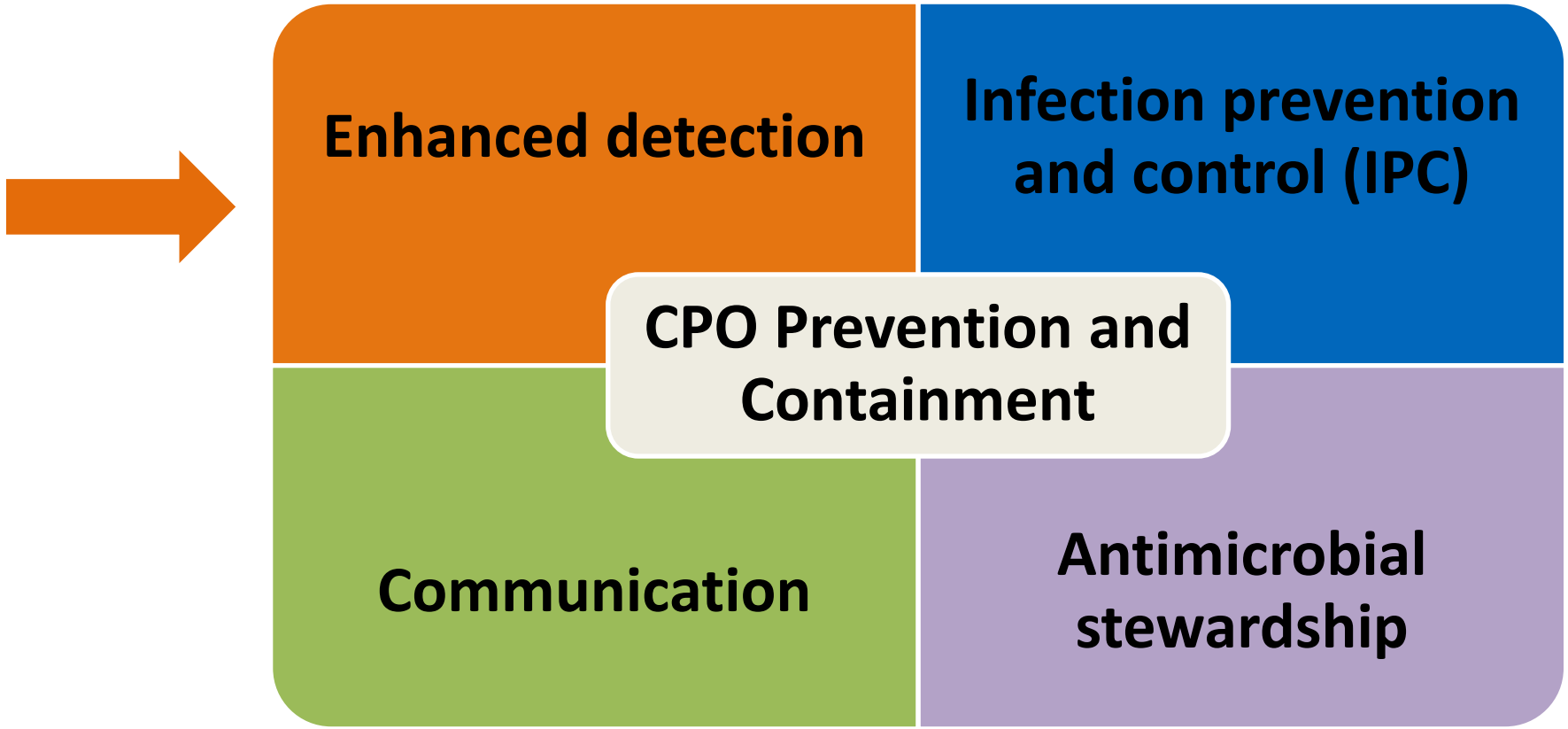
Learn more:

- **Carbapenemase testing, when and how?** webinar by Dr. Romney Humphries
  - Link to slides (PDF)
    (www.cdph.ca.gov/Programs/CHCQ/HAI/CDPH%20Document%20Library/CPO_webinar_102722.pdf)
  - Link to recording (youtu.be/I6LPBB9EQ8c)
- **Carbapenemase testing primer** for labs by Janet Hindler (PDF)
  (www.cdph.ca.gov/Programs/CHCQ/HAI/CDPH Document Library/CRO_PrimerTests_for_Carbapenemases.pdf)

Risk Factors for CPO Colonization or Infection

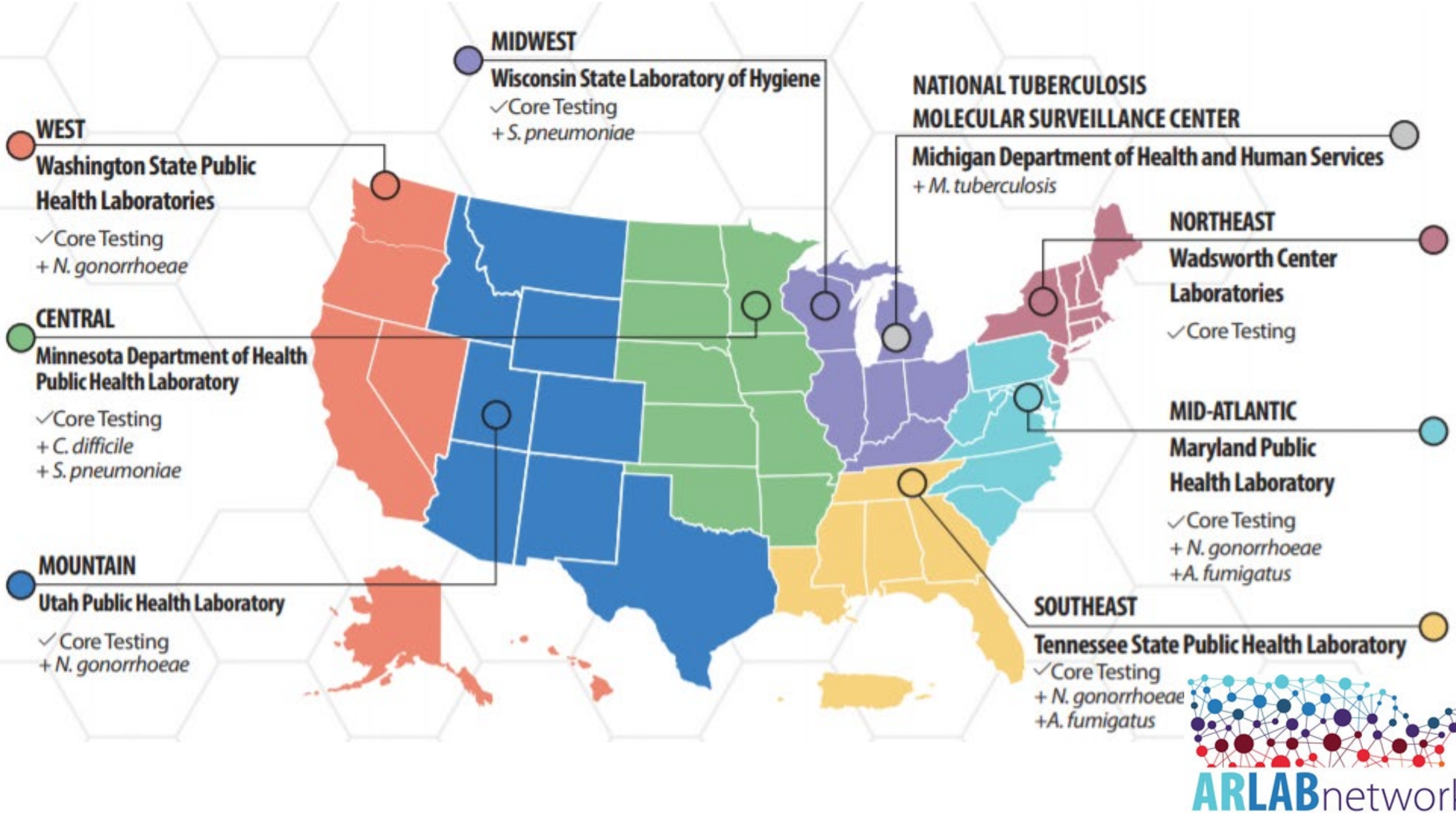
- Frequent healthcare exposure
- Presence of invasive medical devices, mechanical ventilation
- Recent antimicrobial use
- International travel or healthcare exposure

CPOs are a Public Health Threat



AR Regional Lab Network (AR Lab Network) Update

Emily Schneider


MIDWEST
Wisconsin State Laboratory of Hygiene
✓Core Testing
+ S. pneumoniae
NATIONAL TUBERCULOSIS
MOLECULAR SURVEILLANCE CENTER
Michigan Department of Health and Human Services
+ M. tuberculosis
WEST
Washington State Public
Health Laboratories
✓Core Testing
+ N. gonorrhoeae
NORTHEAST
Wadsworth Center
Laboratories
✓Core Testing
CENTRAL
Minnesota Department of Health
Public Health Laboratory
✓Core Testing
+ C. difficile
+ S. pneumoniae
MID-ATLANTIC
Maryland Public
Health Laboratory
✓Core Testing
+ N. gonorrhoeae
+A. fumigatus
MOUNTAIN
Utah Public Health Laboratory
✓Core Testing
+ N. gonorrhoeae
SOUTHEAST
Tennessee State Public Health Laboratory
✓Core Testing
+ N. gonorrhoeae
+A. fumigatus
ARLABnetwork

WA PHL AR Lab Network Test Menu

Carbapenem-resistant Organisms (CRO)- Clinical Isolate Testing

- Carbapenem-resistant Enterobacterales (CRE)
- Carbapenem-resistant *Pseudomonas aeruginosa* (CRPA)
- Carbapenem-resistant *Acinetobacter baumannii* (CRAB)
  - Species ID (MALDI-TOF)
  - Carbapenemase detection
    - mCIM (excluding CRAB)
    - PCR (IMP, KPC, NDM, OXA-48, VIM, and OXA-variants)
  - Antibiotic susceptibility testing (GN7X)
    - Expanded AST for Hard-to-Treat Infections (ExAST)

CPO Colonization Screening

- **Carbapenemase-producing organism (CPO) colonization screening**
  - Cepheid GeneXpert CarbaR
  - Rectal swabs, only
  - IMP, KPC, NDM, OXA-48, VIM
- **Targeted Surveillance Screening**
  - Culture-based
  - Non-rectal sites acceptable
  - OXA-variants found in CRAB (OXA-23, OXA-24/40, OXA-58, OXA-235) and IMP-variants

ARLN Lab Test Menu
(www.doh.wa.gov/ForPublicHealthandHealthcareProviders/PublicHealthLaboratories/ARLNLabTestMenu)

Expanded AST for Enterobacterales (ExAST)

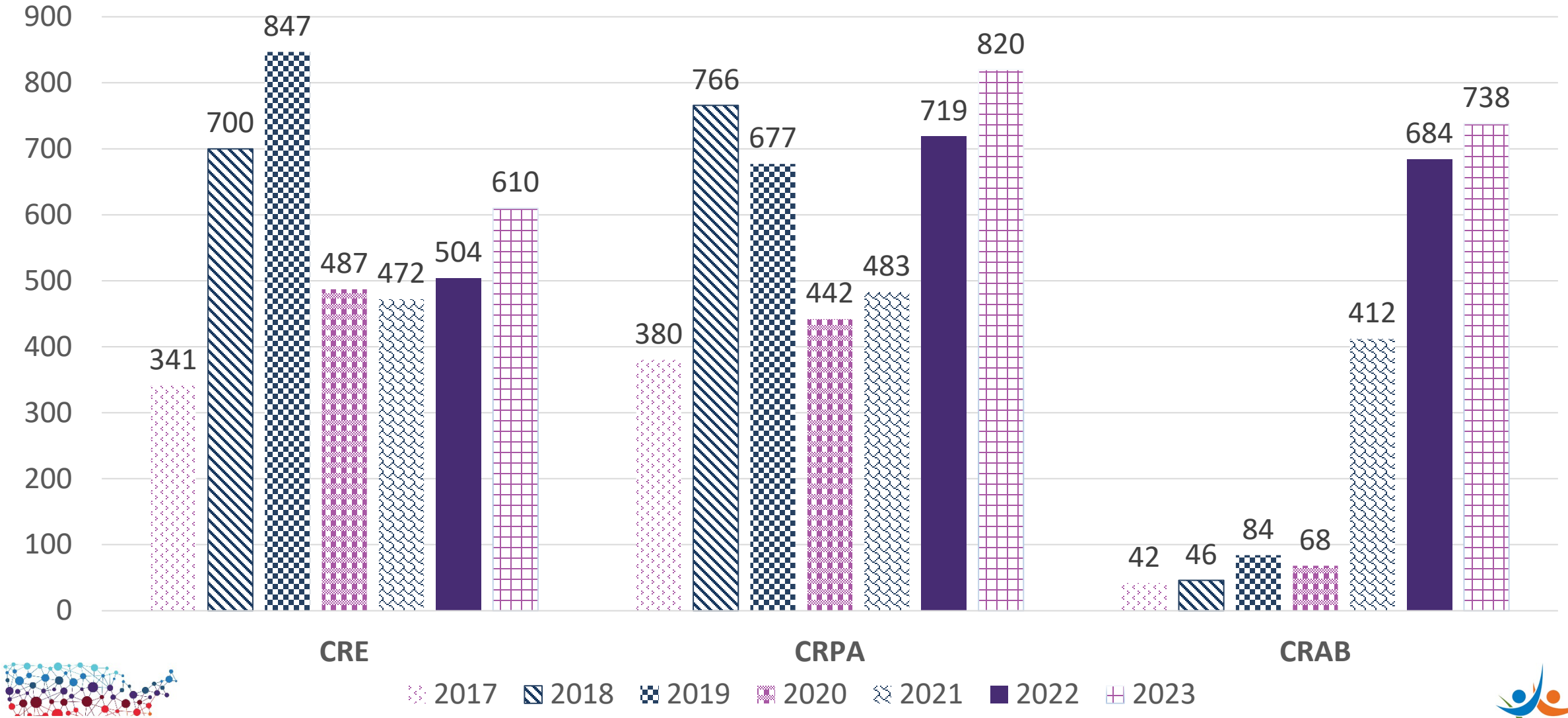
- Results are intended to inform **treatment decisions**, turn-around-time is 3 business days from isolate receipt.
- Eligible **Enterobacterales** isolates must:
  - test non-susceptible to all beta-lactams, including Ceftazidime-Avibactam or Meropenem-Vaborbactam
    OR
  - have NDM, VIM, or IMP genes confirmed by molecular testing
- At WA PHL, isolates will be tested for susceptibility to:
  - Aztreonam
  - Ceftazidime-Avibactam
  - Avibactam-Aztreonam
- Please contact ARLN@doh.wa.gov for approval or questions
  - If testing is approved, you may be directed to ship isolates to WA PHL directly.

