



Multistate Outbreak of *bla*_{VIM-80} & *bla*_{GES-9} Carbapenem-Resistant *Pseudomonas aeruginosa*: Leveraging the Antimicrobial Resistance Laboratory Network for Outbreak Detection

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APHL ID Lab Con

3/14/23

Pseudomonas aeruginosa

- Opportunistic pathogen that causes pneumonia, urinary tract, bloodstream, surgical site infections
- Transmission via environment or person-to-person in healthcare facilities
- Intrinsically resistant to many antibiotics



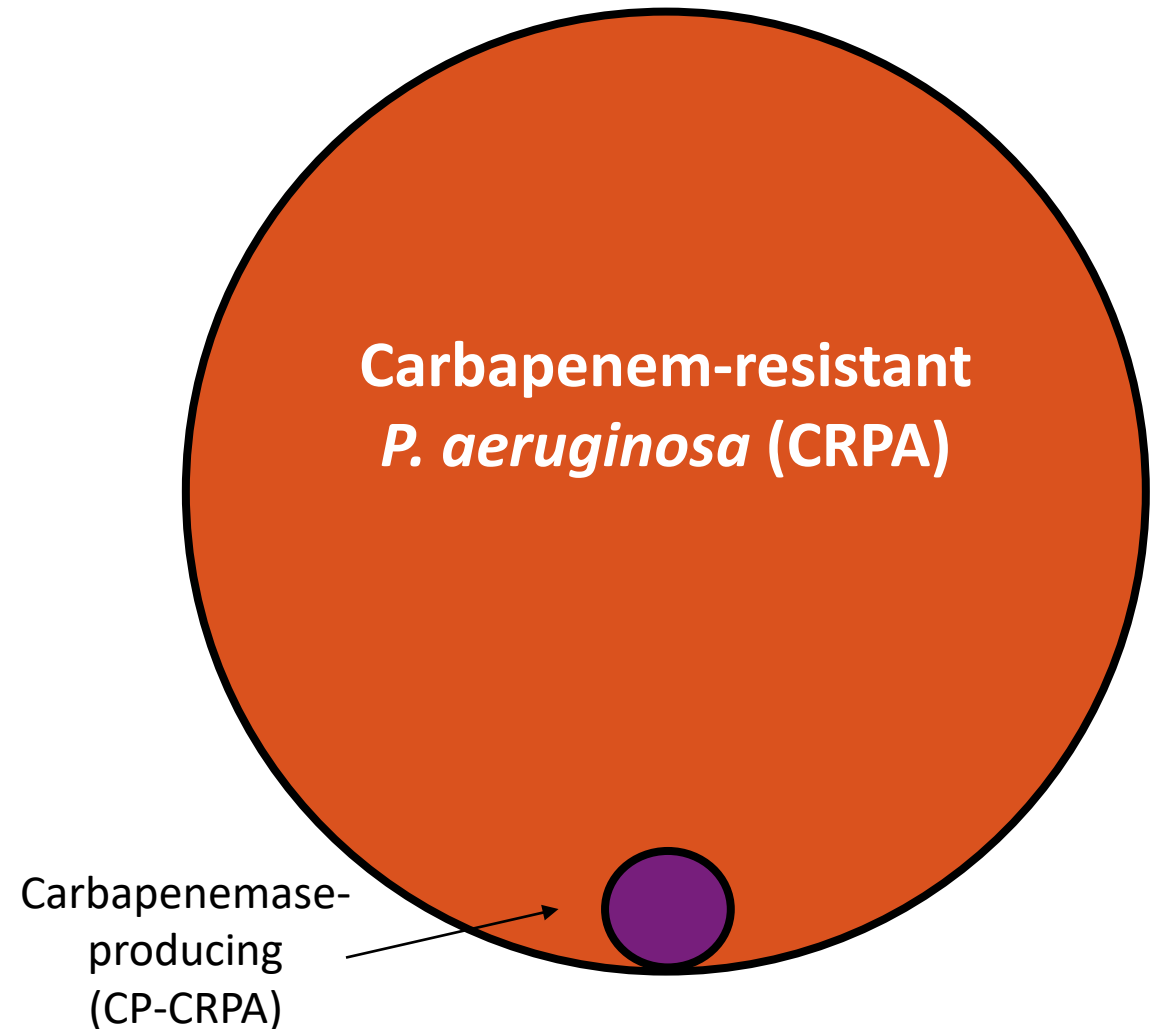
Carbapenem-resistant *Pseudomonas aeruginosa* (CRPA)

■ Multiple resistance mechanisms

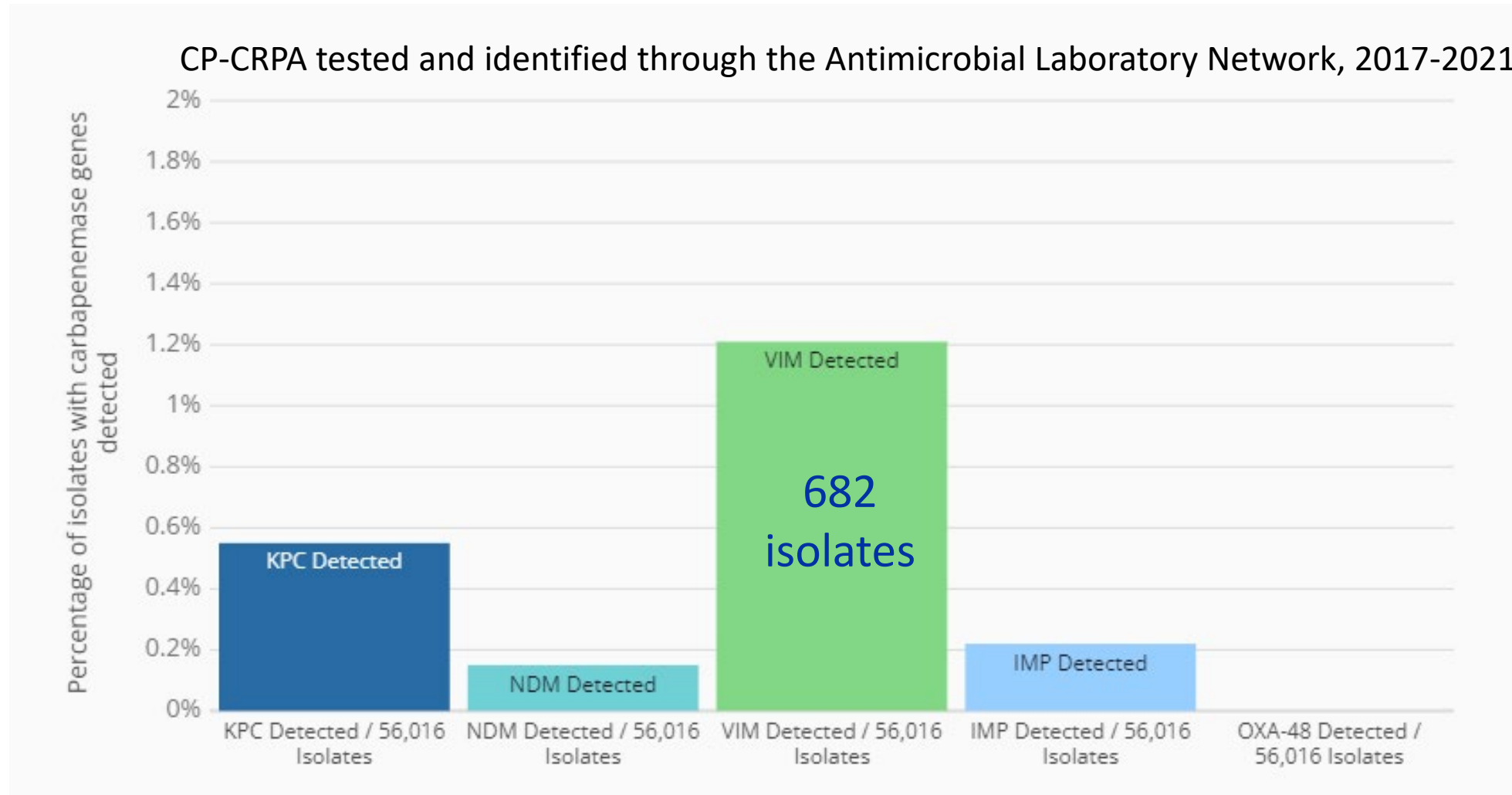
- Porin modification
- Efflux pump upregulation
- Carbapenemase production

