QUARTERLY MDRO UPDATE #8

LOS ANGELES COUNTY DEPARTMENT OF PUBLIC HEALTH

11/01/21

HIGHLIGHTED IN THIS ISSUE

- CP-CRPA
- LAC MDRO Reporting (pg. 8)
- *Candida auris* update (pg. 9)

SUMMARY

Management of all CRPA infections can be challenging. It is particularly important to know when and how to identify CP-CRPA in order to contain their spread.

KEY RESOURCES

LA County N-MDRO Home Page

LA County Reportable Disease List

CDPH CRAB&CRPA Quicksheet

CDC MDR *P. aeruginosa* data

CDC CRPA data

CDC Urgent AR Threats Report (2019)

CDC HAI Lab Resources Home Page

Note: When calling 213-240-7941 to report MDROs (which is currently routed to a COVID-19 Call Center), please state that you are calling to report an MDRO to the Acute Communicable Disease Control (ACDC) Program.

MESSAGE FOR CLINICAL LABORATORIES

This issue focuses on a specific MDRO, carbapenem-resistant *Pseudomonas aeruginosa* (CRPA). Like other carbapenem-resistant gram-negative bacilli, CRPA are often resistant to many other antimicrobial agents and treatment of patients with CRPA infections can be challenging. In addition, carbapenemase-producing (CP)-CRPA is considered to be an urgent public health threat. It is important to use reliable antimicrobial susceptibility test (AST) methods to detect and report CRPA, and to take appropriate measures to contain the spread of CRPA.

We welcome feedback on this Newsletter, previous Newsletters or any other issue related to MDROs (mail hai@ph.lacounty.org).

Previous Newsletters can be found by clicking the links below:

Issue	Featured Content
1 (link)	• Identifying and Reporting *C. auris* • Resources for testing for *C. auris*
2 (link)	• Antifungal susceptibility testing of *C auris* • Validating MALDI-TOF for *C auris*
3 (link)	• Case Study: A team approach to containing *C auris* • The Antibiotic Resistance Lab Network
4 (link)	• Passive surveillance systems for *C auris* • Updated resources for testing for *C. auris*
5 (link)	• Multi-Drug Resistant Organisms
6 (link)	• Carbapenem-resistant *A baumannii* (CRAB) • NDM-CRAB outbreak in Northern California • Testing methods for carbapenemases
7 (link)	• *C. auris* update

CARBAPENEM-RESISTANT *PSEUDOMONAS AERUGINOSA*

DEFINITIONS OF CRPA AND CP-CRPA

CRPA - resistant to imipenem, meropenem or doripenem using standard AST methods and the following breakpoints:

Agent	Disk Content (µg)	Disk Diffusion (mm)			MIC (µg/ml)		
		Susc	Int	Res	Susc	Int	Res
Doripenem	10	≥18	15-17	≤14	≤2	4	≥8
Imipenem	10	≥22	19-21	≤18	≤2	4	≥8
Meropenem	10	≥18	15-17	≤14	≤2	4	≥8

Source: CLSI M100 31st edition.

CP-CRPA – CRPA that are positive for carbapenemase production using a phenotypic assay (e.g., mCIM) and/or a carbapenemase gene as detected using a molecular assay (e.g., GeneXpert® Carba-R).

CARBAPENEM RESISTANCE MECHANISMS IN CRPA

Carbapenem resistance (CR) can stem from:

- Carbapenemase (e.g., VIM, KPC, IMP, NDM)
- Non-carbapenemase due to changes in permeability or activation of efflux pumps and/or increased cephalosporinase activity

Note that carbapenem resistance in a single isolate can be due to either or both mechanisms, and some isolates may harbor more than one carbapenemase gene. Routine AST results will reveal if an isolate is CRPA, however an additional test for carbapenemase is needed to determine if an isolate is CP-CRPA.