ARLABnetwork

Expanded Antimicrobial Susceptibility Testing for Hard-to-Treat Infections (PDF)
(www.cdc.gov/antimicrobial-resistance-laboratory-networks/media/pdfs/drug-susceptibility-tests-p.pdf)

CDPH California Department of PublicHealth

AR Lab Network West Region* Isolate Testing, 2017-2023



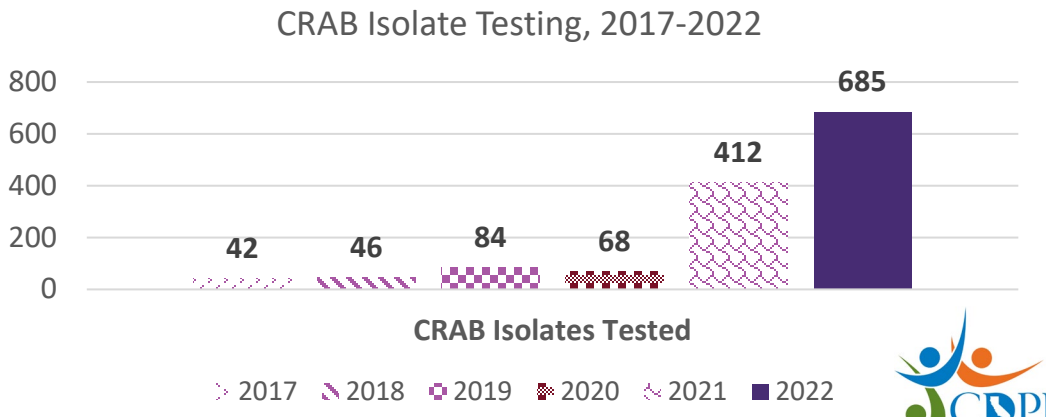
*Samples originate from Alaska, California, Guam, Hawaii, Nevada, Oregon, and Washington. 2023 Data are preliminary

CRAB Testing in the AR Lab Network West Region

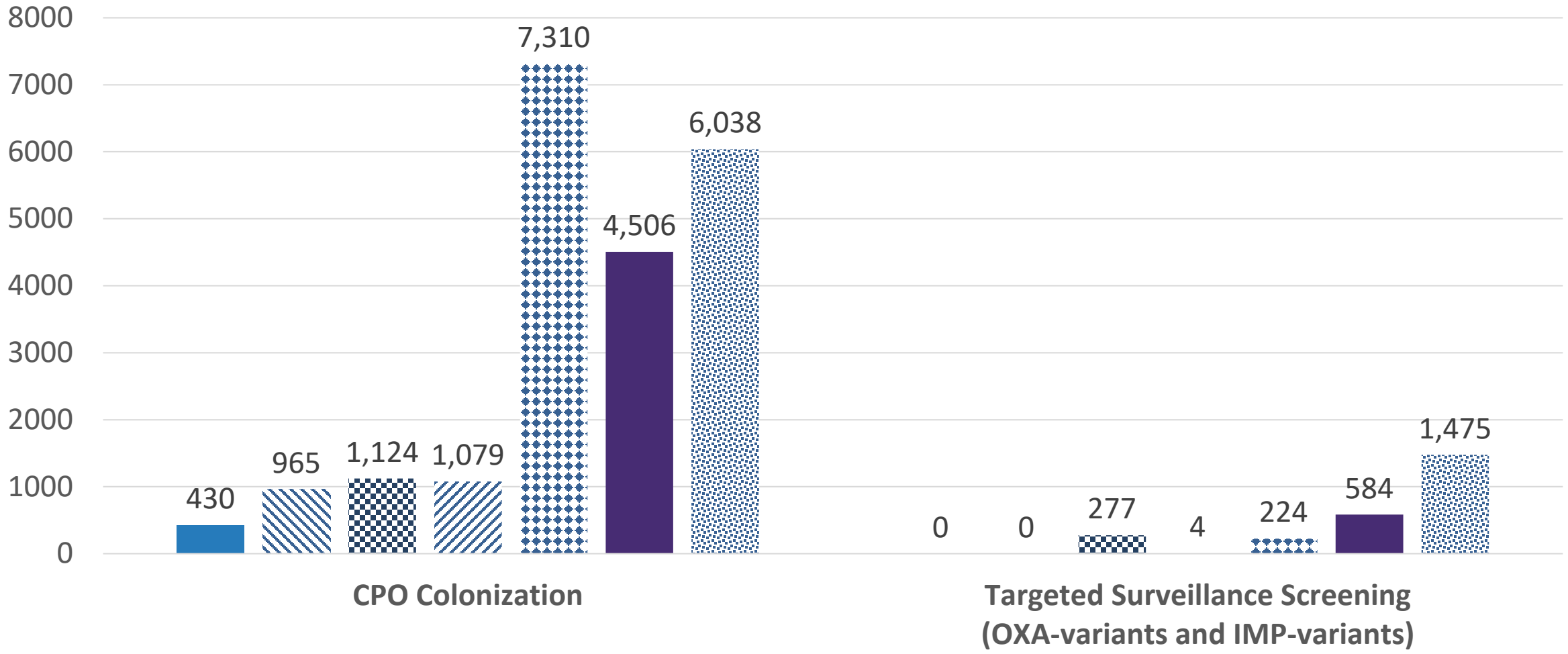
- Prior to 2021, <90 isolates CRAB isolates were tested, annually

- The OXA-variants assay was brought on in 2019, leading to an increased understanding of OXA-variants in CRAB
  - OXA-23-like positive isolate identified on the first run, launching a large investigation
  - OXA-235-like added as a target in September 2022 and was quickly identified

- In 2020, CRAB+NDM/OXA-23 was detected in California. Large clusters were subsequently identified.
  - Large effort to increase sentinel lab participation, resulting in a major increase in CRAB isolate submissions, and increased understanding of CRAB epidemiology.



AR Lab Network West Region* Colonization Screening Testing, 2017-2023



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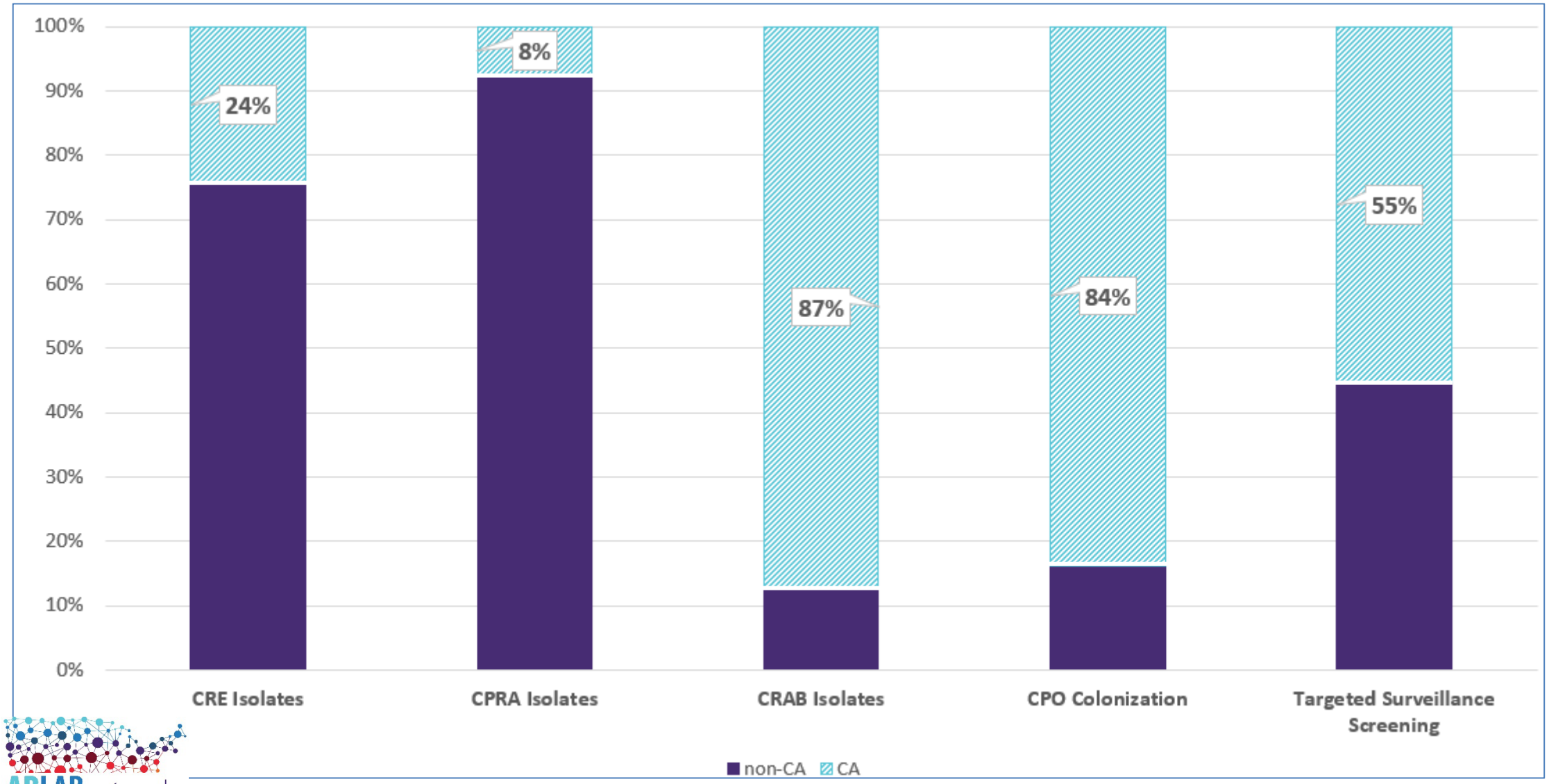
California Isolate and Colonization Screening Submissions, 2017-2023



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Microbial Diseases Laboratory (MDL) Update