■ Carbapenemase

- Enzyme that breaks down carbapenem antibiotics
- Encoded on mobile genetic elements (e.g., plasmid)



Carbapenemase-producing CRPA is rarely identified in the U.S.



CDC. Antibiotic Resistance & Patient Safety Portal (AR&PSP) AR Lab Network Data. Atlanta, Georgia: U.S. Department of Health and Human Services, CDC. <https://arpsp.cdc.gov/>.

Antimicrobial Resistance Laboratory Network (ARLN)

- **Enhancing testing capacity** in all 50 states, five local jurisdictions, and Puerto Rico
- **Transforming national lab infrastructure** with new, improved lab methods and technology
- **Opening communication channels** among all partners
- **Improving public health response** with actionable data



ARLN tiered testing for rapid response



CLINICAL LABS

Collect and submit patient samples for testing at public health department and regional labs



PUBLIC HEALTH DEPARTMENT LABS

Characterize patient samples for species type, carbapenemase production, and resistance profiles



7 REGIONAL LABS AND NATIONAL TB CENTER

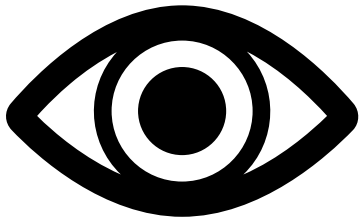
Detect antibiotic resistance, track changes in resistance, and identify outbreaks



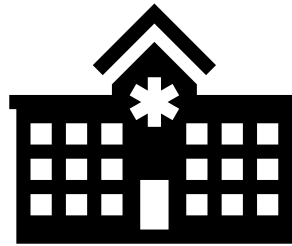
CDC

Coordinates the network, provides technical expertise, and supports outbreak responses

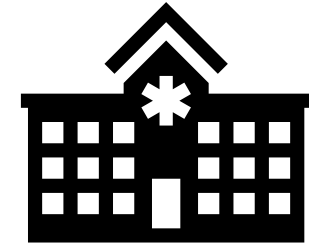
Summer of 2022: 3 VIM-CRPA clusters under investigation



**Ophthalmology Clinic
California (n=4)**



**Long Term
Care Facility
Utah (n=3*)**



**Long Term
Care Facility
Connecticut (n=21^)**

*3 additional cases recently, total n=6

^2 additional cases recently, total n=23

Data are preliminary and subject to change.

Whole genome sequencing links cases

- ST1203, VIM-80, GES-9
 - ST1203 is rare; only 5 HAI sequences in US previously
 - First report of VIM-80 & GES-9 in US
 - First sequence of *bla*_{VIM-80} (2018) from *P. aeruginosa* ST308 from Asia
 - First sequence of *bla*_{GES-9} (2014) from *P. aeruginosa* ST316 from Asia
 - 0-14 SNPs difference between isolate sequences
- No clear epidemiologic links between cases in different states suggested source is a **common product**



Case definition

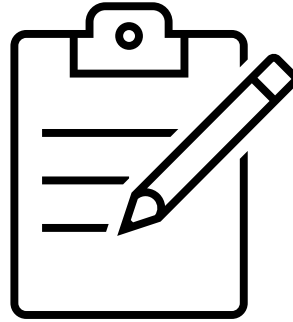
**Carbapenem-resistant *Pseudomonas aeruginosa*,
MLST 1203 with VIM-80 & GES-9 from any
specimen source collected on or after Jan 1, 2022.**