CARBAPENEMASES AND *P. AERUGINOSA*

CDC recently reported results of CRPA isolates tested in the USA from 2017-2020: [1]

- Among 43,018 CRPA isolates encountered nationwide through the AR Laboratory Network, 900 (2.09%) were positive for a carbapenemase gene. See *Figure 1*.
- The most common gene was VIM followed by KPC, IMP and NDM. No isolates were shown to have OXA-48; however, there have been reports of this gene in *P. aeruginosa* [2]
- Among 1,411 CRPA isolates from California, 59 (4.2%) were positive for a carbapenemase gene with 51 VIM, 8 IMP, 4 NDM, 2 KPC; some isolates contained >1 carbapenemase gene

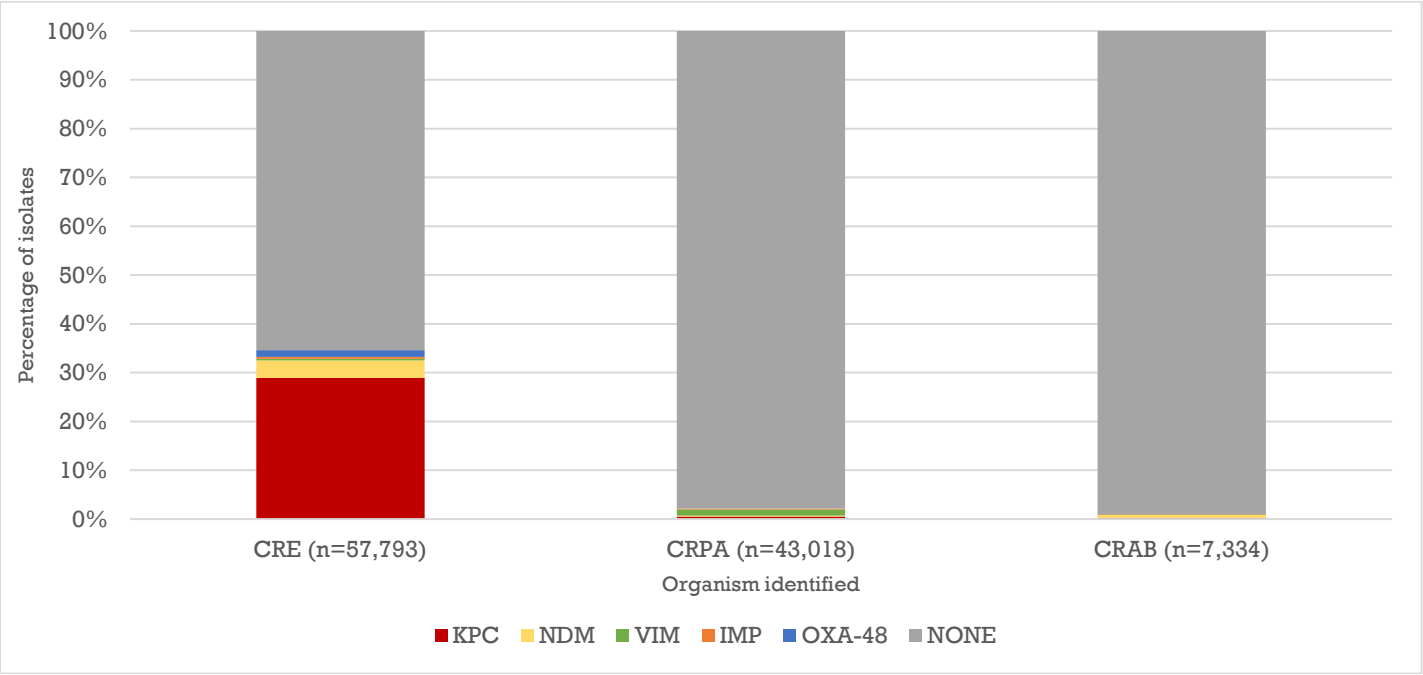
[1] https://arpsp.cdc.gov/profile/arln/crpa

[2] F. Tarafdar,1 B. Jafari,1,* and T. Azimi. 2020. New Microbes New Infect. 37:100686. doi: 10.1016/j.nmni.2020.100686