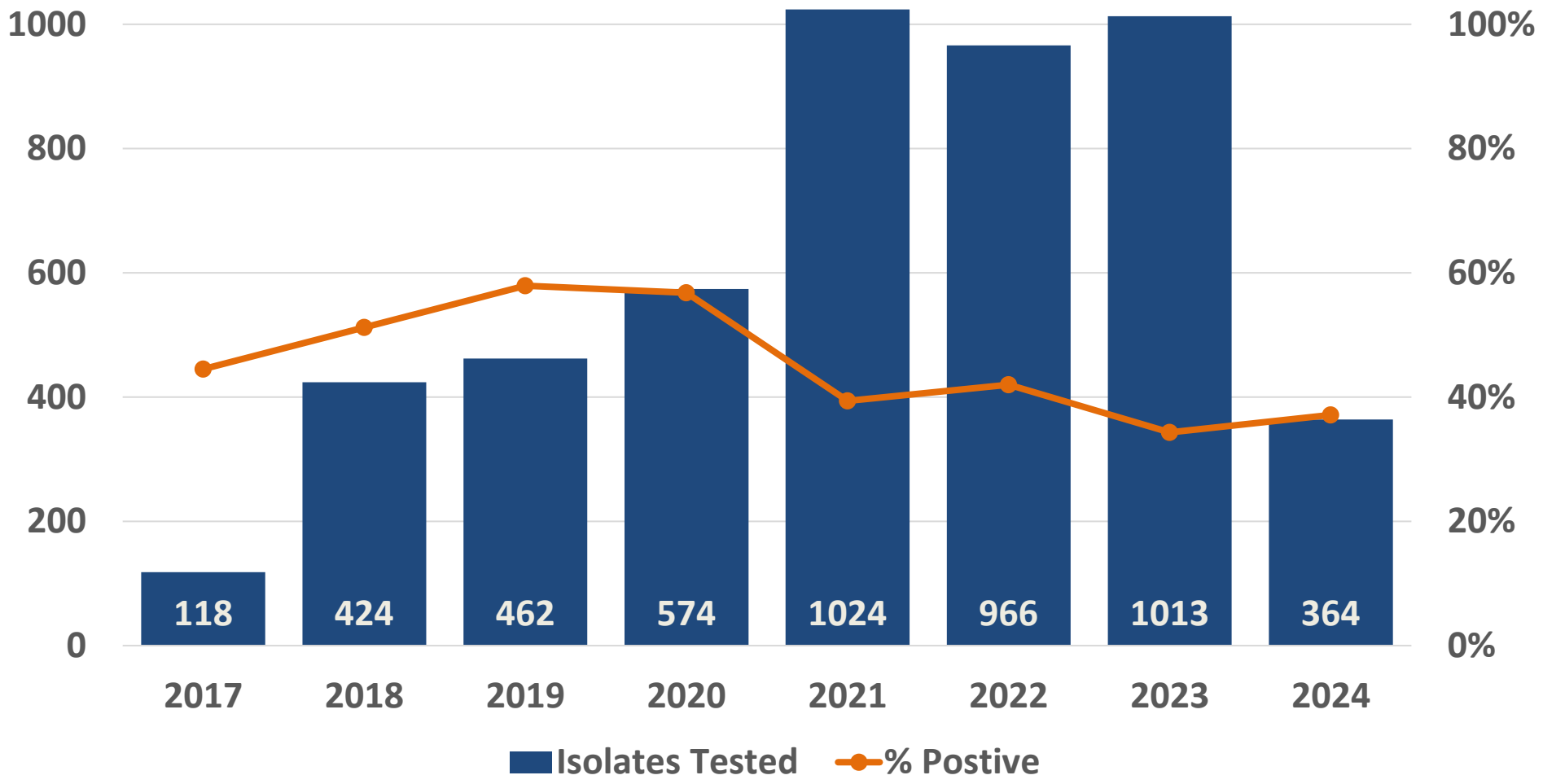
Namrata Mohanty and Anusha Murshed

MDL Isolate Testing Submission Guidance

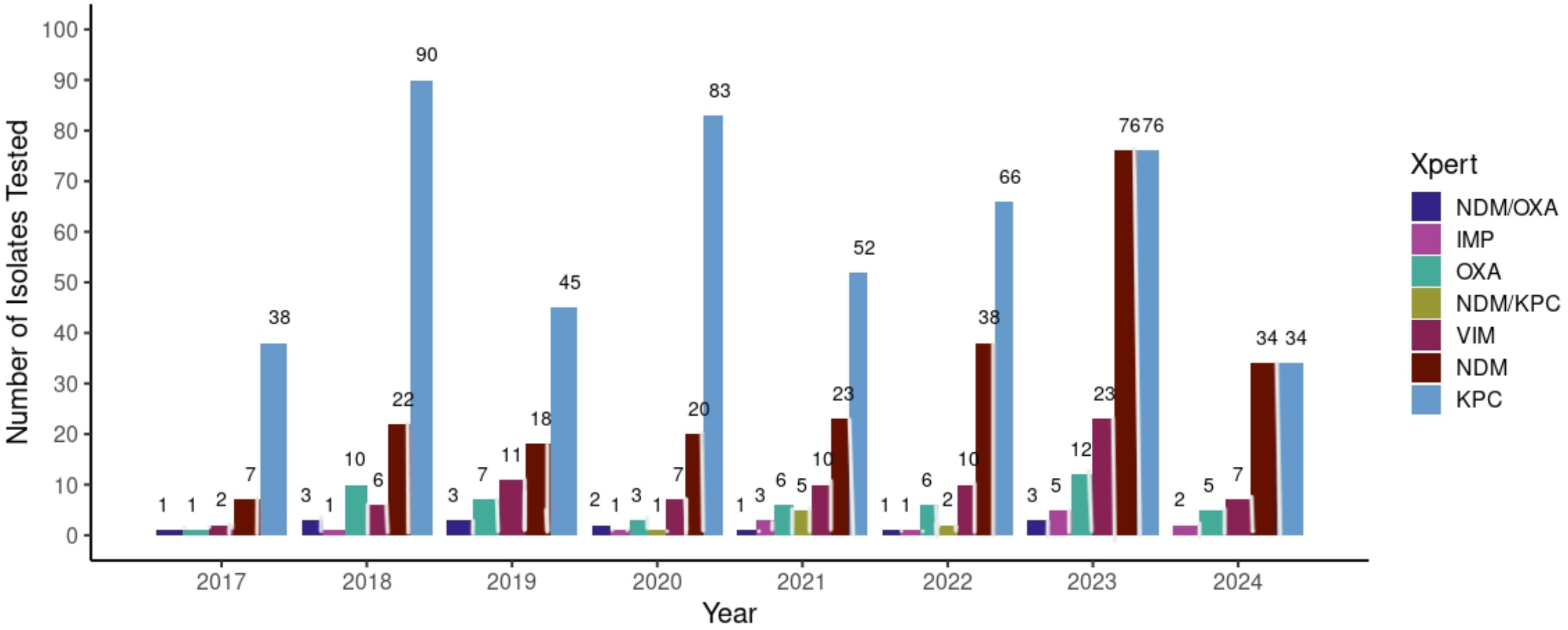
- MDL currently accepts:
  - **Carbapenem-resistant Enterobacterales (CRE)**
    - Includes *Escherichia coli*, *Klebsiella oxytoca*, *Klebsiella pneumoniae*, and *Enterobacter* spp.
    - Testing for other CRE, including *Providencia*, *Proteus*, *Morganella*, *Citrobacter*, and *Serratia* spp. done on a case-by-case basis with approval from CDPH HAI Program (HAIProgram@cdph.ca.gov)
  - **Carbapenem-resistant *Pseudomonas aeruginosa* (CRPA)** non-susceptible to cefepime or ceftazidime
  - **Pan-nonsusceptible carbapenem-resistant *Acinetobacter baumannii* (CRAB), CRE, and CRPA**

- Routine surveillance samples should be submitted to your local public health lab (LPHL) and subsequently forwarded to MDL's Bacterial Diseases Section
- Please use MDL form '**Antimicrobial Susceptibility Testing-AST**' in ETOR to submit CRO testing samples – visit website for most up-to-date submission form and instructions (www.cdph.ca.gov/Programs/CID/DCDC/Pages/MDLSubmissionInstructionsandForms.aspx)
- Refer to Expanded Carbapenemase Testing Services FAQ for additional submission guidance (www.cdph.ca.gov/Programs/CID/DCDC/Pages/MDL-Expanded-Carbapenemase-Testing-Services-FAQs.aspx)

MDL CRO Isolates Tested, % CP-positive, January 2017–April 2024



MDL Isolates Tested Positive by Xpert, January 2017–April 2024

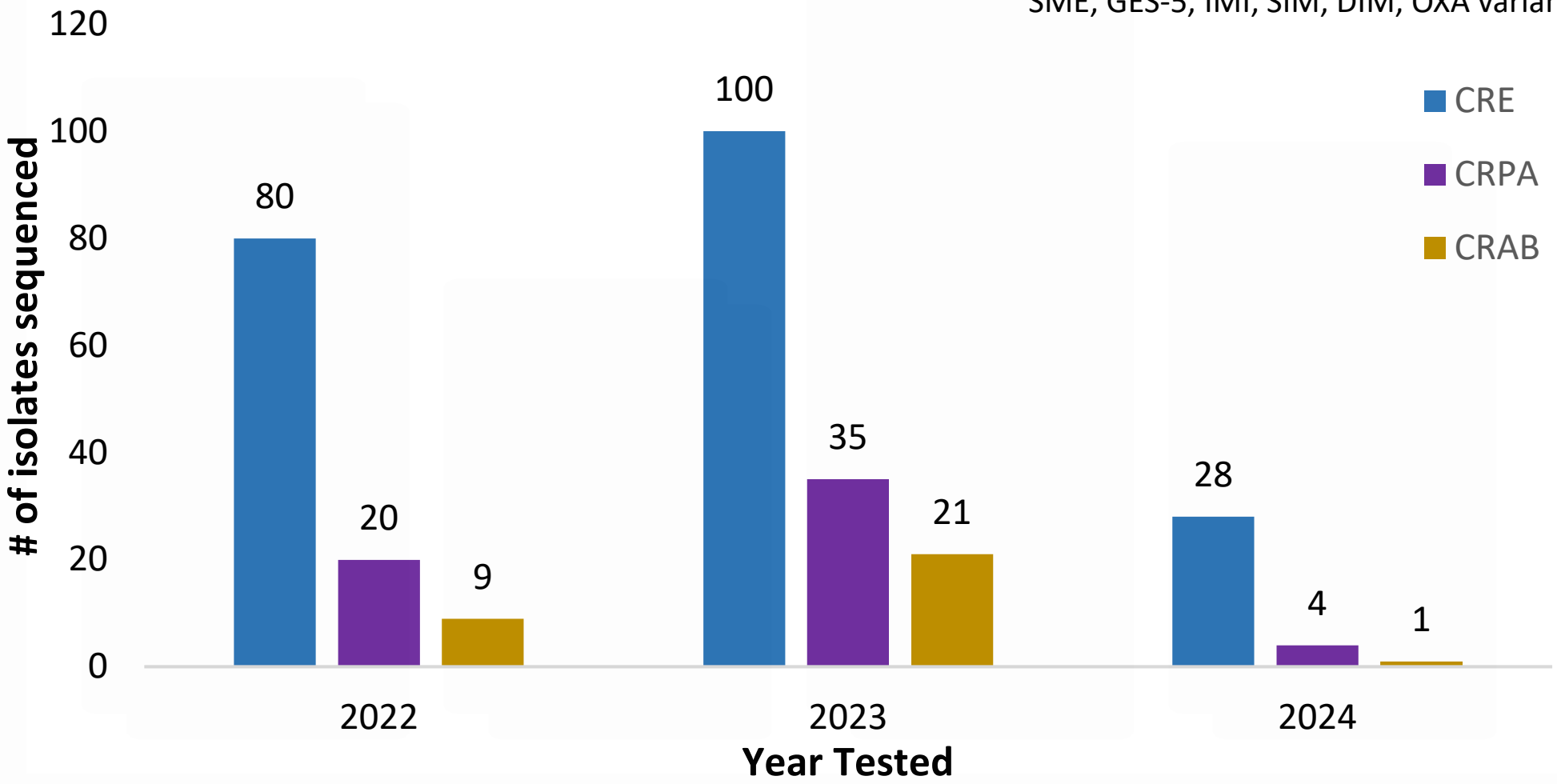


MDL Updates – Whole Genome Sequencing (WGS)

- WGS assay on Illumina MiSeq platform
  - Select HAI AR isolates submitted that test positive for carbapenemases are sequenced
- WGS submission criteria
  - **Approval is required from HAIprogram@cdph.ca.gov prior to submission**
  - Please go through your local public health laboratory to submit HAI AR isolates for sequencing
  - When submitting to MDL (for LPHLs), please use the AST form in ETOR to enter the requisition (www.cdph.ca.gov/Programs/CID/DCDC/Pages/MDL-eform-AST-Instructions.aspx)
  - Pure isolates are accepted; mixed cultures will not be tested
  - Isolates must be identified by the submitter

MDL CRO Isolates Sequenced, January 2022-April 2024

Carbapenemase genes detected by WGS:
SME, GES-5, IMI, SIM, DIM, OXA variants, IMP variants



MDL Updates – 2023 Carbapenemase Tests Launched

- **CPO Colonization Swab Screening**
  - Performed using Xpert Carba-R assay
  - Detects common carbapenemase genes (KPC, NDM, OXA-48, VIM, and IMP) from patient rectal swab specimen
  - Prior approval is required from HAIprogram@cdph.ca.gov and CARLprogram@cdph.ca.gov