Investigation of outbreak source

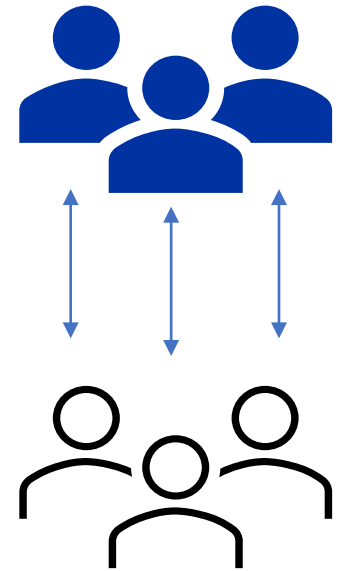
Case finding

Epi-X The Epidemic
Information Exchange

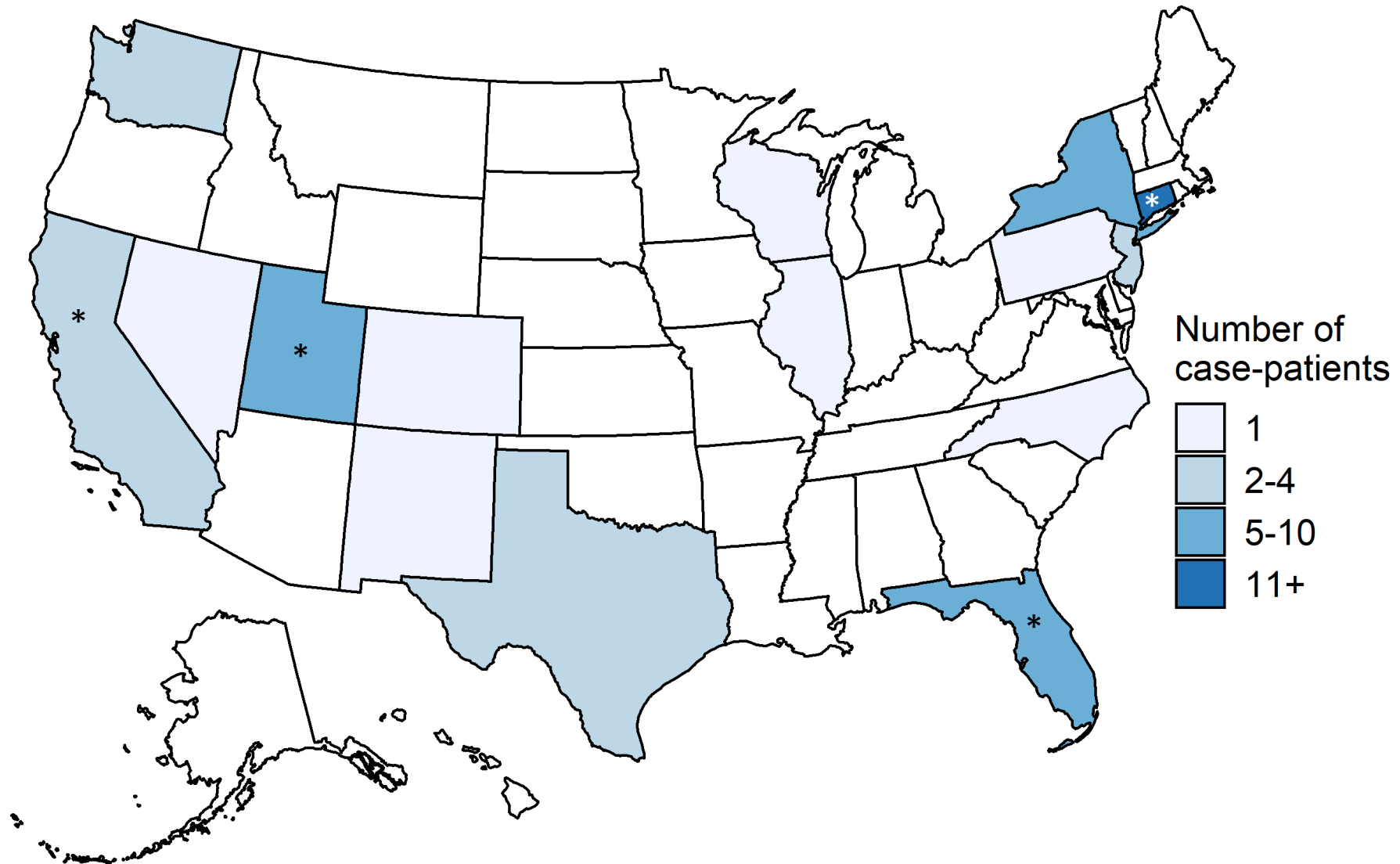
Case Report Forms &
Product Lists



Matched case-control
study

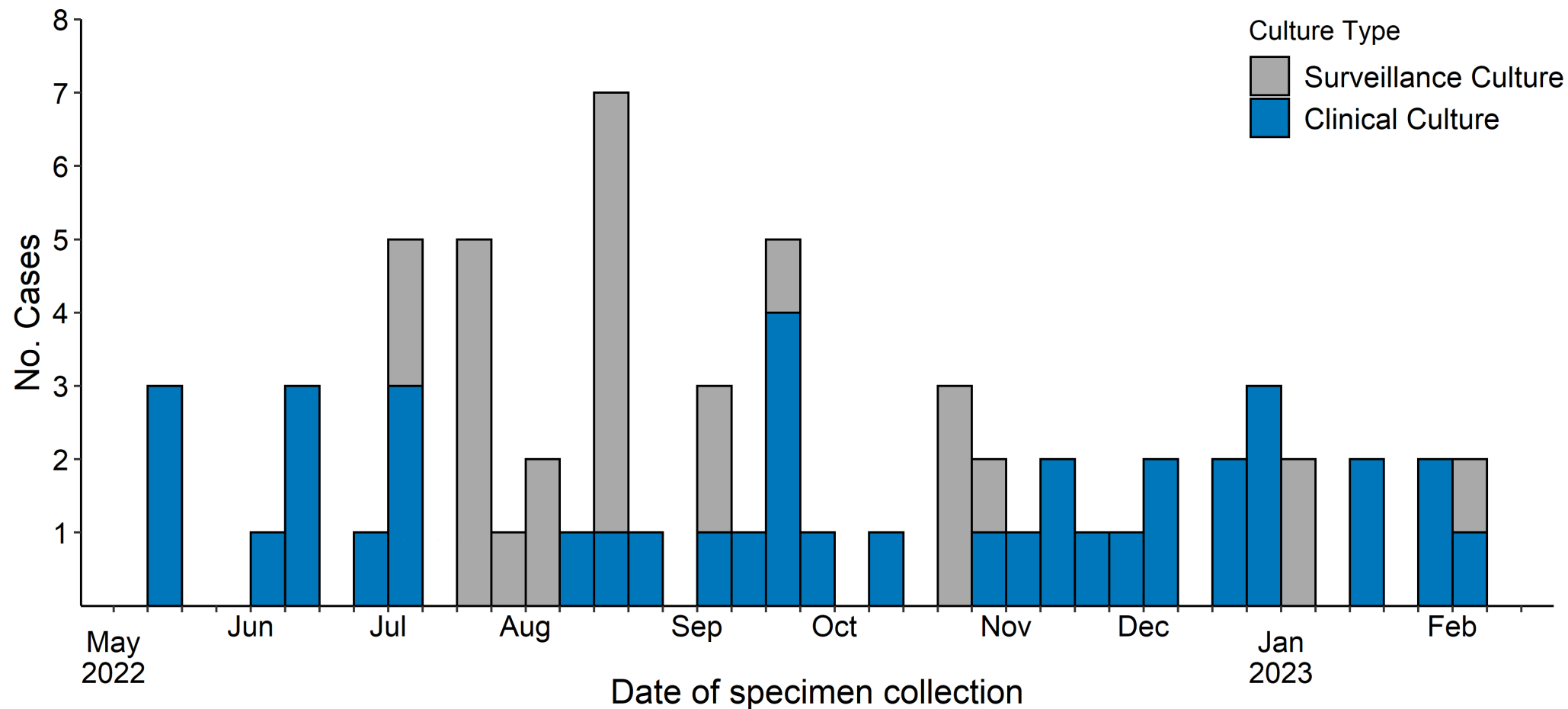


As of March 7, 2023: 66 case-patients with VIM-GES-CRPA



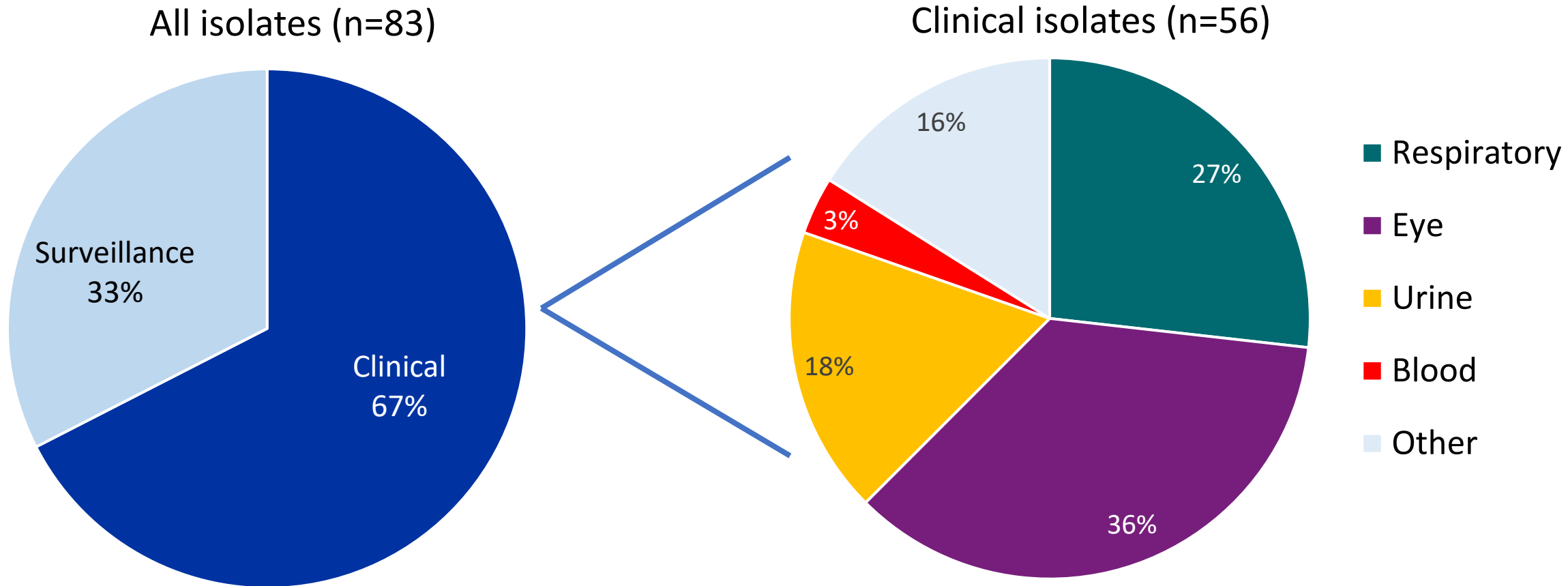
Data are preliminary and subject to change.

Number of case-patients by date of first VIM-GES-CRPA positive culture, as of March 6, 2023 (n=66)



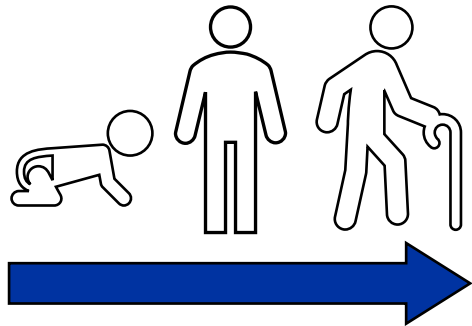
Data are preliminary and subject to change.

Diversity of specimen sources for confirmed cases



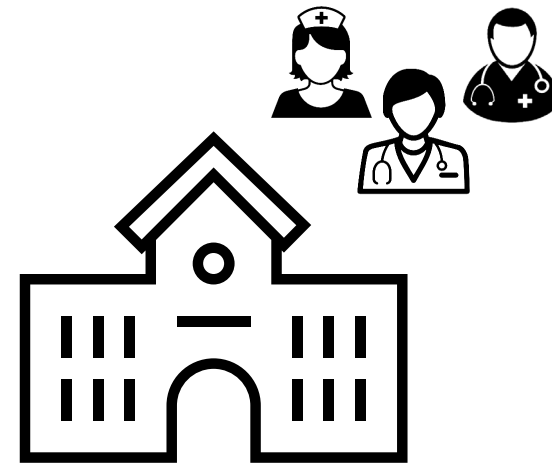
Data are preliminary and subject to change.

Case-patients were of all ages and identified in a variety of healthcare settings



Age

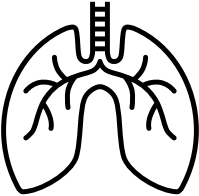
Median= 61 years
Range= 6 months-
102 years



Setting of specimen collection

Long Term Acute Care Hospital=26
Acute Care Hospital = 23
Outpatient clinic=12
Skilled Nursing Facility = 4

Underlying conditions differed by initial specimen source (N=66)

	Underlying Condition	Eye culture, N=17 n(%)	Other clinical culture, N=23 n(%)	Surveillance culture, N=26 n(%)