From 2015-2020, 23 (2.6%) of 870 CRPA isolates tested at the Los Angeles County (LAC) Public Health Laboratories (PHL) were positive for a carbapenemase with VIM only (n=11, 47%), VIM+IMP (n=6), NDM (n=3), IMP (n=2), and KPC (n=1). This contrasts with carbapenem-resistant Enterobacterales (CRE) in LAC, where nearly 90% of 1,088 CRE isolates and 92% of 28 carbapenem-resistant *Acinetobacter baumannii* (CRAB) isolates tested at the LAC PHL were carbapenemase positive.

Although it is important to contain the spread of all CRPA, CDC targets CP-CRPA for detection and response because carbapenemases and other plasmid-mediated antimicrobial resistance genes can be spread easily.[1] Treatment options for all CRPA are limited. *Table 1* lists newer agents that may and may not have activity against CRPA.

Figure 1. Carbapenemase gene detection among CR isolates in the United States, 2017-2020 (n=108,145)



Note that CR isolates with more than 1 gene identified were excluded.
Source: https://arpsp.cdc.gov/profile/antibiotic-resistance?tab=ar-lab-network

Table 1. Activities of Newer Agents for CRPA [1,2,3]

Beta-Lactam Combination Agents	
Ceftazidime-avibactam	Yes
Ceftolozane-tazobactam	Yes
Imipenem-relebactam	Yes
Meropenem-vaborbactam*	No
Other Agents	
Cefiderocol	Yes
Eravacycline	No
Omadacycline	No

*Not active beyond meropenem alone

1 https://www.idsociety.org/practice-guideline/amr-guidance/
2 Tamma PD, Aitken SL, Bonomo RA, et al. 2021. Clin Infect Dis. 72(7):e169-e183. doi: 10.1093/cid/ciaa1478.
3 Delgado-Valverde M, Conejo MDC, Serrano L, et al. 2020. J Antimicrob Chemother. 75(7):1840-1849. doi: 10.1093/jac/dkaa117.

IDENTIFICATION OF CP-CRPA

A recent report from CDC suggests that the antimicrobial susceptibility profile of a CRPA isolate can help determine if the isolate is more likely to be a CP-CRPA. Thus, the phenotype can help the laboratory determine which isolates to select for carbapenemase testing.[2] (*Table 2*) For example, in Row 1, of 6159 CRPA tested, 195 (3%) were carbapenemase producers. A result of "not susceptible (NS)" [i.e., intermediate (I) or resistant (R)] for cefepime was obtained for 83% (sensitivity) of carbapenemase producers. However, 47% or CRPA that were intermediate or resistant to cefepime were not carbapenemase producers (specificity). If results for either cefepime OR ceftazidime were evaluated, the sensitivity increased but specificity decreased. When isolates with an intermediate or resistant result to ceftolozane-tazobactam was used as a marker, all CP-CRPA were identified, but 14% of isolates that were intermediate or resistant to ceftolozane-tazobactam did not produce carbapenemase. Breakpoints used to categorize results for the agents evaluated are shown in *Table 3*.

The study concluded that there should be a high suspicion for carbapenemases in CRPA isolates that are NS to ceftazidime and/or cefepime and a very high suspicion for CRPA that are NS to ceftolozane-tazobactam; these isolates should be targeted for carbapenemase testing and infection control interventions. Please see LAC MDRO Update #6 that lists methods for testing for carbapenemases in CRPA.

[1] https://arpsp.cdc.gov/profile/arln/crpa
[2] Vallabhaneni, Huang, Grass et al. 2021. J Clin Microbiol. 59:e02874-20.