- **Sensititre Antimicrobial Susceptibility Testing (AST)**
  - Sensititre GNX2F panel for CRE, CRPA, CRAB
  - Performed on select CROs submitted to MDL for surveillance
  - Results are reported to CDC via HL7 messaging

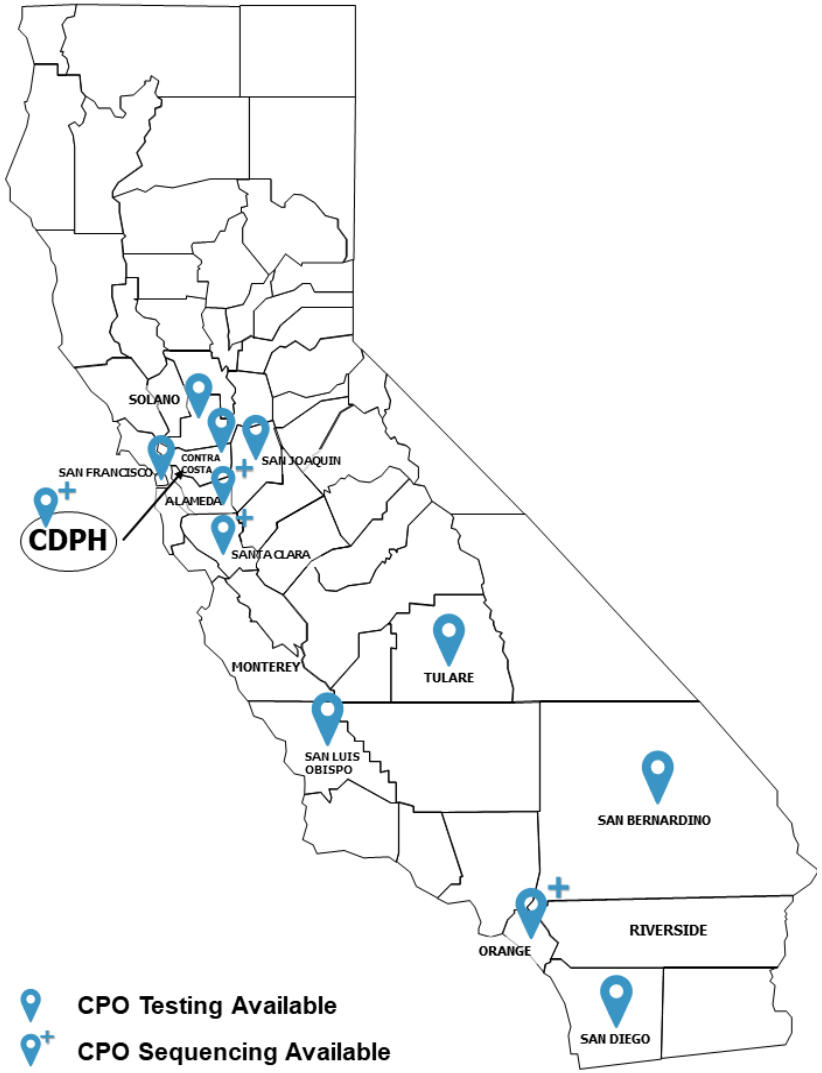
MDL Updates – Upcoming Carbapenemase Tests

- **STAR-BL Carba assay by Bruker**
  - Phenotypic test (carbapenemase +/-) for CRE, CRPA, CRAB
  - Shorter turn-around-time (TAT) than mCIM

- **ARM-D OXA assay by Streck**
  - Real Time PCR assay that detects more OXA variants/groups compared to Xpert
    - Includes OXA 23/24/40 groups found in *Acinetobacter* spp.
    - Much faster TAT and cheaper than whole genome sequencing

Local Public Health Laboratory (LPHL) Update
Namrata Mohanty

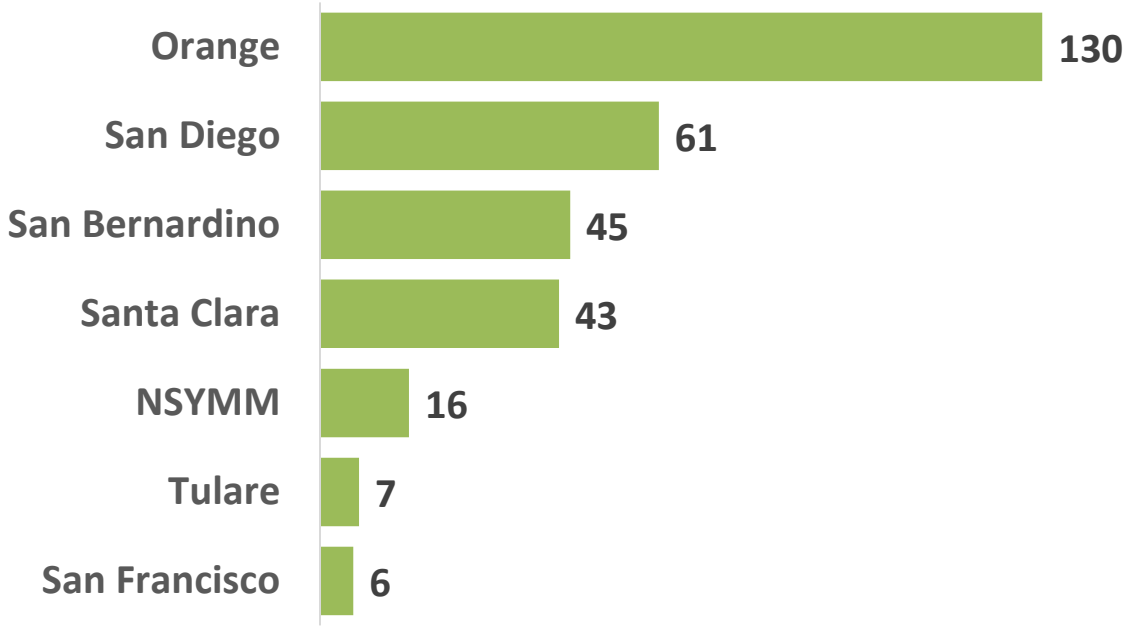
LPHL Carbapenemase Testing Capacity



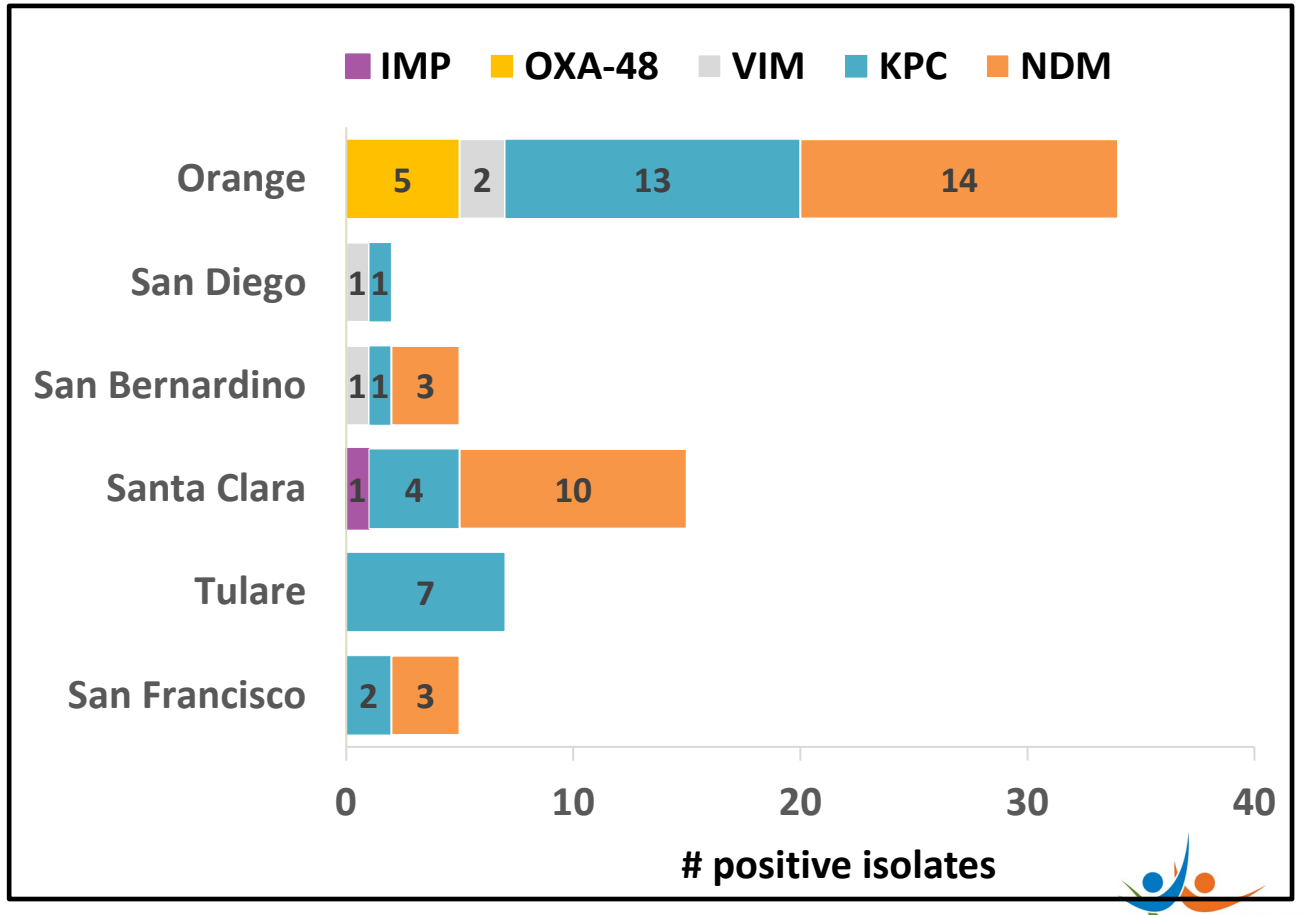
County	CPO swab testing	CPO isolate testing	CPO sequencing
Alameda		X	X
Contra Costa	X		
Solano	X	X	
Orange		X	X
San Bernardino	X	X	
San Diego		X	
San Francisco	X	X	
San Joaquin	X	X	
San Luis Obispo	X	X	
Santa Clara	X	X	X
Tulare		X	

LPHL Isolate Testing, January–March 2024

LPHL isolates tested for carbapenemases

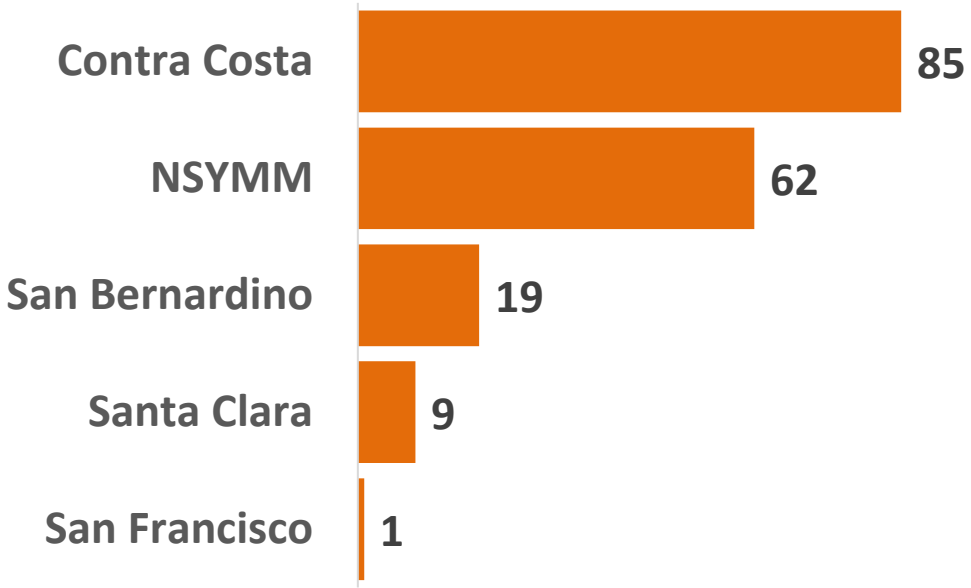


LPHL Xpert carbapenemase-positive results



LPHL CPO colonization testing, January–March 2024

LPHL CPO colonization screening swabs tested



If you're interested in doing CPO screening and/or isolate testing at your facility or in your jurisdiction, please reach out to your local public health laboratory for more information!

Additionally, you're welcome to contact CARLprogram@cdph.ca.gov and HAIprogram@cdph.ca.gov for information to start CPO screening!