	Respiratory disease	5 (29%)	9 (39%)	23 (88%)
	Neurological disease	3 (18%)	9 (39%)	20 (77%)
	Eye disease	16 (94%)	4 (17%)	4 (15%)

Data are preliminary and subject to change.

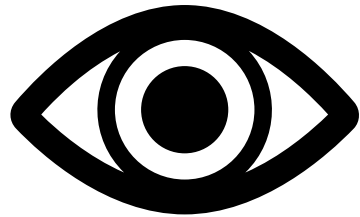
Indwelling devices differed by initial specimen source (N=66)



Medical device	Eye culture, N=17 n(%)	Other clinical culture, N=23 n(%)	Surveillance culture, N=26 n(%)
Tracheostomy	0 (0%)	9 (39%)	25 (96%)
PEG tube (feeding tube)	0 (0%)	6 (26%)	21 (81%)
Mechanical ventilation	1 (5.9%)	9 (39%)	14 (54%)

Data are preliminary and subject to change.

Case-patients with clinical cultures suffered vision loss and were hospitalized (N=43*)



Eye Infections (n=17)

Outcome	N	% ¹
Vision loss ²	8	62%
Enucleation	4	31%

¹outcome information available for only 13 patients

²not including enucleation



Patients with any clinical culture (n= 43)

Outcome	N	% ¹
Hospitalization ²	19	54%
Intensive Care Unit ²	6	17%
Death within 30 days	3	9%

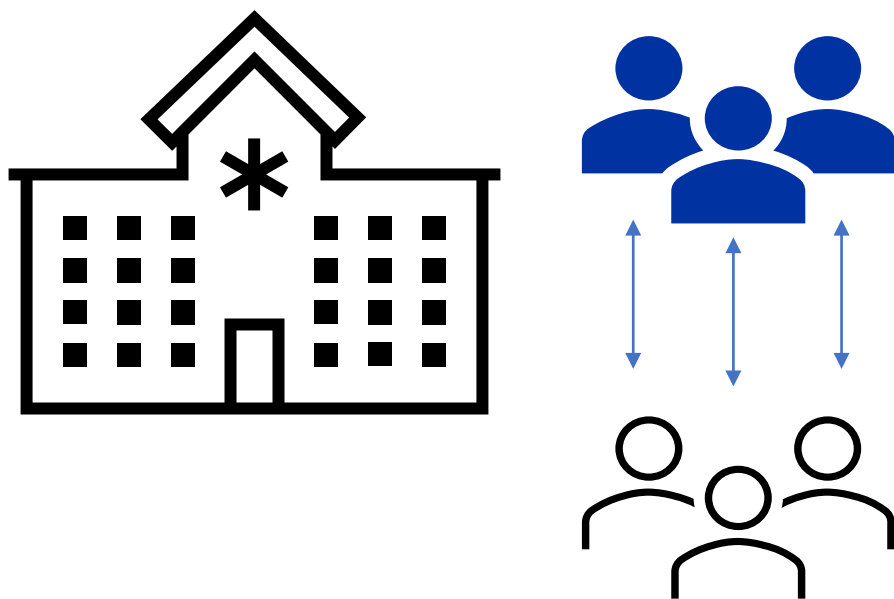
¹information available for 35 patients

²three days before – 2 weeks after culture collection

*3 case-patients had clinical cultures after surveillance cultures

Data are preliminary and subject to change.