Table 2. Sensitivity and Specificity of AST-based Definitions for Identifying Carbapenemase Producers among P. aeruginosa Isolates R to Imipenem and/or Meropenem[1]

Definition	No.*	No. (%) Confirmed as CP-CRPA	No. of True Positives	No. of False Positives	Sensitivity	Specificity
NS^ to cefepime	6159	195 (3)	161	2778	83	53
NS to ceftazidime	5299	147 (3)	139	2021	94	61
NS to cefepime OR ceftazidime	6192	195 (3)	178	2979	91	50
NS to ceftolozane-tazobactam	903	223 (25)	223	94	100	86

*Number (No.) varies as results were not available for all agents for all isolates examined
^NS, not susceptible (e.g., I or R)
[1] Extracted from Vallabhaneni, Huang, Grass et al. 2021. J Clin Microbiol. 59:e02874-20.

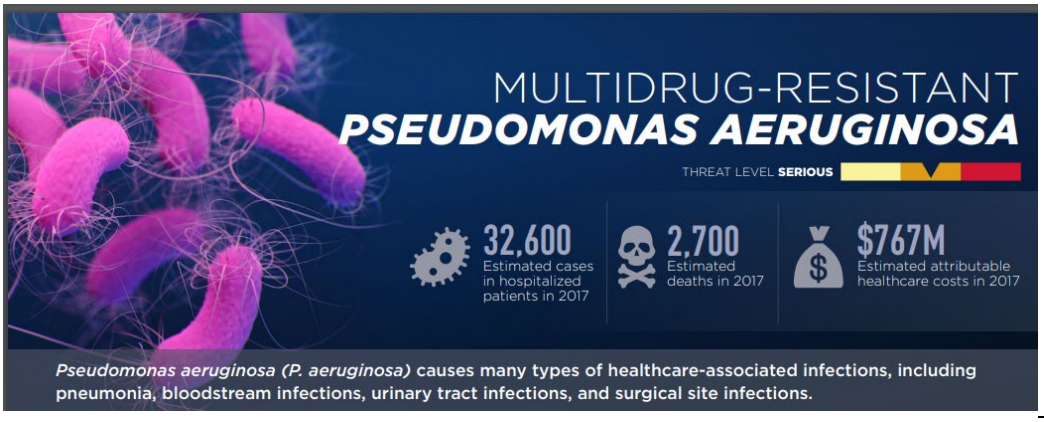
Table 3. Breakpoints Used in CDC Study (Table 2) to Evaluate AST Results for CRPA

Agent	Disk Content (µg)	Disk Diffusion (mm)			MIC (µg/ml)		
		Susc	Int	Res	Susc	Int	Res
Cefepime	30	≥18	15-17	≤14	≤8	16	≥32
Ceftazidime	30	≥18	15-17	≤14	≤8	16	≥32
Ceftolozane-tazobactam	30/10	≥21	17-20	≤16	≤4/4	8/4	≥16/4

Source: CLSI M100 29th edition (same as breakpoints in CLSI M100 31st edition)

WHERE DOES CRPA FIT ON THE PRIORITY LIST WITH OTHER MDRO?

In the CDC AR Threats Report (2019), multidrug-resistant *P. aeruginosa* are considered a serious threat to the public's health and require prompt and sustained action. In 2019, CDC reported that 7.9% of *P. aeruginosa* isolates reported through the National Healthcare Safety Network (NHSN) were multidrug resistant.



CP-CRPA IN LA COUNTY

In the 2017 LAC antibiogram data submitted from more than 80 hospitals, approximately 20% of nearly 24,000 isolates of *P. aeruginosa* were NS to meropenem and/or imipenem. However, the rate varied widely among submitters. The prevalence of CRPA in LAC appears at or above that reported in other parts of the country.

CP-CRPA and Medical Tourism

In 2019, the CDC alerted providers and laboratories in the United States (US) of an emerging threat of VIM-CRPA from Mexico- see here. In LAC, very few VIM-CRPA cases identified have occurred in individuals who traveled from the US to Mexico specifically for weight loss surgery. Several cases were associated with surgical site infections- and one of these led to an outbreak of VIM-CRPA in an LAC skilled nursing facility. In February 2021, the California Department of Public Health (CDPH) sent an alert of the ongoing threat of VIM-CRPA primarily among patients who had invasive procedures *or* hospitalizations in Mexico.