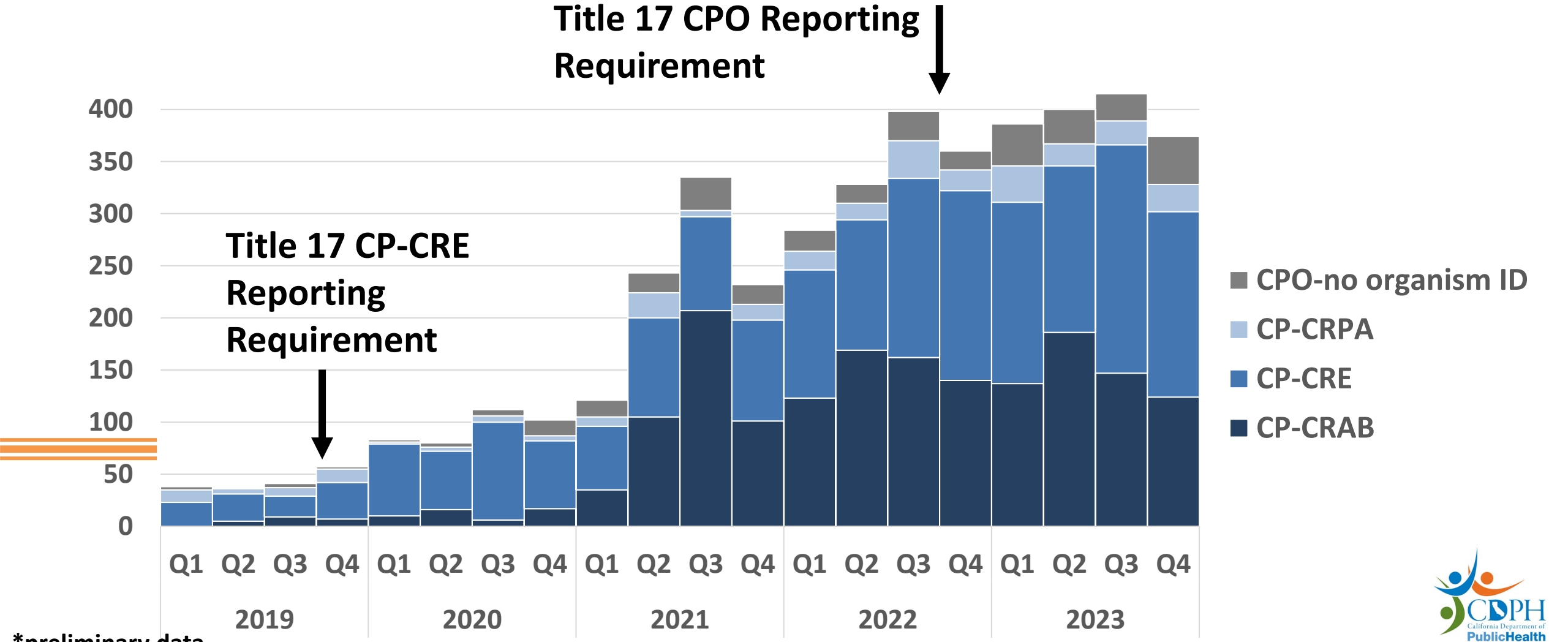
Epidemiology Updates
Kiara Velasquez

Title 17 CPO Laboratory Reporting

- **October 2019–September 2022 – CP-CRE**
  - *E. coli, Klebsiella* and *Enterobacter* spp.

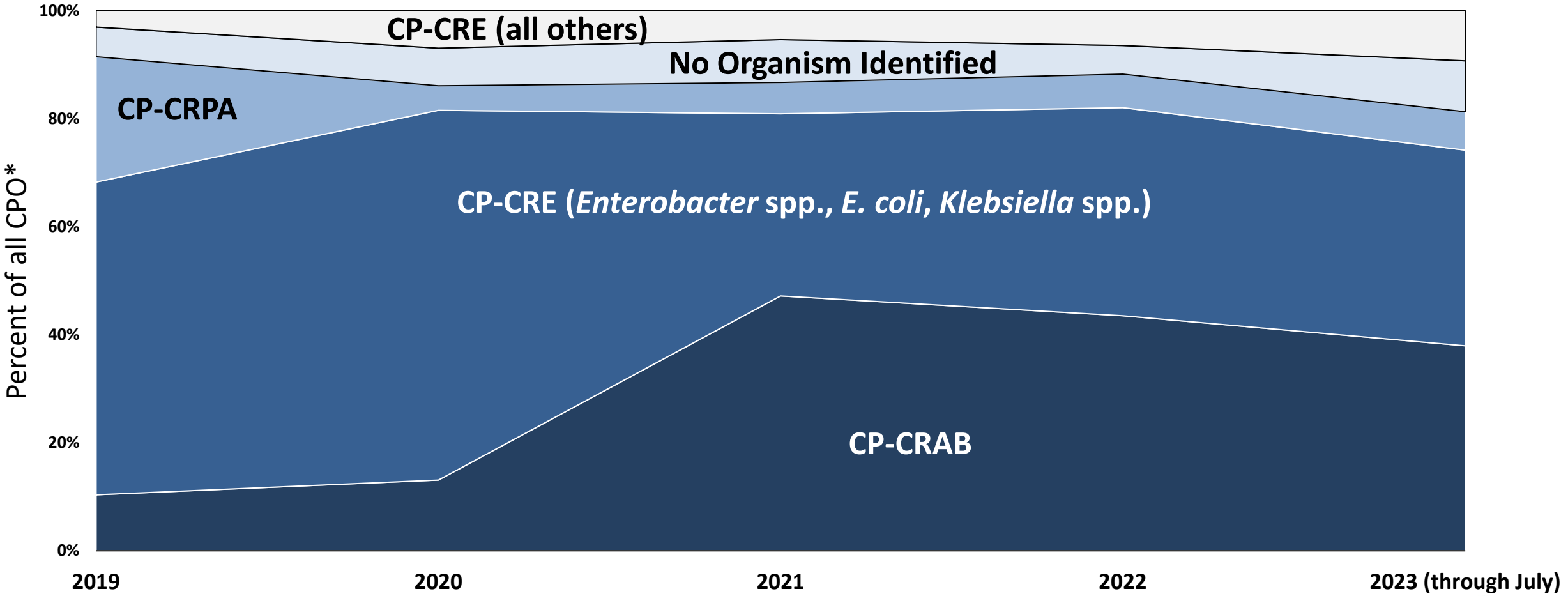
- **From September 2022 – all CPOs**
  - Positive phenotypic test result for carbapenemase production, with or without identification of a specific carbapenemase type
  - Positive molecular test result detecting a carbapenemase gene
  - Detection of a carbapenemase gene by next-generation sequencing (e.g., WGS)
  - Specimen positive for a carbapenemase gene without bacterial species identification (e.g., rectal swab)

