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

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

for the Presidential Advisory Council on Combating Antibiotic-Resistant Bacteria

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Carbapenemase-Producing *Pseudomonas aeruginosa*

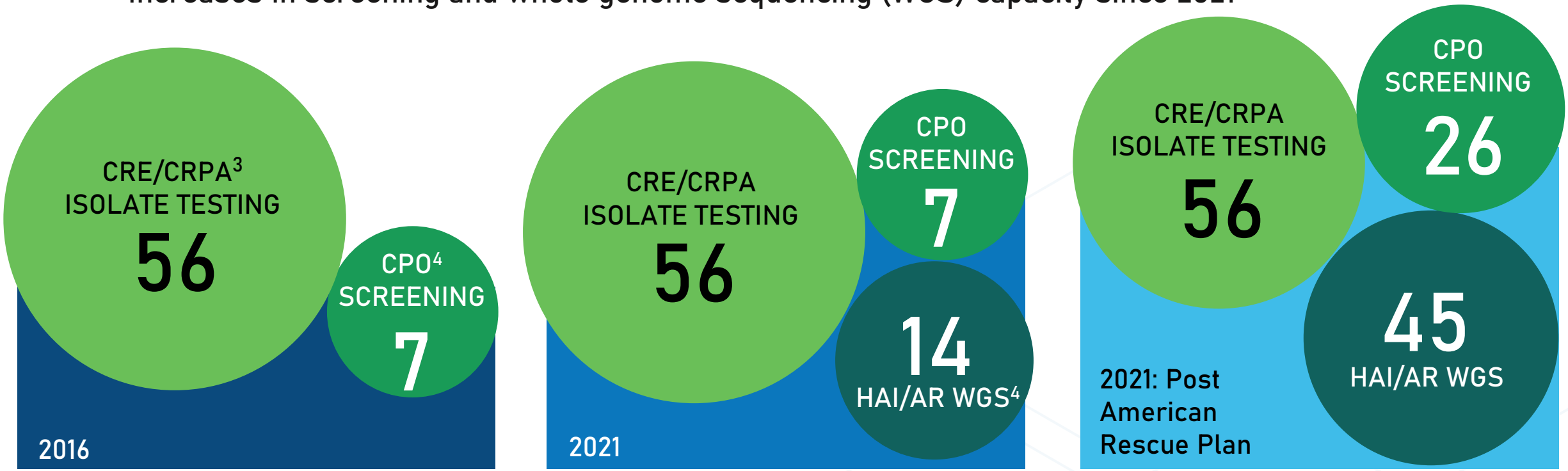
- Typically extremely resistant
- Associated with higher mortality compared to non-carbapenemase-producing strains
- Small proportion of carbapenem-resistant *P. aeruginosa* in the U.S.
  - Higher proportions in some other countries