Please be suspicious for VIM-CRPA when the following is encountered:

- CRPA isolate that is NS to cefepime, ceftazidime, and/or ceftolozane-tazobactam **AND**
- The patient recently had an invasive procedure and/or overnight stay in a healthcare facility in Mexico

PAN-RESISTANT CRPA CASE EXAMPLE

Specimen: abscess
Culture results:
Pseudomonas aeruginosa
Candida parapsilosis
Coagulase-negative *Staphylococcus*

IP makes Contact

- An LAC clinical laboratory identifies a suspect pan-drug resistant (PDR) CRPA isolate (see *Table 4*, Clinical Lab Results).
- The IP reports the case to the HOU noting that the patient was recently hospitalized in Mexico, suggesting the CRPA isolate might be a VIM producer.

Isolate gets tested

- The HOU requests the isolate be sent to the LAC PHL.
- The LAC PHL conducts testing in-house, and sends the isolate to a CDC laboratory for confirmatory carbapenemase testing (molecular and phenotypic) and expanded AST.

Public Health investigates

- While awaiting final results, HOU epidemiologists work with the IP to identify potential exposures.
- No other patients were exposed at the hospital; staff implemented Contact Precautions upon admission because of the patients history.
- No other healthcare facilities were exposed; patient came straight from Mexico.

Follow-Up

- CDC concluded the isolate was not "true PDR" (S to cefiderocol, I to colistin) and did not warrant more extensive investigation (see *Table 4*, CDC Lab Results).
- LACDPH reminded the IP to ensure this patient's MDRO be communicated to the next healthcare facility upon discharge, and to notify LACDPH of any further suspect VIM-CRPA or PDR isolates.

Table 4. Pseudomonas aeruginosa AST Results

Antimicrobial Agent	MIC (µg/mL)	
	LA Clinical Lab	CDC Lab
Amikacin	>=64 R	>64 R
Aztreonam	NT	>64 R
Cefepime	>=64 R	>32 R
Cefiderocol	NT	1 S
Ceftazidime	>=64 R	>128 R
Ceftazidime-avibactam	>=256 R (Etest @ ref lab)	16/4 R
Ceftolozane-tazobactam	NT	>16/4 R
Ciprofloxacin	>=4 R	>8 R
Colistin	NT	1 I
Gentamicin	>=16 R	>16 R
Imipenem	NT	16 R
Imipenem-relebactam	NT	8/4 R
Levofloxacin	NT	>8 R
Meropenem	>=16 R	>8 R
Piperacillin-tazobactam	R (disk diffusion)	128/4 R
Tobramycin	>=16 R	>16 R

NT, not tested

CDC Report Comment: *The isolate is PCR negative for the most common carbapenemase genes: blaKPC, blaNDM, blaOXA-48-like, blaVIM and blaIMP.*

WHAT CAN WE DO ABOUT CONTAINING CRPA IN LA COUNTY?

What should clinical laboratories do to contain the spread of CP-CRPA in LAC?

- Use appropriate AST methods, including current breakpoints (see CLSI M100 31st ed.), to identify and report CRPA.
- Consider confirming AST results for CRPA if uncommon in your facility (see CLSI M100 31st ed Appendix A).
- Consider performing carbapenemase testing on CRPA that are NOT susceptible (I or R) to cefepime, ceftazidime, and/or ceftolozane-tazobactam.
- Communicate results of all CRPA, especially CP-CRPA, to infection preventionists ASAP. Discuss with supervisor/director any potential communication delays due to retesting to confirm/expand results.
- Maintain ability to test agents beyond those on routine test panel (in-house or refer out) on CRPA upon request.
- Report CP-CRPA and suspect PDR CRPA to LACDPH (see *Table 5* below).

What IS LAC Public Health Laboratory and the AR Lab Network doing?

- Testing screening swabs related to outbreak investigations and regional response activities
- Collecting and analyzing CRPA isolates obtained from select laboratories
- Informing stakeholders about the CRPA situation in LAC

Analysis includes testing for carbapenemases and incorporates whole genome sequencing, when indicated.