4x more CPO cases* were reported in 2023 than in 2020



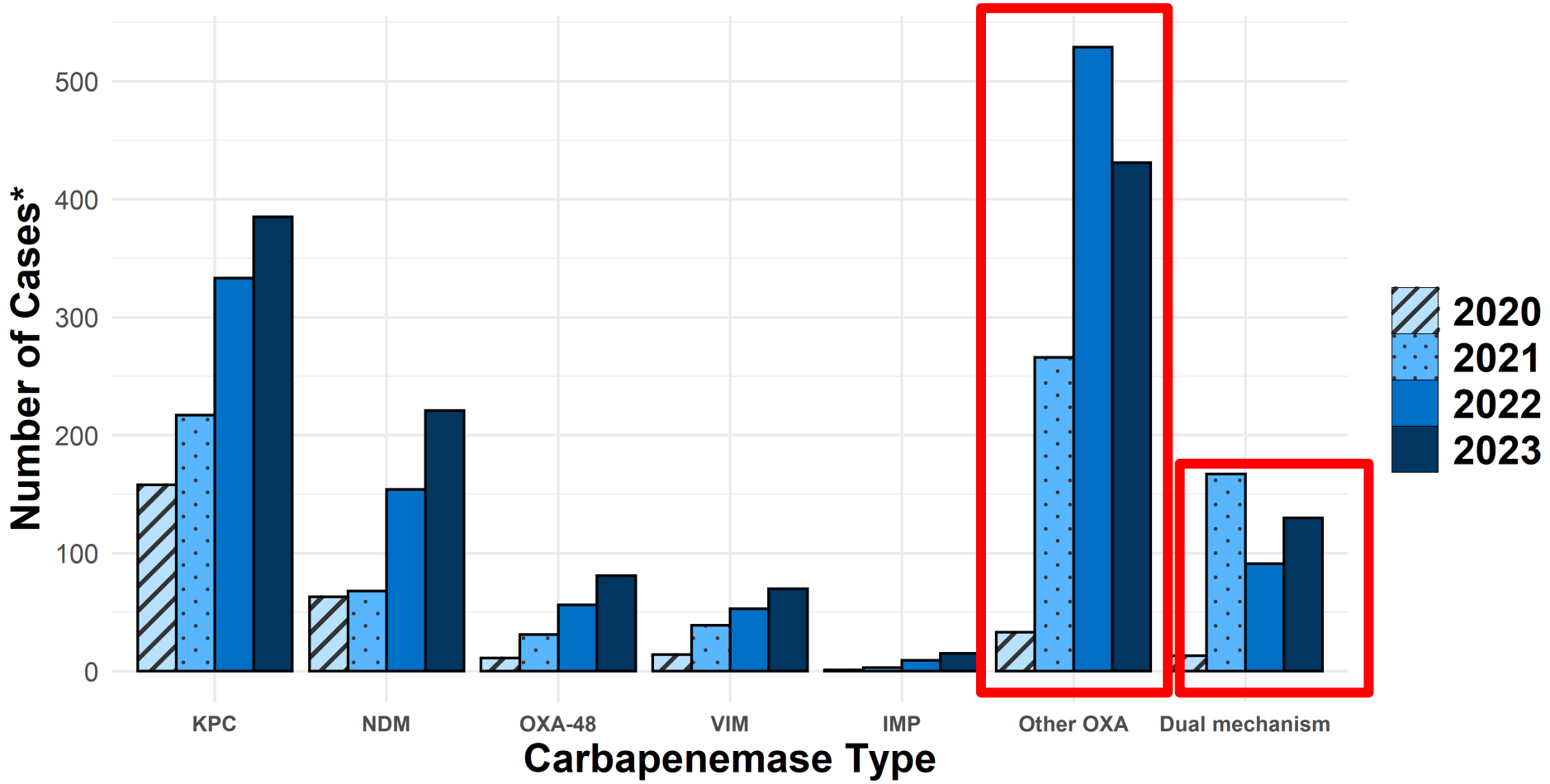
*preliminary data

The proportion of CP-CRAB increased considerably after 2020



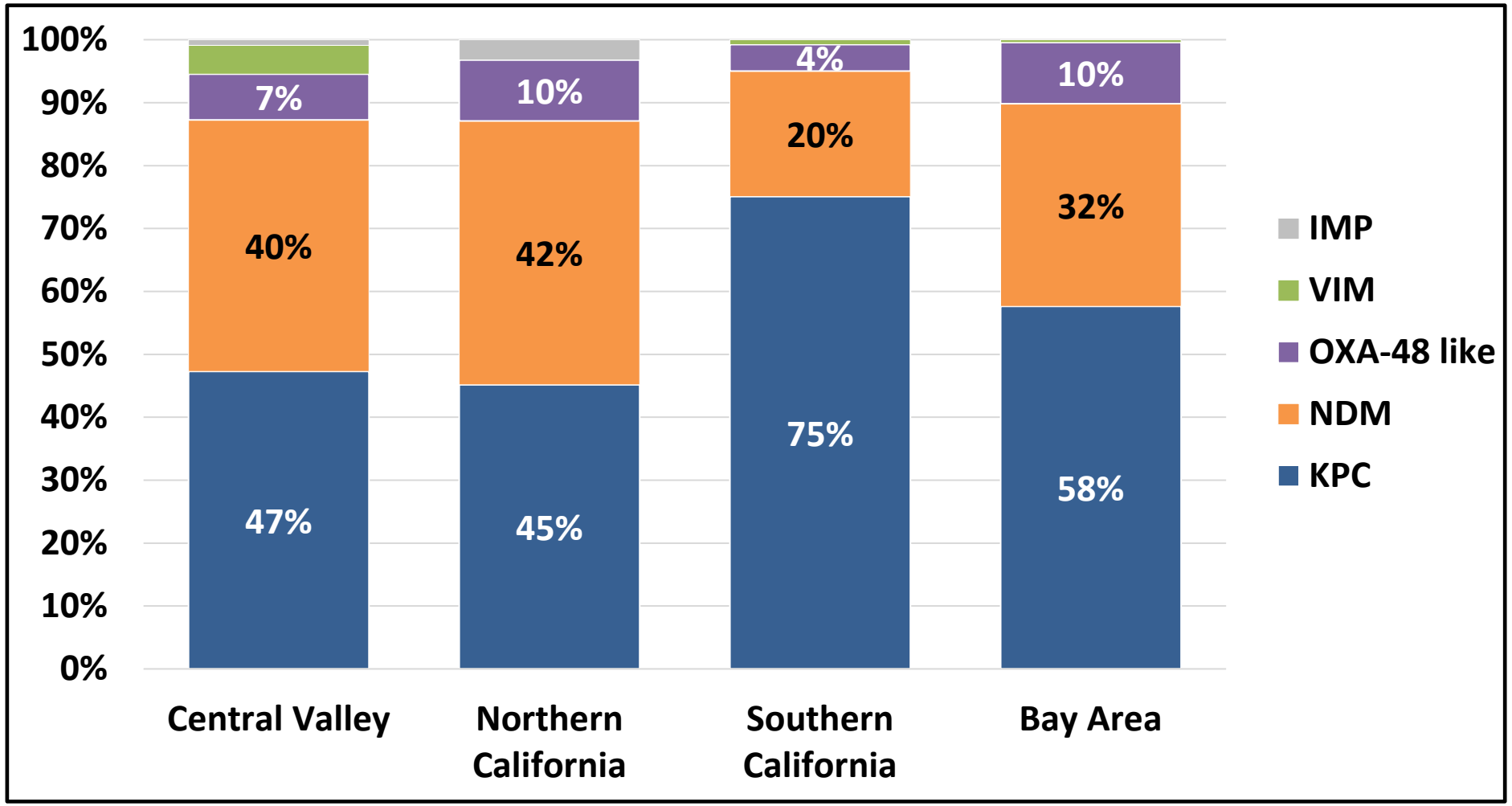
*preliminary data

In California, we're seeing more and different carbapenemases



*preliminary data

Distribution of carbapenemases among CP-CRE cases* differs by region

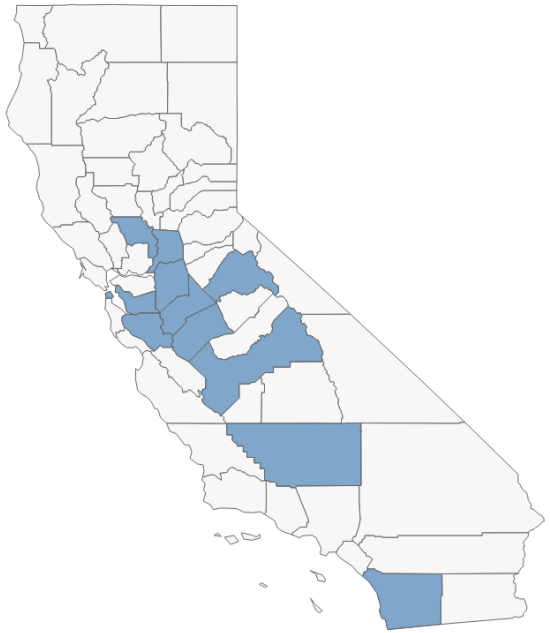


* preliminary data 2020–June 2023

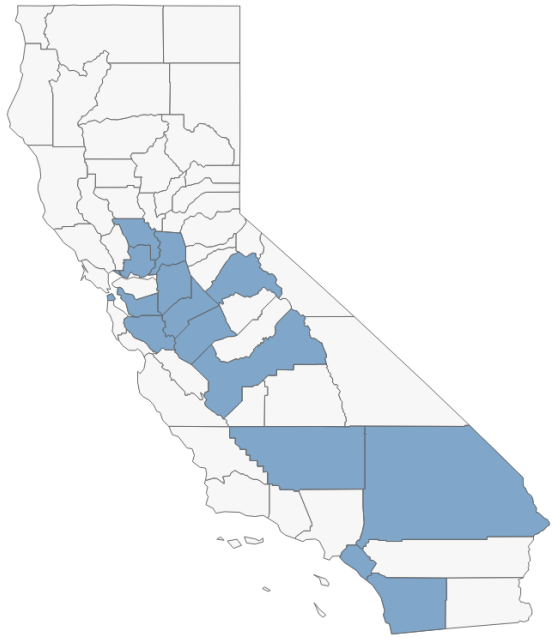
Previously rare CPOs* are spreading across the state

Jan 2021
n= 11

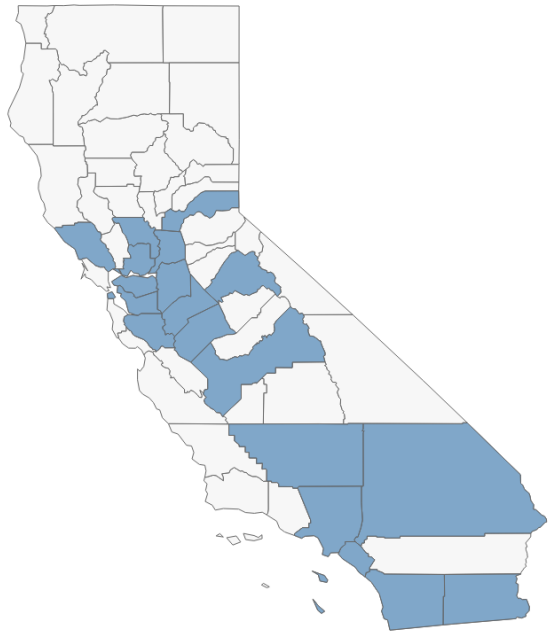
Jan 2022
n = 207



Jan 2023
n = 276



Jan 2024
n = 432



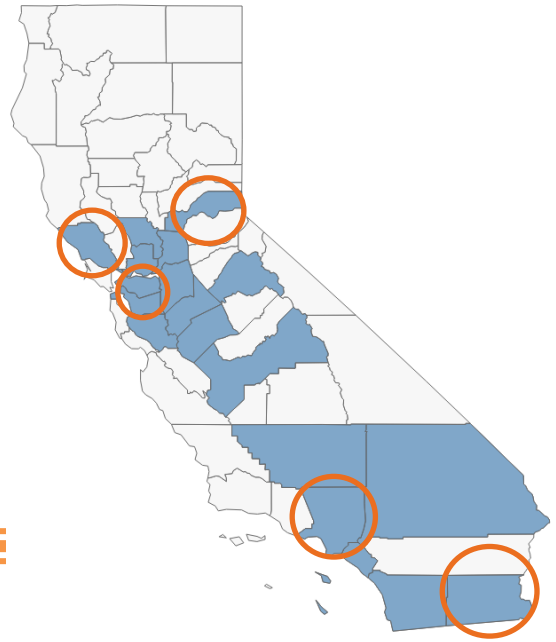
Data preliminary

*E.g., NDM-producing *Acinetobacter baumannii* spread from Central to Southern California, 2021-2024

California Health Advisory (PDF) (www.cdph.ca.gov/Programs/CHCQ/HAI/CDPH%20Document%20Library/CAHAN_NDM_OXA23_CRAB_May2021.pdf)

NDM-producing CRAB Cases Identified in 5 New Counties in 2023

Jan 2024



- As of January 2024, cases identified in **5 additional LHJs**
- 57% increase in cases from 2023 to 2024
- Additional cases attributed to transmission and **increased surveillance at clinical AND public health labs**

CPOs implicated in national cluster from contaminated products

- VIM-GES-producing *Pseudomonas aeruginosa*, highly drug-resistant
  - As of May 2023, CDC reported 81 patients in 18 states

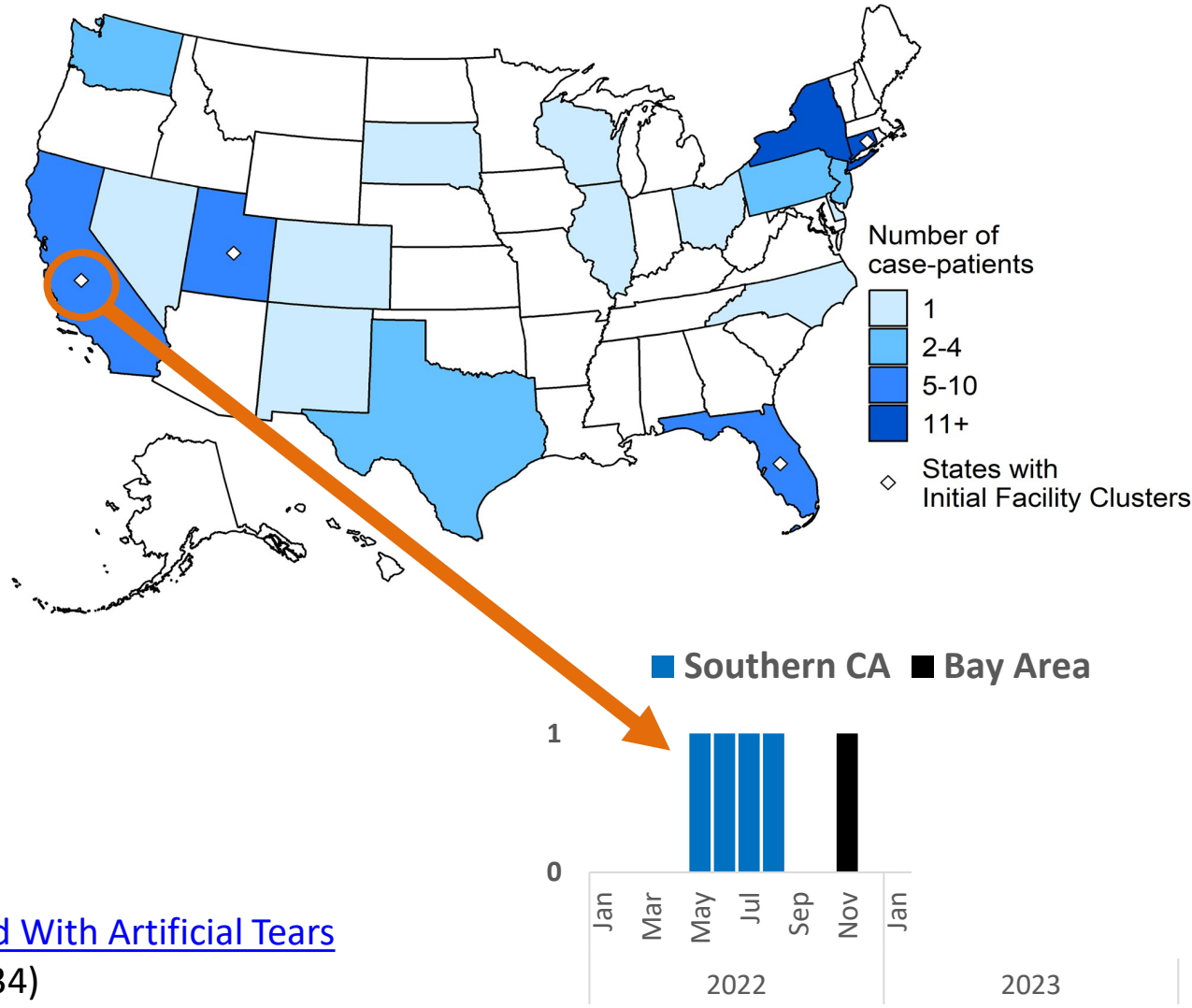
Check in central supply/medication rooms and patient/resident rooms:

NOTE: If product is found at your facility please DISCARD ALL product and monitor for infection

For additional questions, please refer to CDC website: **Outbreak of Extensively Drug-resistant Pseudomonas aeruginosa Associated with Artificial Tears** (archive.cdc.gov/#/details?url=https://www.cdc.gov/hai/outbreaks/crpa-artificial-tears.html)

Lab testing and reporting helped identify cases in California

- Of the 81 cases,
  - **4 cases part of initial facility cluster in Southern CA**
  - **1 case identified in Bay Area**



Extensively Drug-Resistant *Pseudomonas aeruginosa* Outbreak Associated With Artificial Tears
(academic.oup.com/cid/advance-article/doi/10.1093/cid/ciae052/7601234)