Matched 1:1 Case-Control Study in CT Long-term Care Facility

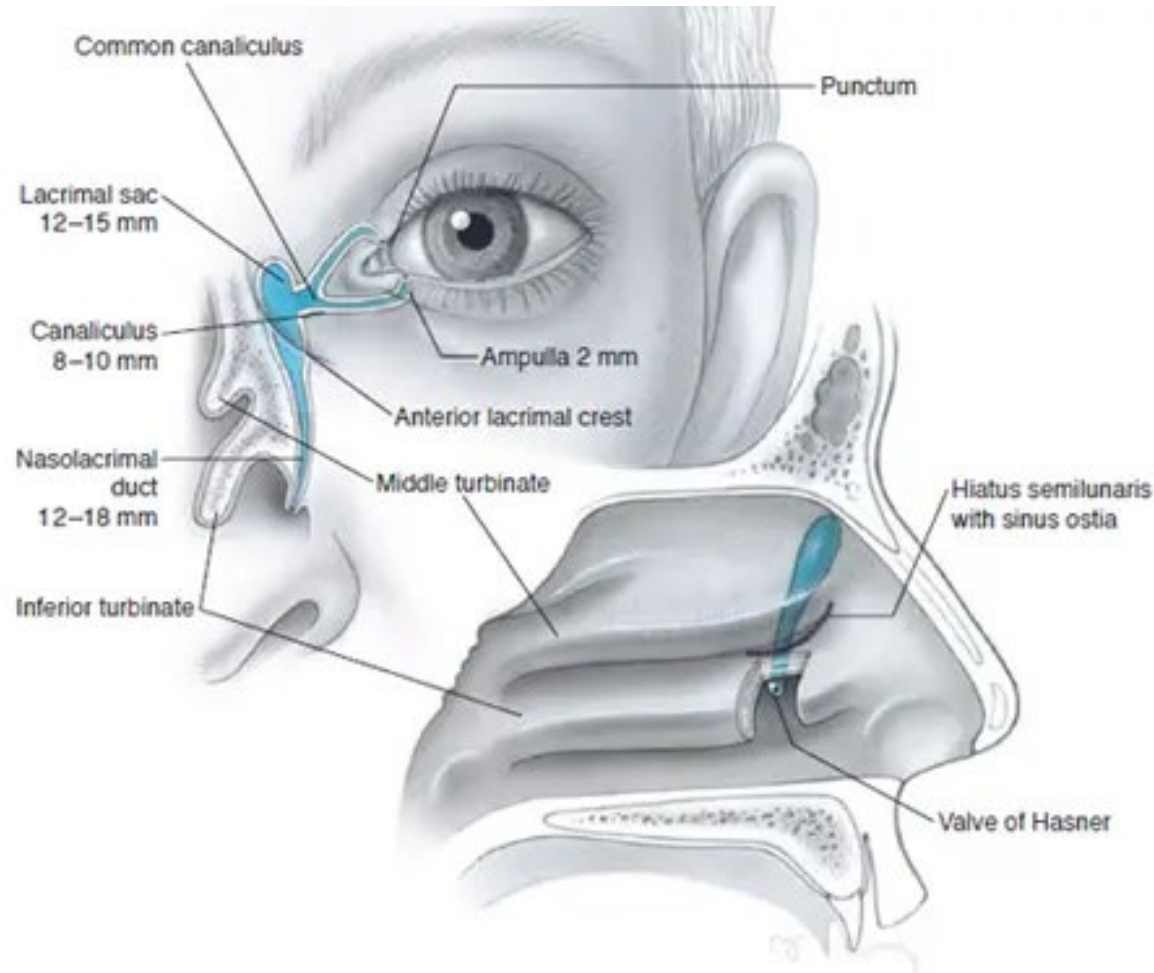


	Cases (n=16)	Controls (n=16)	Crude OR (95% CI)	Adj OR (95% CI)*
Artificial Tears	14 (87.5%)	6 (37.5%)	5.0 (1.10, 22.82)	4.7 (0.98, 22.52)

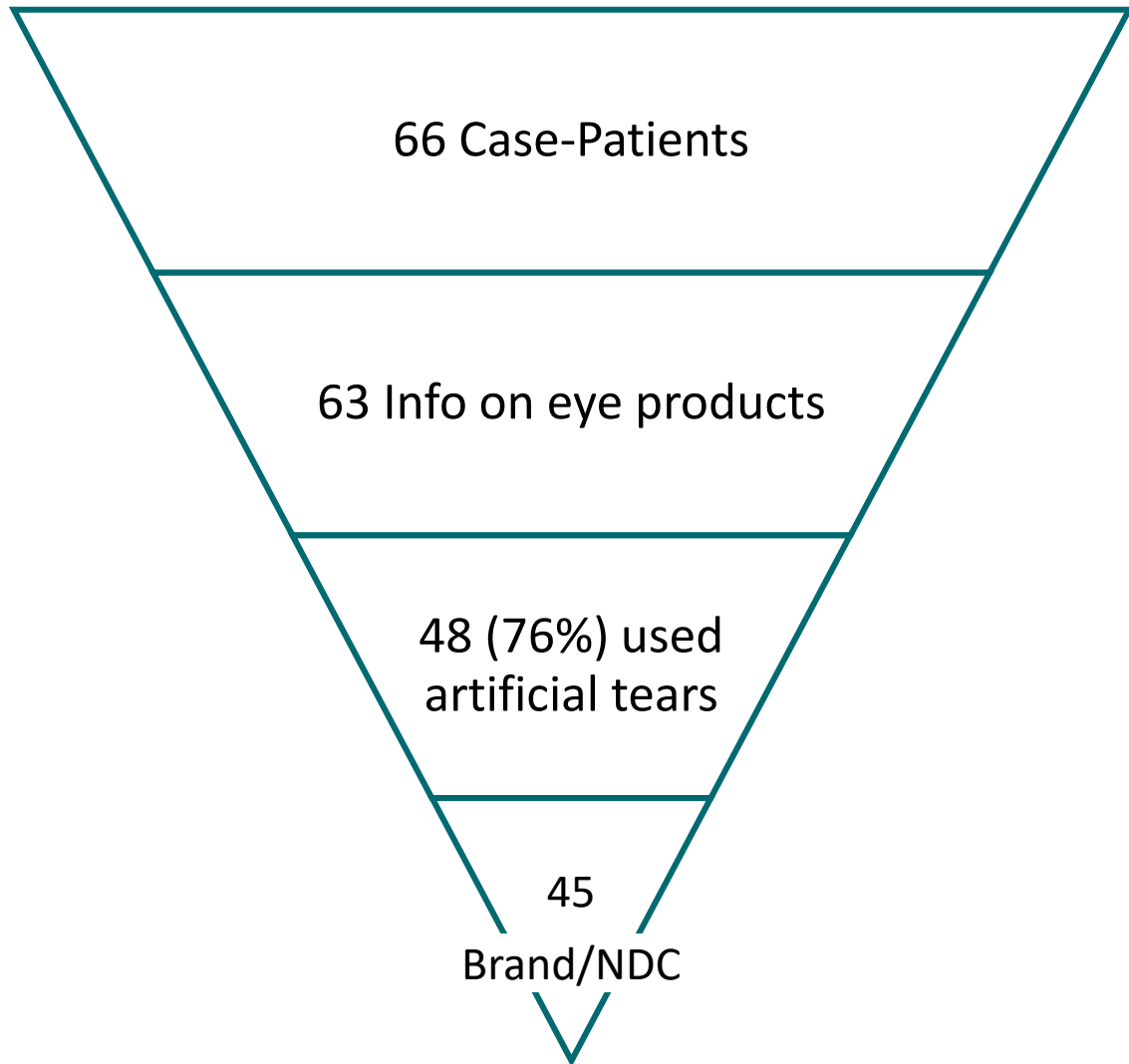
*Adjusted for use of mechanical ventilation