Proportion of carbapenem-resistant *P. aeruginosa* (CRPA) with carbapenemasese

J. Reyes et. al., Lancet Microbe 2023; 4: e159–70

Detecting Carbapenemase-Producing *P. aeruginosa*

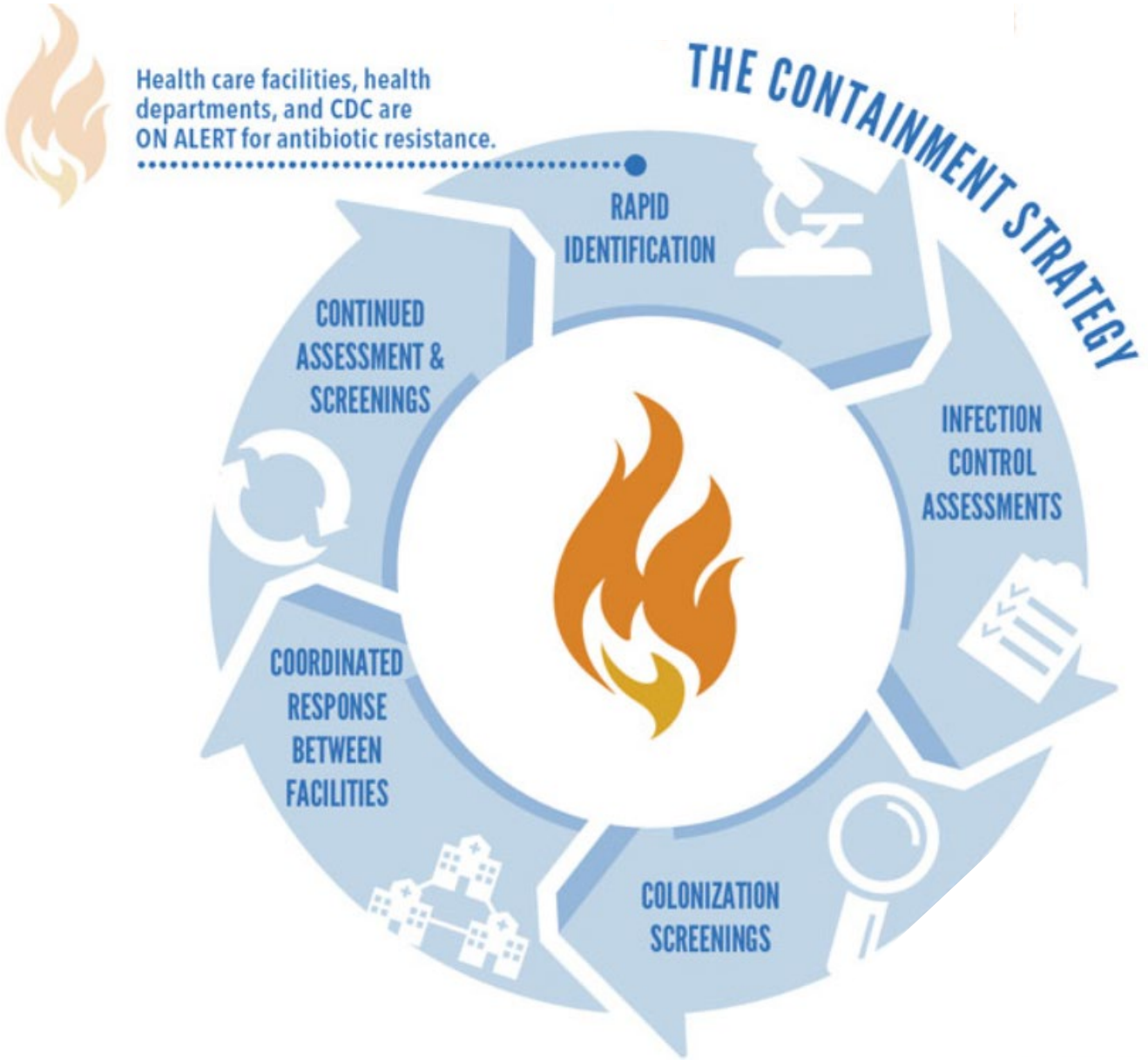
- Detection challenge: In 2021, 28% U.S. hospitals served by clinical laboratories that tested carbapenem-resistant *P. aeruginosa* for carbapenemases [1]
- Beginning 2016, Antimicrobial Resistance (AR) Lab Network expanded testing in public health laboratories
  - From 2017-2021, tested >56,000 carbapenem-resistant *P. aeruginosa* [2]
  - Increases in screening and whole genome sequencing (WGS) capacity since 2021



[1]CDC National Healthcare Safety Network, unpublished and preliminary data, [2]CDC AR & Patient Safety Portal, [3] CRE: Carbapenem-resistant Enterobacterales, [4] HAI: Healthcare-associated Infection, [4]CPO: carbapenemase-producing organism(s)

Responding to Carbapenemase-Producing *P. aeruginosa*

- CDC recommends a public health response when carbapenemase-producing *P. aeruginosa* are identified[1]
- Responses implemented by Healthcare-Associated Infections/Antimicrobial Resistance (HAI/AR) Programs in 64 health departments
  - >1,000 MDRO[2] responses/year
- Identified outbreaks linked to medical tourism, contaminated premise plumbing, and interfacility transmission across patient sharing networks



[1]CDC Containment Guidance: https://www.cdc.gov/hai/mdro-guides/con

[2]MDRO: multidrug-resistant organism

Identification of the Outbreak

June-August 2022: Health department HAI/AR Programs report 3 facility clusters of VIM*-producing *P. aeruginosa* infections

Ophthalmology Clinic, California

Long-Term Care Facility, Utah

Long-Term Care Facility, Connecticut

September-October 2022: Whole genome sequencing (WGS) showed that all 3 outbreaks and isolated infections in 2 additional states caused by same strain

*VIM: Verona integron metallo-β-lactamase, the most common carbapenemase identified in *P. aeruginosa* in the U.S.