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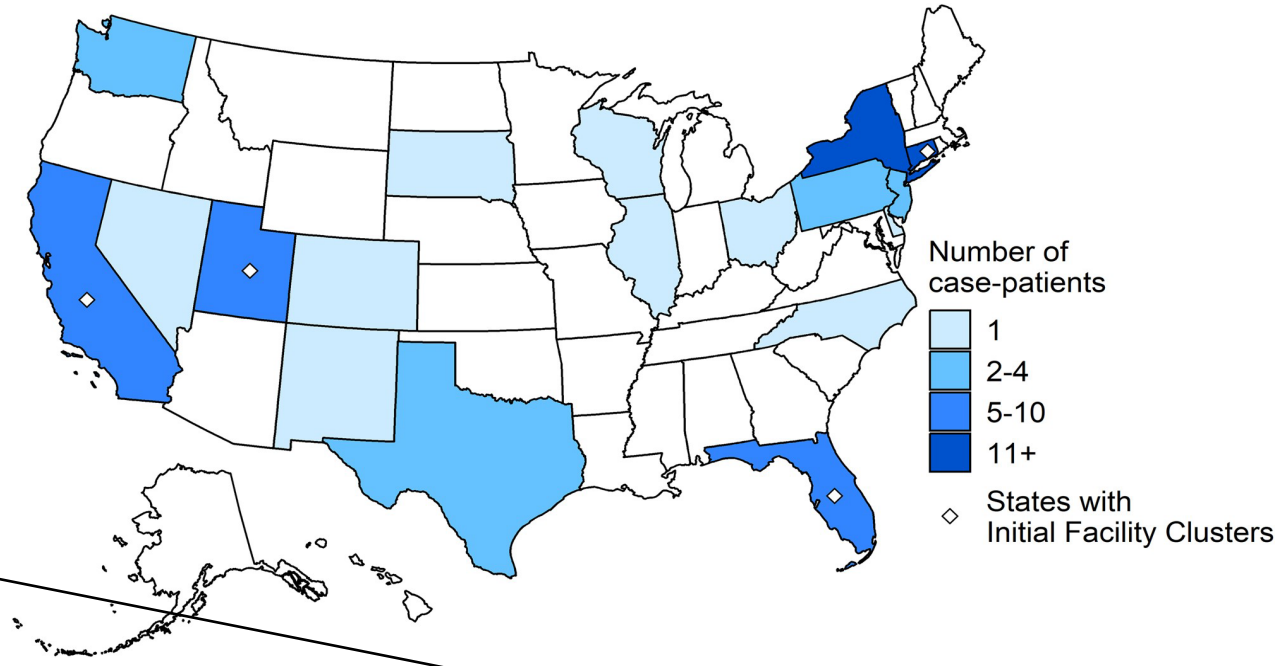

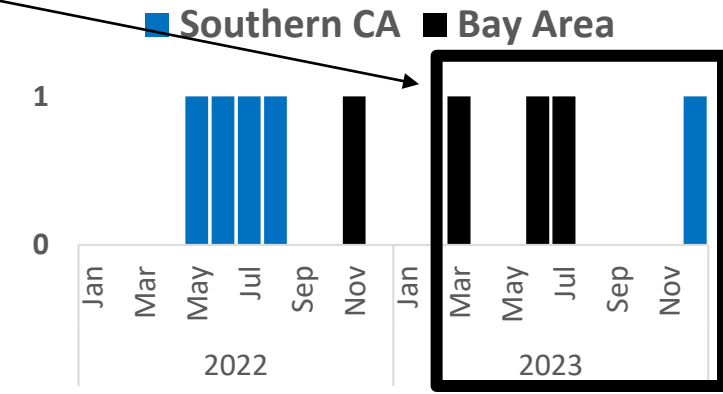

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  - ***4 cases part of initial facility cluster in Southern CA***
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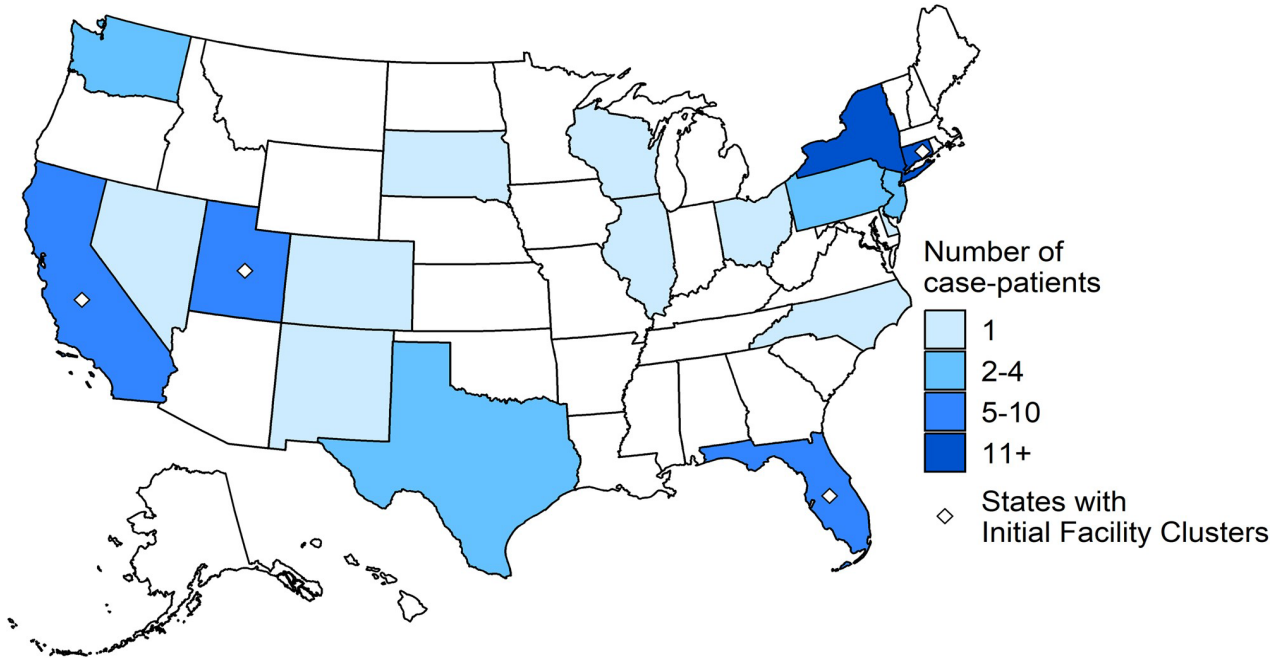
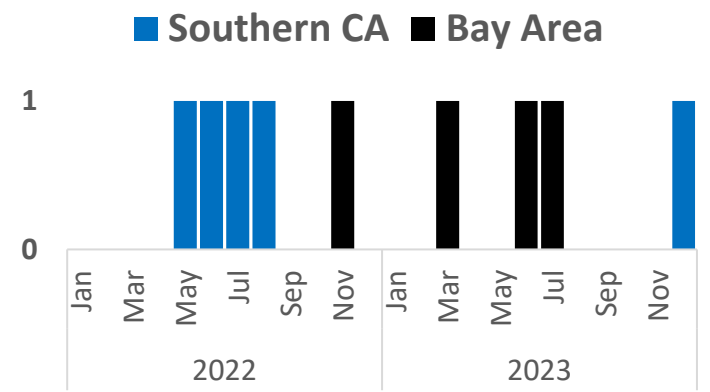
- ***4 more CA cases identified later in Bay Area and Southern CA***
- Epi-linked screening identified cases associated with transmission
- WGS linked isolates to national cluster
  - VIM-80 in ST-1203, GES-9





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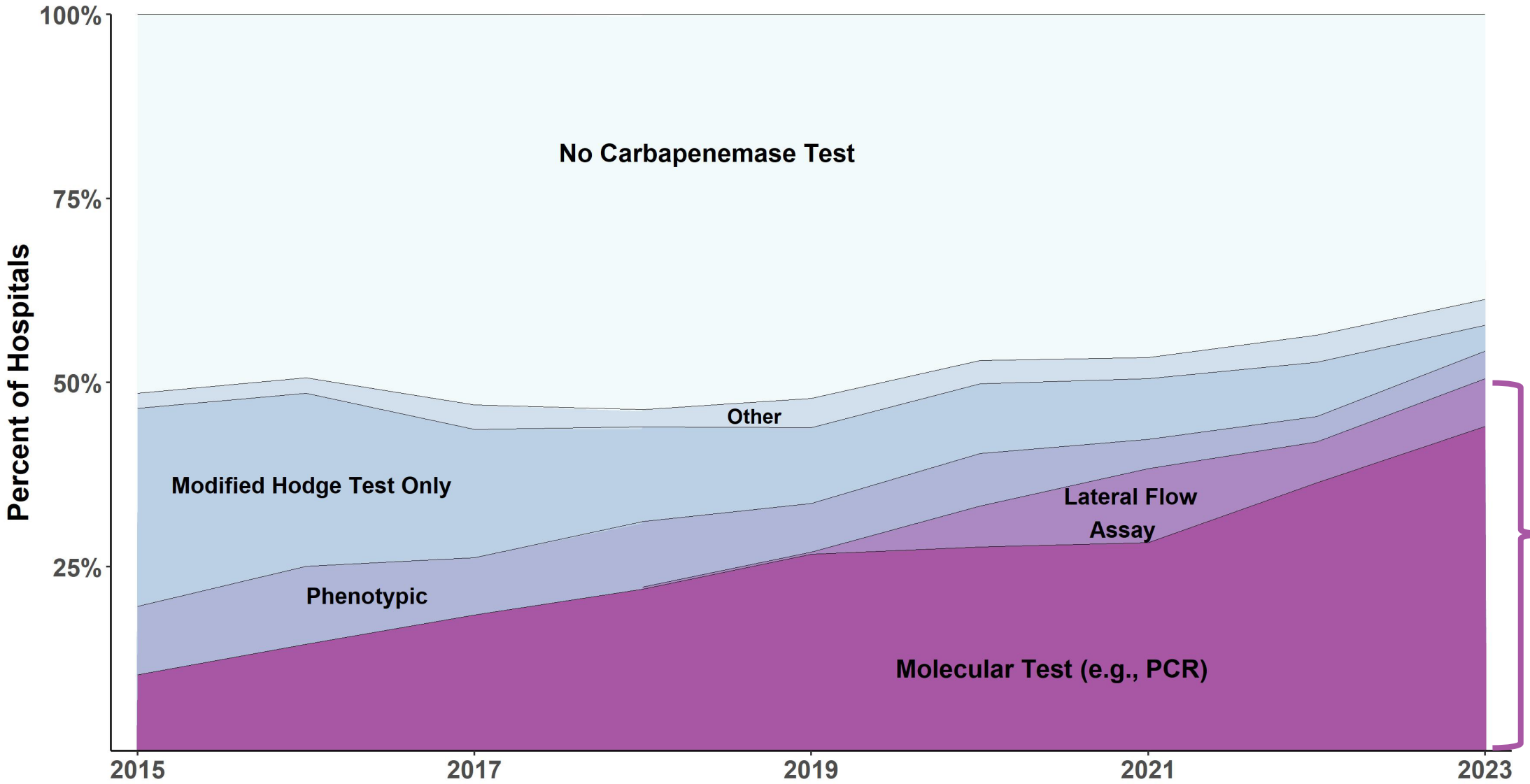
Opportunities for Improvements in Carbapenemase Testing and CPO Reporting

More hospitals report access to molecular testing; 44% don't test



Lateral flow assays and molecular tests can distinguish the type of carbapenemase (e.g., KPC vs. NDM)

Source: NHSN Patient Safety Annual Hospital Survey (www.cdc.gov/nhsn/faqs/faq-annual-survey.html#Annual-Hospital-Survey)

Features of Some Carbapenemase Tests

Tests method	Accuracy	TAT	Relative Cost	Limitation	Accessibility
Phenotypic					
Modified Hodge test	Moderate	Next day	$	**NOT RECOMMENDED**: Poor sensitivity for NDM and poor specificity with AmpC	Lab developed test
mCIM	High	Next day	$	For CRE and CRPA only	Lab developed test
CarbaNP	Moderate	Next day	$-$$$	For CRE and CRPA only, poor sensitivity for OXA-48	Commercial
Molecular/Other					
Lateral flow assay	High	< 24 hrs	$$	Limited to specific CPs, not validated for CRAB	Commercial
PCR (multiplex, real-time PCR)	High	< 24 hrs	$$$-$$$$	Limited to specific gene targets	Commercial or lab developed test
Whole-genome sequencing	High	Several days	$$$$	Unable to detect novel carbapenemase	Lab developed test

Adapted from Baek, Y., et al. *Biomed Sci Letters* (2023). doi: 10.15616/BSL.2023.29.3.109 and Carbapenemase Testing for CROs: A Primer for Clinical and Public Health Laboratories (PDF) (www.cdph.ca.gov/Programs/CHCQ/HAI/CDPH%20Document%20Library/CRO_PrimerTests_for_Carbapenemases.pdf)

CDPH California Department of PublicHealth

Carbapenemase Testing Primer: A Resource for Labs

Table 2. Features of Various Tests for Carbapenemases

Feature	Phenotypic				Genotypic						
	mCIM / eCIM	CarbaNP	bioMerieux Rapidec® Carba NP	BD Phoenix™ CPO Detect	Cepheid Xpert® Carba-R	Hardy NG-Test® CARBA 5[1]	OpGen Acuitas® AMR Gene Panel	Biofire® FilmArray® BCID Panel	GenMark® ePlex BCID	Luminex® VERIGENE	Check-Points Check-Direct CPO for BD MAX™
Test system											
Special equipment needed	No[2]	Yes (pH meter)	No	Yes (BD Phoenix)	Yes	No	Yes	Yes	Yes	Yes	Yes
Kit storage temperature	NA	NA	2-8°C	≈20°C (RT)	2-28°C	4-30°C	15-25°C 2-8°C	15-25°C	2-8°C	2-30°C -20°C	2-25°C
Relative cost / test	$	$ - $$$	$$	$$$	$$$	$$	$$$	$$$$	$$$$	$$$$	$$$
Time to Result	Overnight	≈0.5-2 hr	≈0.5-2 hr	Overnight	≈75 min	≈25 min	≈2.5 hr	≈1 hr	≈1.5 hr	≈2 hr	≈5 hr
Relative expertise/ training requirement	++	+++	++	++	+	+	+++	+	+	+++	+++