Cases had **5 times** the odds of exposure to **artificial tears** than controls.

How could eye drops cause infections and colonization at other anatomic sites?



Artificial Tears Use Among Case-Patients



- >10 brands of artificial tears reported
- Multiple brands of artificial tears reported for most case-patients
- The brand reported in highest frequency across all 45 case-patients with brand information was EzriCare artificial tears

Artificial Tears (AT) Use Among Case-Patients

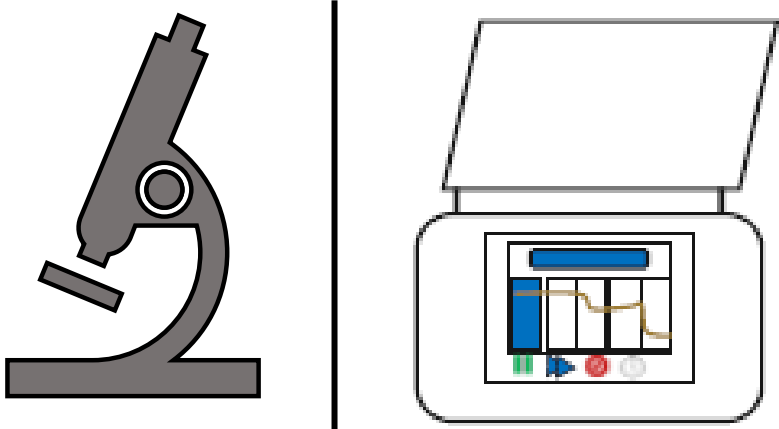
- **CT** (n=22); LTCF. 18 had record of AT. Multiple brands purchased during exposure period; EzriCare purchased in highest quantity. **14 patients likely exposed.**
- **LAC** (n=4); Eye clinic. **Facility purchased** EzriCare; **patient use unconfirmed.** Person-to-person transmission highly suspected.
- **UT** (n=6); LTCF. 5 had record of AT. All **5 confirmed use** of EzriCare.
- **FL** (n=5); Eye clinic. 3 reported use of AT. All 3 used same facility pharmacy dispensing EzriCare during exposure period; **patient use probable but unconfirmed.**
- **No other brand was reported across all 4 clusters**
- Case-patients with **eye cultures** not in clusters (n=8): 7 used AT. All **7 confirmed use** of EzriCare.

CDC product testing recovered the outbreak strain from opened EzriCare bottles

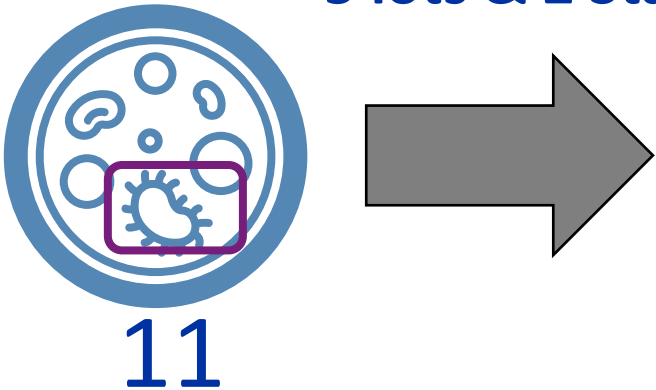


Unopened bottles from
2 lots & 2 States

Opened bottles from
5 lots & 2 States



Bottles tested
at CDC



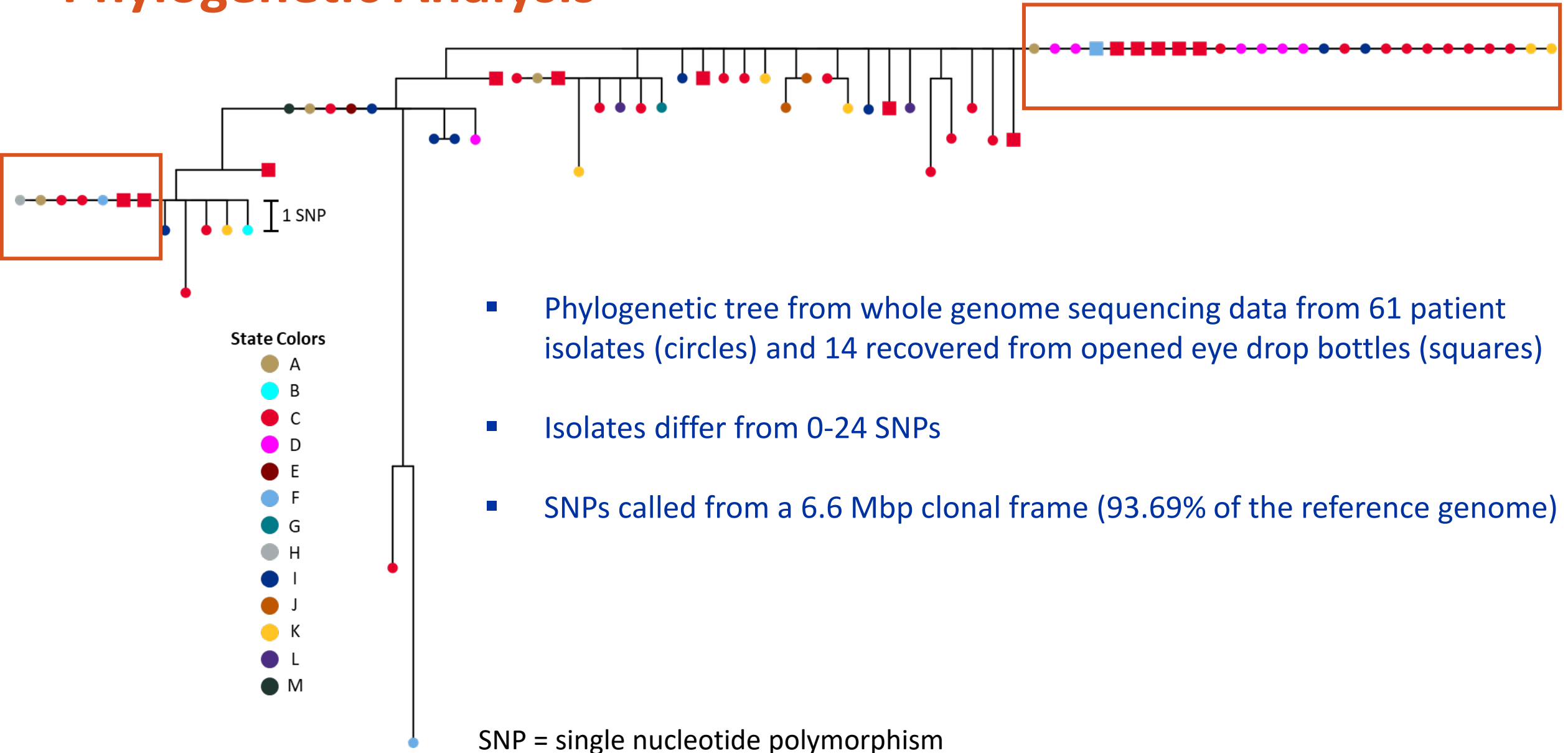
Opened bottles w/bacterial
growth from 2 States