What is LAC Healthcare Outreach Unit doing?

The Healthcare Outreach Unit (HOU) has employed several strategies to detect and prevent the spread of CRPA in LAC, particularly CP-CRPA, including the following:

- Generate County-level prevalence of CRPA vs other MDROs using the LAC antibiogram, to target interventions
- Made CP-CRPA a reportable condition as of 2019, to enhance surveillance and response activities
- Investigate reports of CP-CRPA, including screening of high-risk contacts when novel CP-CRPA are detected
- Support healthcare providers and laboratorians on how to detect and contain CRPA and CP-CRPA
- Educate providers on antimicrobial stewardship activities, to slow the onslaught of MDROs

REPORTING MDROS TO LACDPH

As a reminder, the following organisms are reportable to LACDPH as of November 2019. When Electronic Laboratory Reporting (ELR) is not set up, laboratories may submit reports via the LACDPH MDRO REDCap Reporting Portal: https://redcap.link/LACMDROPortal. All reports submitted to the LACDPH MDRO Reporting Portal will be received in a secure format. Reporters will have the options to save their progress, upload lab reports, and download a PDF copy of what was submitted to LACDPH. The Healthcare Outreach Unit (HOU) will follow-up on reports as needed.

Table 5. List of Reportable MDROs in Los Angeles County

Organism	Disease categories	Criteria	Who reports
Candida auris (C. auris)	*C. auris*	*Candida auris*	Lab and provider
	Presumptive *C. auris*	Commonly misidentified organisms per laboratory instrument (Refer to https://www.cdc.gov/fungal/candida-auris/recommendations.html)	Provider only
Carbapenem-resistant Enterobacterales (CRE)*	CRE	Enterobacterales that are resistant to one or more carbapenems (independent of any carbapenemase testing)	Provider only (hospitals via NHSN)
	CP-CRE	• Carbapenemase positive (CP)-CRE by phenotypic or molecular test, OR • Carbapenemase unknown (no carbapenemase test performed)	Lab only
CP- *Acinetobacter baumannii*	CP- *Acinetobacter* spp.	*Acinetobacter* spp. positive for carbapenemase by phenotypic or molecular test	Lab only
CP- *Pseudomonas aeruginosa*	CP- P. aeruginosa	*P. aeruginosa* positive for carbapenemase by phenotypic or molecular test	Lab only
Vancomycin-resistant *Staphylococcus aureus* (VRSA)	VRSA	*S. aureus* with a vancomycin MIC ≥ 16 µg/ml	Lab only
Pan-resistant organisms (Suspect PDR)	Suspect PDR	Gram negative bacteria that are not susceptible (intermediate or resistant) to all antibiotics tested	Lab only

**E. coli, Klebsiella oxytoca, Klebsiella pneumoniae, Enterobacter spp.*

For additional guidance on how to report MDROs, please visit the following links:

- MDRO Compliance Instructions
- MDRO Reporting FAQs
- MDRO Reporting Webinar Slides (2.5.20)
- MDRO Reporting Webinar Recording (2.5.20)

CANDIDA AURIS UPDATE

C. auris continues to pose a threat to persons residing in LA County healthcare facilities. LACDPH recommends that clinical labs increase detection of *C. auris* within LAC to control its spread via two key actions:

- *C. auris* admission screening
- Identifying *Candida* spp. to the species level for non-sterile sites

If conducting these actions is not possible for all patients/residents, LACDPH advises laboratories work with clinical/IP staff to find high-risk patients on which to focus this testing. High risk patients for *C. auris* include:

- Persons being admitted from any long-term acute care hospital (LTACH) (per 3/18/21 CAHAN) or any subacute unit of a skilled nursing facility (aka ventilator-capable SNFS (vSNFs))
- High-risk contacts of new *C. auris* cases (i.e., roommates) -use CDPH Screening Decision Tree
- Persons on a mechanical ventilator or with presence of tracheostomy
- Persons who are colonized with MDROs, especially rare carbapenemase-producing organisms
- Persons who have had a recent overnight stay in a healthcare facility outside of the US