Carbapenemase Testing for CROs: A Primer for Clinical and Public Health Laboratories (PDF)
(www.cdph.ca.gov/Programs/CHCQ/HAI/CDPH%20Document%20Library/CRO_PrimerTests_for_Carbapenemases.pdf)

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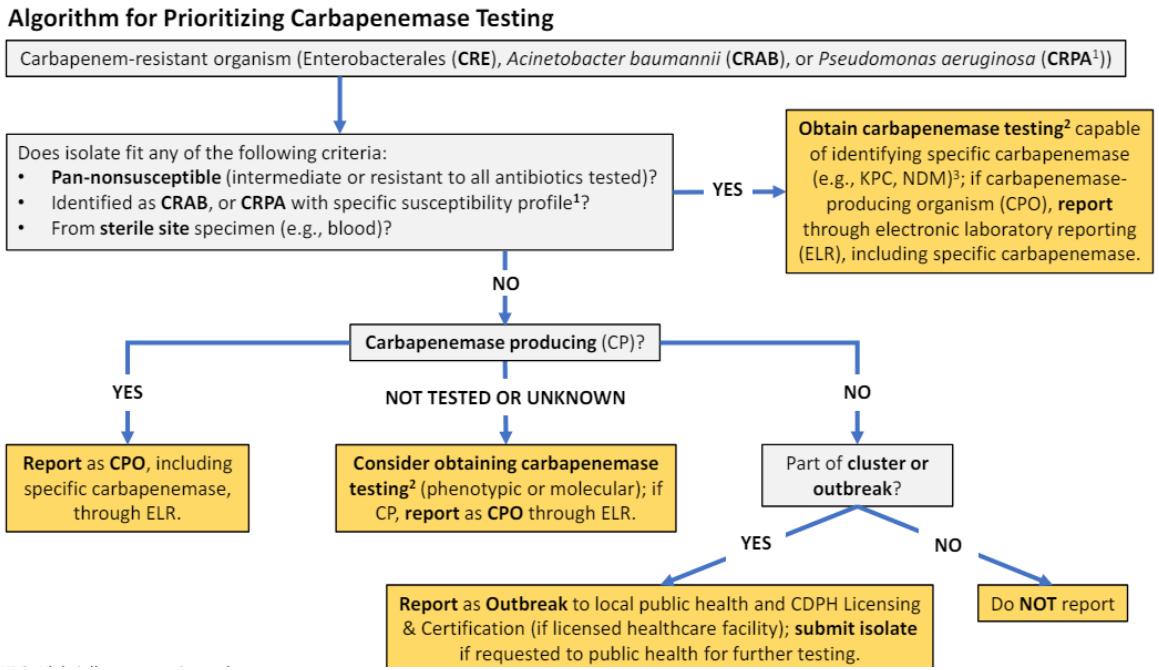
When do we recommend conducting carbapenemase testing?

- **For screening**
  - Testing high-risk patients **on admission**
  - **Routine point prevalence survey** (PPS) of patients at long-term acute care hospital (LTACHs) and ventilator-equipped skilled nursing facility (vSNF) vent units
  - **Responding** to new cases (healthcare contacts)



- **For clinical isolates**
  - All CRE, CRAB; CRPA nonsusceptible to ceftazidime or cefepime

CDPH Algorithm for Prioritizing Carbapenemase Testing (PDF)
(www.cdph.ca.gov/Programs/CHCQ/HAI/CDPH%20Document%20Library/CPTestingPrioritizationAlgorithm.pdf)

How do we prioritize public health CPO screening resources?

- ✓ Public health-recommended **response-related screening** of close healthcare contacts (e.g., roommates, point prevalence survey) at any facility
  - excludes admission screening
- ✓ **Prevention-based** routine admission screening and PPS at LTACHs and vSNFs

When should labs submit CRO isolates to public health for testing?

If your lab is able to test CROs for carbapenemases:

- Submit CRAB negative for Big 5 (KPC, VIM, NDM, OXA-48, IMP) to MDL via your local public health lab for additional testing

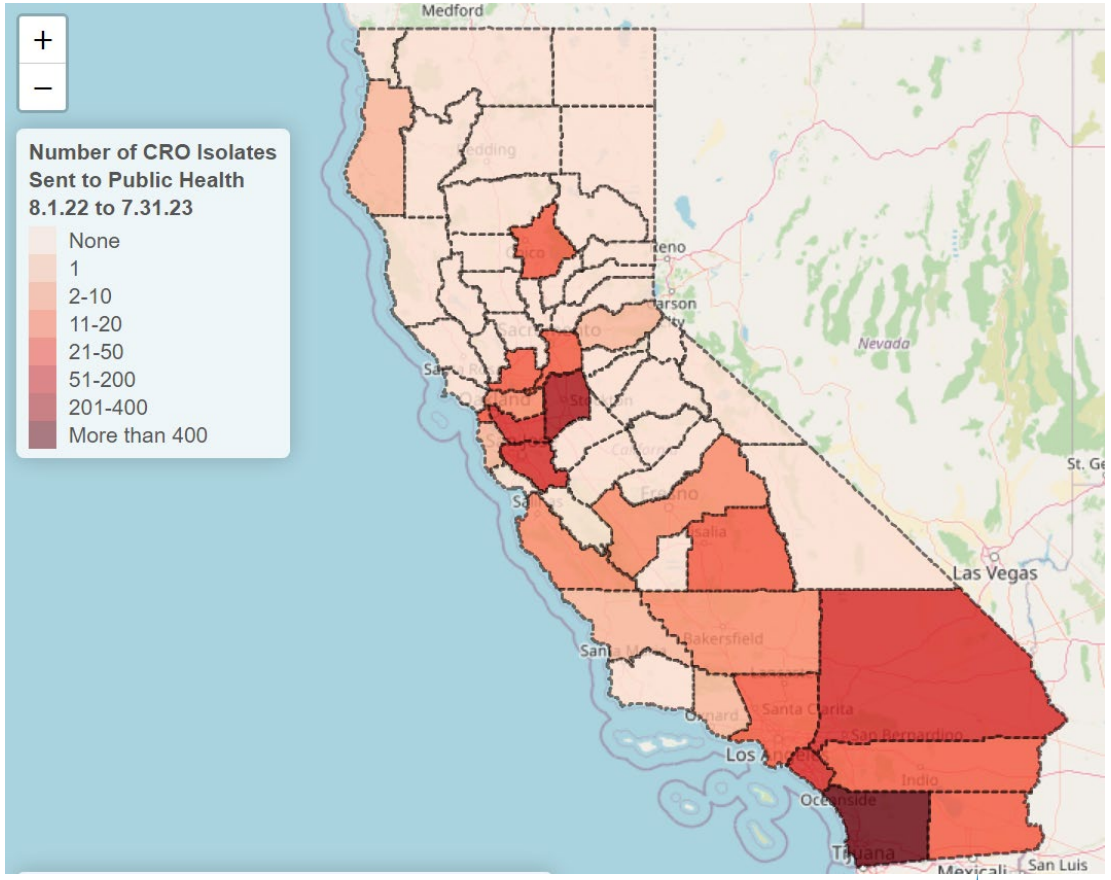
If your lab is not able to test CROs for carbapenemases:

- Consider adding this capability to inform treatment, infection prevention and control measures
- Forward CROs meeting criteria* to MDL via local public health lab for carbapenemase testing

*See CDPH MDL Carbapenemase Testing FAQs (www.cdph.ca.gov/Programs/CID/DCDC/Pages/MDL-Expanded-Carbapenemase-Testing-Services-FAQs.aspx)

Which labs are submitting isolates to public health?

- We encourage submission in counties with no or very few isolates being sent to public health (shown in light pink)
- Thank you to all facilities who are participating in surveillance! Your efforts are appreciated.



*See [CDPH MDL Carbapenemase Testing FAQs](www.cdph.ca.gov/Programs/CID/DCDC/Pages/MDL-Expanded-Carbapenemase-Testing-Services-FAQs.aspx)
(www.cdph.ca.gov/Programs/CID/DCDC/Pages/MDL-Expanded-Carbapenemase-Testing-Services-FAQs.aspx)

Improving CPO Reporting

- The CalREDIE team and HAI Program are committed to working with laboratories to ensure full compliance with CPO [and *C. auris*] ELR requirements

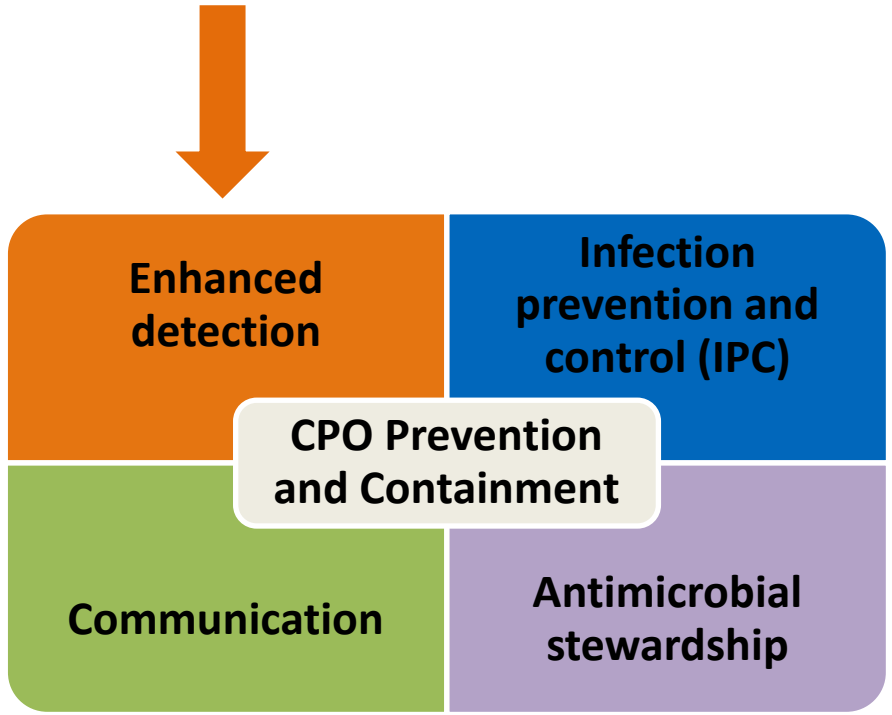
- Thank you for working with us to support complete and accurate reporting!

Testing and Reporting Help Improve Patient Safety

Carbapenemase testing allows for:

- case and outbreak detection
- implementation of appropriate infection prevention & control measures
- promotion of antimicrobial stewardship (www.cdph.ca.gov/Programs/CHCQ/HAI/Pages/AntimicrobialStewardshipLandingPage.aspx) through informed treatment decision-making
- public health surveillance to understand epidemiology and implement focused prevention and response strategies

Thank you to all of our laboratory and healthcare facility partners!



Carbapenemase Testing Resources

- Algorithm for testing CRO for carbapenemases (PDF) (www.cdph.ca.gov/Programs/CHCQ/HAI/CDPH%20Document%20Library/CPTestingPrioritizationAlgorithm.pdf)
- Carbapenemase testing for CROs: a primer for clinical and public health labs (PDF) (www.cdph.ca.gov/Programs/CHCQ/HAI/CDPH%20Document%20Library/CRO_PrimerTests_for_Carbapenemases.pdf)
- Carbapenemase testing at MDL FAQ (www.cdph.ca.gov/Programs/CID/DCDC/Pages/MDL-Expanded-Carbapenemase-Testing-Services-FAQs.aspx)
- Laboratory testing validation resources are available from public health upon request (contact HAIProgram@cdph.ca.gov or CARL@cdph.ca.gov)

Resources for Implementing Carbapenem Breakpoints

Effective January 2024, clinical laboratories performing AST are required to use breakpoints currently recognized by the Clinical and Laboratory Standards Institute (CLSI) or US Food and Drug Administration (FDA).

2023 Breakpoint Implementation Toolkit (2023 BIT)

CLSI APHL AMERICAN SOCIETY FOR MICROBIOLOGY COLLEGE of AMERICAN PATHOLOGISTS

COLLEGE of AMERICAN PATHOLOGISTS

The following tools can be helpful:

- Maintaining Current Breakpoints for AST (info.cap.org/ antimicrobial-susceptibility-testing/)
- CLSI 2023 Breakpoint Implementation Toolkit (clsi.org/meetings/ast/breakpoints-in-use-toolkit/)
- CLSI: Free Microbiology, Method Evaluation, COVID-19 Resources (clsi.org/all-free-resources/)

Questions?

Contact us at HAIProgram@cdph.ca.gov or CARL@cdph.ca.gov