7 bottles from 4 lots
27 isolates

Pseudomonas aeruginosa
ST1203 | *bla*VIM-80 | *bla*GES-9

Phylogenetic Analysis



EzriCare is a preservative-free product in a multidose vial

- New to market, 2021
- Sold through wholesalers & medical product distributors
- Distributed nationwide in the US
- Manufactured in India



CDC and FDA actions



U.S. FDA Recalls @FDArecalls · 2m

Global Pharma Healthcare Issues Voluntary Nationwide Recall of Artificial Tears Lubricant Eye Drops Due to Possible Contamination

fda.gov/safety/recalls...

EpiX The Epidemic
Information Exchange

Update #1: Multistate Cluster of VIM- and GES-producing Carbapenem-resistant *Pseudomonas aeruginosa* Associated with Artificial Tears -- January 20, 2023

Outbreak of Extensively Drug-resistant *Pseudomonas aeruginosa* Associated with Artificial Tears

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Distributed via the CDC Health Alert Network
February 1, 2023, 7:00 PM ET
CDCHAN-00485



U.S. FOOD & DRUG
ADMINISTRATION

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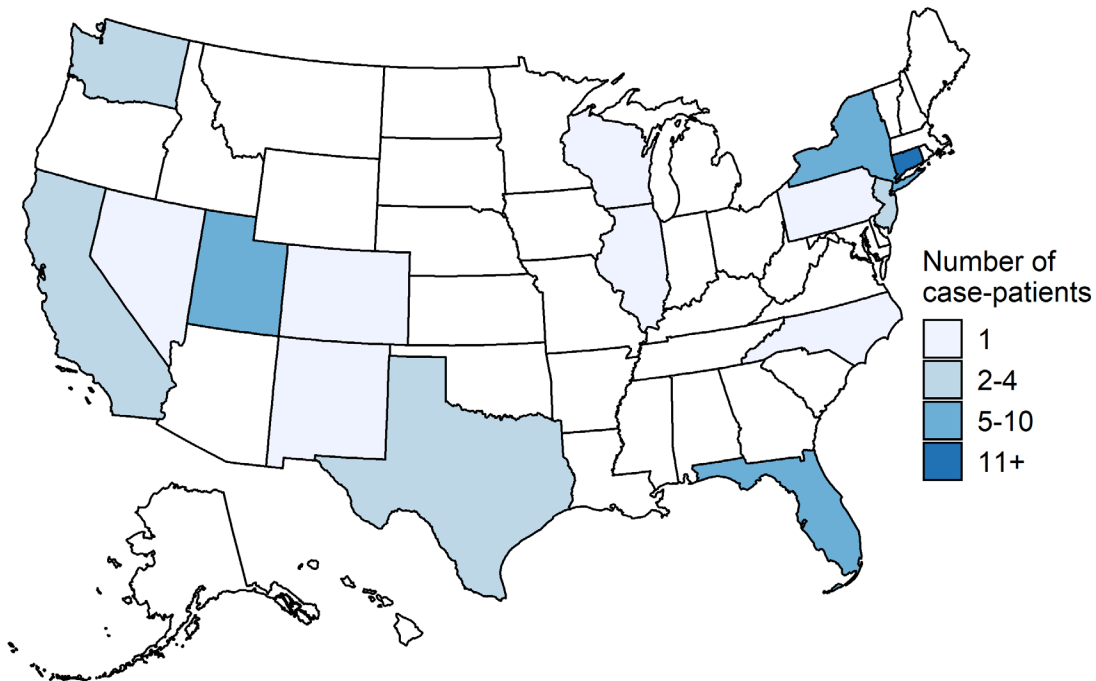
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**FDA warns consumers not to purchase
or use EzriCare Artificial Tears due to
potential contamination**

Summary



- Outbreak of an extensively drug-resistant strain of *Pseudomonas aeruginosa* ST1203 | *bla*VIM-80 | *bla*GES-9 identified through ARLN.
- As of March 7, 66 case-patients from 15 states with dates of specimen collection from May 2022 – Feb 2023.

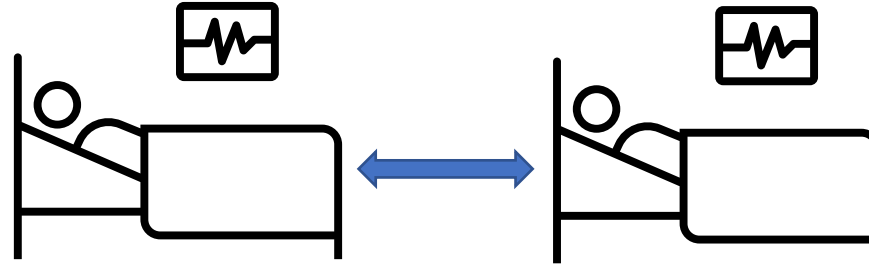


- 1:1 matched case-control study identified artificial tears as the product of interest.
- EzriCare was the brand most frequently reported and used across all 4 facility clusters.
- EzriCare was recalled on Feb 2, 2023