The Outbreak Strain

Outbreak strain susceptible only to cefiderocol[1]

- New strain: *P. aeruginosa* MLST *1203 with the carbapenemase VIM-80 and β-lactamase GES-9
  - ST 1203 previously identified in 5 U.S. isolates
  - VIM-80 previously identified in Asia and South America
  - GES-9 previously identified in Africa, Asia, Europe, and North America
- All isolates very closely related by whole genome sequencing analysis
- Targeted a specific genotype to identify outbreak strain among all VIM-producing *P. aeruginosa* reported to CDC

https://wwwn.cdc.gov/ARIsolateBank/Panel/IsolateDetail?IsolateID=10561&PanelID=10[1]

*MLST: multilocus sequence type

MIC (µg/ml) Results and Interpretation

Drug	MIC (µg/ml)	INT
Amikacin	>64	R
Aztreonam	>32	R
Cefepime	>32	R
Cefiderocol	0.5	S
Ceftazidime	>128	R
Ceftazidime/avibactam [1]	>16	R
Ceftolozane/tazobactam [1]	>16	R
Ciprofloxacin	>8	R
Colistin [2]	1	I
Gentamicin	>16	R
Imipenem	16	R
Imipenem/relebactam [1]	8	R
Imipenem+chelators [3]	2	---
Levofloxacin	>8	R
Meropenem	>8	R
Piperacillin/tazobactam [1]	64	I
Tobramycin	>16	R

S – I –R Interpretation (INT) derived from CLSI 2022 M100 S32

[1] Reflects MIC of first component

[2] Clinical and PK/PD data demonstrate colistin has limited clinical efficacy, even if an intermediate result is obtained. Alternative agents are strongly preferred. Colistin should be used in combination with one or more active antimicrobial agents. Consultation with an infectious disease specialist is recommended.

[3] Screen for metallo-beta-lactamase production [Rasheed et al. Emerging Infectious Diseases. 2013. 19(6):870-878]

Investigation Methods

Prospective and retrospective case finding

Epi-X The Epidemic Information Exchange

October 2022
Submit carbapenem-resistant *P. aeruginosa* to AR Lab Network

- Carbapenemase testing
- WGS for isolates with VIM

December 2022
Clinical alert to Ophthalmology Professional Societies

Review of products used by patients

Health department HAI/AR programs

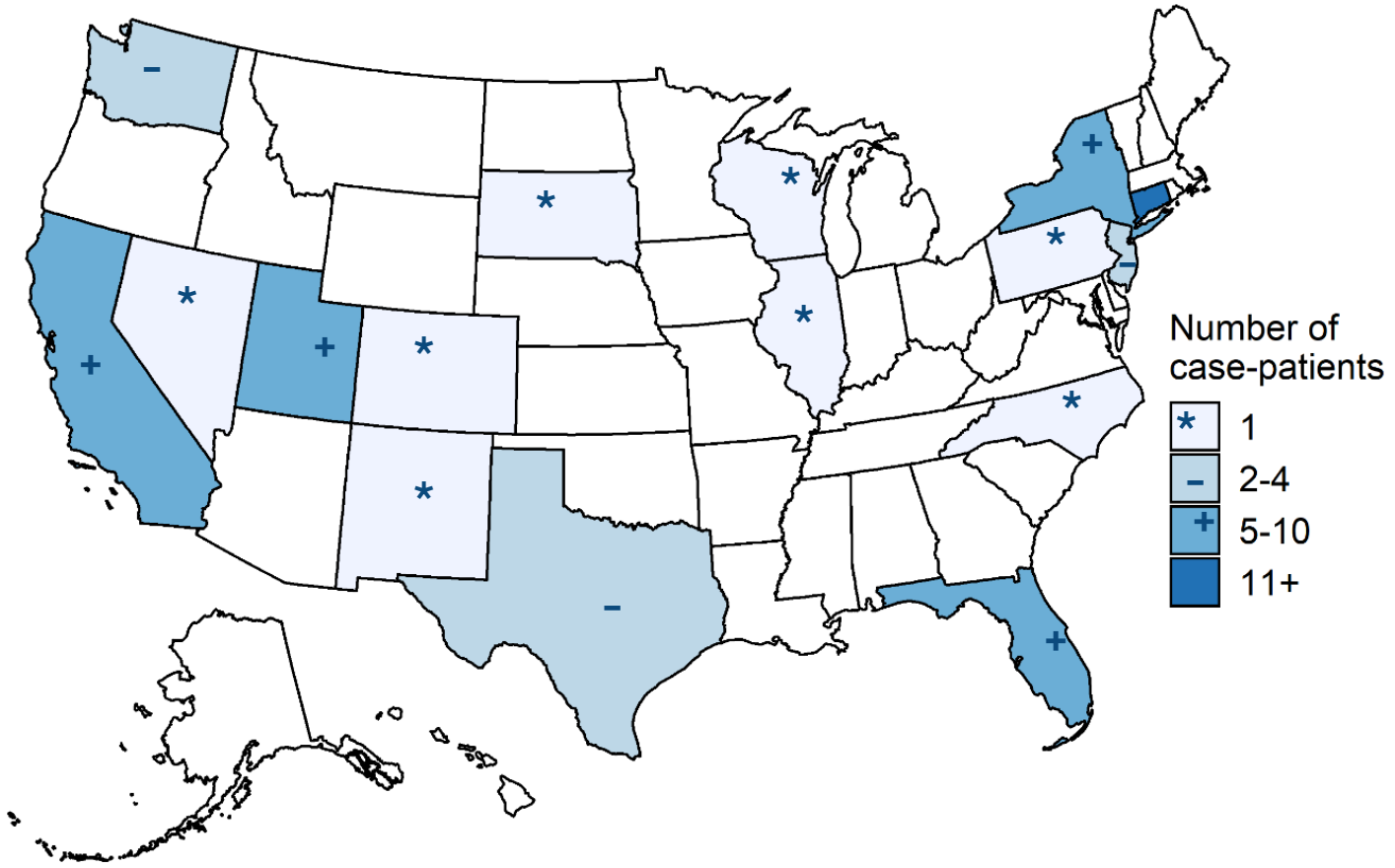
- Conducted chart reviews and patient interviews to identify products used and shared data with CDC
- Reviewed healthcare exposures and facilitated contact screening