If your laboratory cannot conduct *C. auris* testing on-site, refer to the LACDPH List of Laboratories with *C. auris* Testing Capacity to find a reference lab that provides this service for you. Note that the LAC Public Health Laboratories (PHL) can only conduct rule-out *C. auris* testing at this time for confirmed or presumptive *C. auris* isolates. **Please do not send any *C. auris* isolates nor swabs to LAC PHL without contacting the HOU first.** You may either call us at 213-240-7941 or email us at hai@ph.lacounty.gov.

C. AURIS BY THE NUMBERS (Updated 11/01/21)

To date, 61 bloodstream infections have been reported in LA County (6.6% of total LAC *C. auris* cases).

Table 6. ***C. auris cases in Los Angeles County by facility and case type, 2020-2021 (n=922)***

HCF Type	Surveillance*	Clinical^	Surveillance-to-clinical†	Total
General Acute Care Hospital (GACH)	44	33	12	89
Long Term Acute Care Hospital (LTACH)	650	31	99	780
Skilled Nursing Facility (SNF)	45	0	6	51
Other	2	0	0	2
Total	**741**	**64**	**117**	**922**

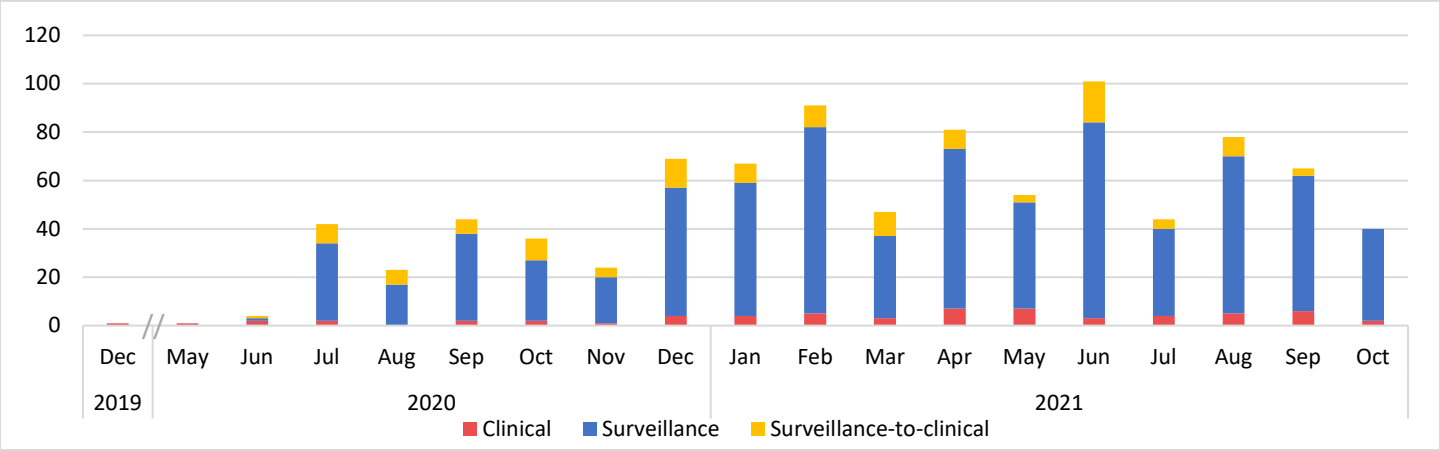
Note that all cases are counted by facility type and case type at time of first positive specimen collection.

** Swab collected for the purpose of screening for C. auris colonization.*

^ Specimen collected for clinical purposes.

† *Cases who were first identified via screening swab and later had one or more positive clinical specimen(s).*

Figure 2. C. auris cases in Los Angeles County by month, 2020-2021 (n=922)



See footnotes from *Table 6* above.