Limitations & Challenges



**Determining brands
& manufacturers**

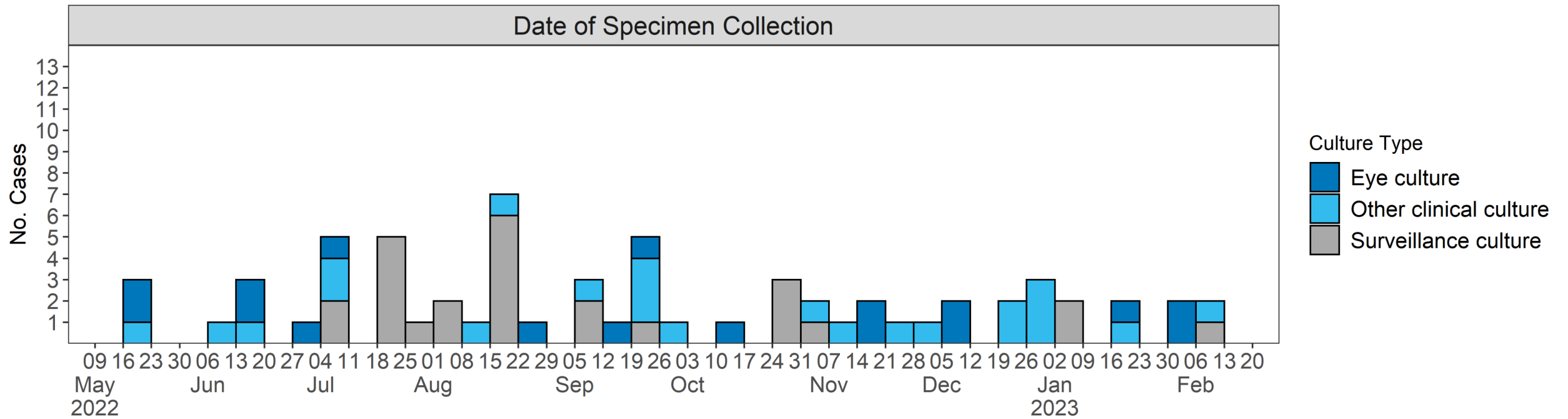


Person-to-person transmission



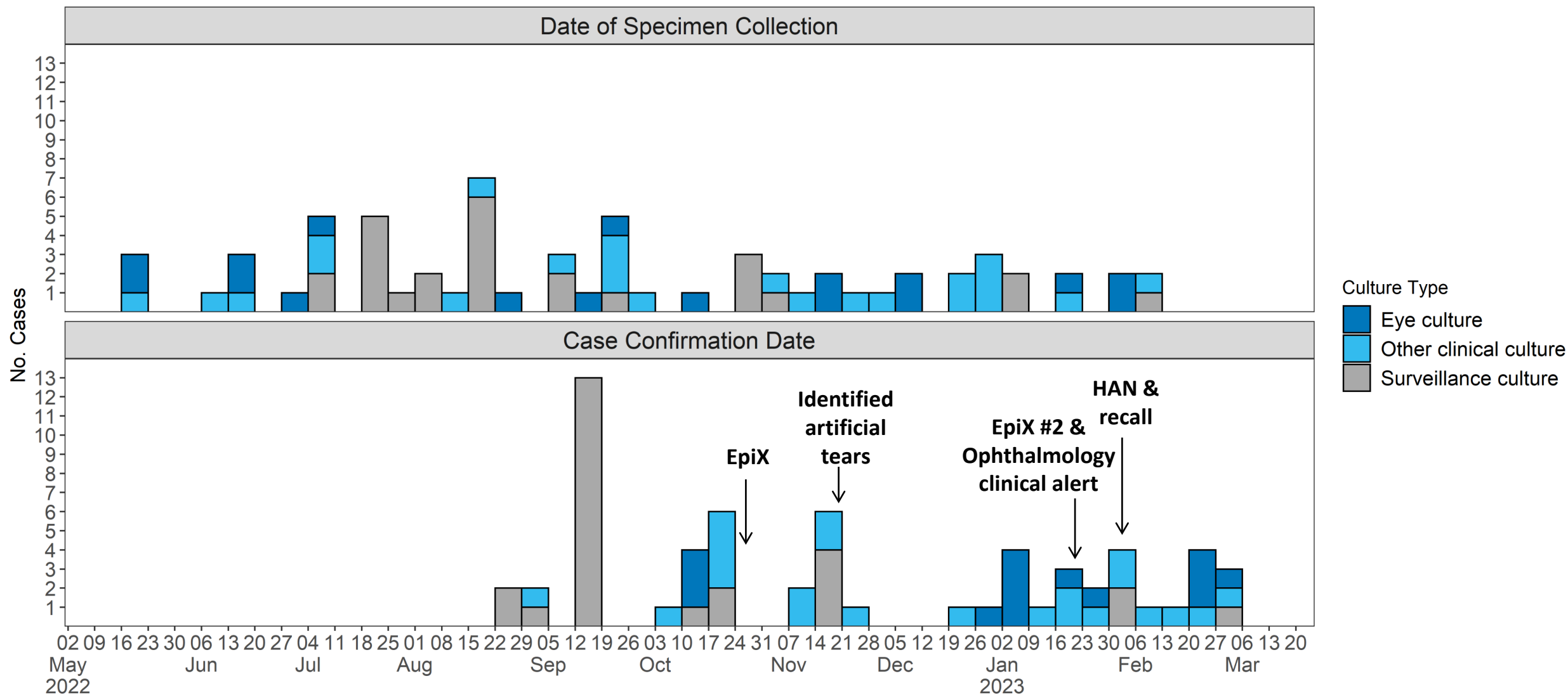
Case definition that relies on WGS

Case-patients by date of first VIM-GES-CRPA positive culture as of March 6, 2023 (n=66)



Data are preliminary and subject to change.

Case-patients by date of first VIM-GES-CRPA positive culture as of March 6, 2023 (n=66)



Data are preliminary and subject to change.

Conclusions

- **Enhanced lab capacity & communication** through **AR Lab Network** facilitated detection of outbreak
- **Ongoing surveillance necessary** given widespread availability of product
- **Patient colonization** may limit our ability to contain pathogen
- **Collaboration** across health departments, federal agencies, and clinicians is essential in a multi-state outbreak



Thank you!

- **Health Department Staff**
- **Public Health Laboratories**
- **FDA Center for Drug Evaluation and Research**
- **FDA Office of Emergency Operations**
- **CDC Prevention & Response Branch**
 - Maroya Walters
 - Danielle Rankin
 - Richard Stanton
 - Belinda Ostrowsky
 - Cal Ham
- **CDC Clinical & Environmental Microbiology Branch**
 - Paige Gable
 - Health Moulton-Meissner
 - Judith Noble-Wang
- **CDC DHQP Communications Team**
 - Bonnie Herring

For more information, contact CDC
1-800-CDC-INFO (232-4636)
TTY: 1-888-232-6348 www.cdc.gov

The findings and conclusions in this report are those of the authors and do not necessarily represent the official position of the Centers for Disease Control and Prevention.