Culture of potentially contaminated products

As of March 14, we identified 68 patients with the outbreak strain, from 16 states*

- 37 patients part of 4 facility clusters
- Median age: 61 years (range: <1-102)
- Cultures collected
  - From May 2022-Feb 2023
  - Across a variety of clinical settings
  - Many different specimen types
    - Surveillance (n=26, 46%)
    - Eye source (n=18, 26%)
    - Other clinical source[1] (n=24, 35%)

Patients with the *P. aeruginosa* outbreak strain as of March 14, by state, N=68



[1]urine (10), sputum (n=9), blood (2), wound/tissue (2), body fluid (1)

Patient underlying conditions, by initial specimen source, N=68

- Most patients had at least one serious underlying condition
- Most patients with eye infections had underlying eye disease

Condition	Surveillance Culture N=26 n (%)	Non-Eye Clinical Culture N=24 n (%)	Eye Culture N=18 n (%)
No underlying conditions	0	1 (4)	1 (6)
Chronic lung disease or respiratory failure[1]	20 (77)	8 (33)	5 (28)
Diabetes mellitus	4 (15)	6 (25)	7 (39)
Eye disease[2]	4 (15)	4 (17)	16 (89)

[1]Includes patients with asthma, chronic obstructive pulmonary disease, hypersensitivity lung disease, and respiratory failure
[2]Includes patients with glaucoma, cataracts, and macular degeneration

Outcomes among patients with clinical culture, by initial specimen source, N=42[1]

Outcome	Any Clinical Culture N=42 n/N (%)	Non-Eye Clinical Culture N=19 n/N (%)	Eye Culture N=18 n/N (%)
New Hospitalization[2]	19/33 (58)	11/19 (58)	8/14 (57)
Intensive Care Unit Admission[2]	5/10 (50)	5/16 (31)	0
Death within 30 days[3]	3/29 (10)	2/15 (13)	1/14 (7)
Vision Loss (eye preserved)	8/12 (67)	0	8/12 (67)
Enucleation	4/12 (33)	0	4/12 (33)

[1]Excludes 3 patients initially identified by surveillance culture, who had a subsequent clinical culture.
[2]New hospitalization or ICU admission defined as new admission from 3 days prior to 2 weeks after culture collection.
[3]P. aeruginosa infection listed as cause of death for 1 of 3 patients who died within 30 days of culture.

Multiple Investigative Approaches Pointed to Single Artificial Tears Brand

Case-control study at long-term care facility

- Cases had 5 times greater odds of exposure to artificial tears than controls

  (Crude OR: 5.0 [95% CI 1.10–22.82])
- Unable to differentiate artificial tears brands
- EzriCare Artificial Tears: largest purchasing volume

4 facility clusters

- 2 with eye infections; 2 without
- EzriCare Artificial Tears used across all facilities
- 28/37 (76%) patients used Artificial Tears
- 22/26 (59%) confirmed or probable use of EzriCare Artificial Tears

31 patients not linked to clusters

- 17/27 (63%) used artificial tears
- 11/16 (69%) with product information used Ezricare Artificial Tears
  - 8/8 (100%) with eye infections

EzriCare Artificial Tears

- Preservative-free formulation
- Dispensed in multidose vials
- Distributed nationwide
- Manufactured in India

CDC identified outbreak strain in opened product

23

Opened EzriCare Artificial Tears bottles from 5 lots & 2 states

11

Bottles w/bacterial growth from 2 states

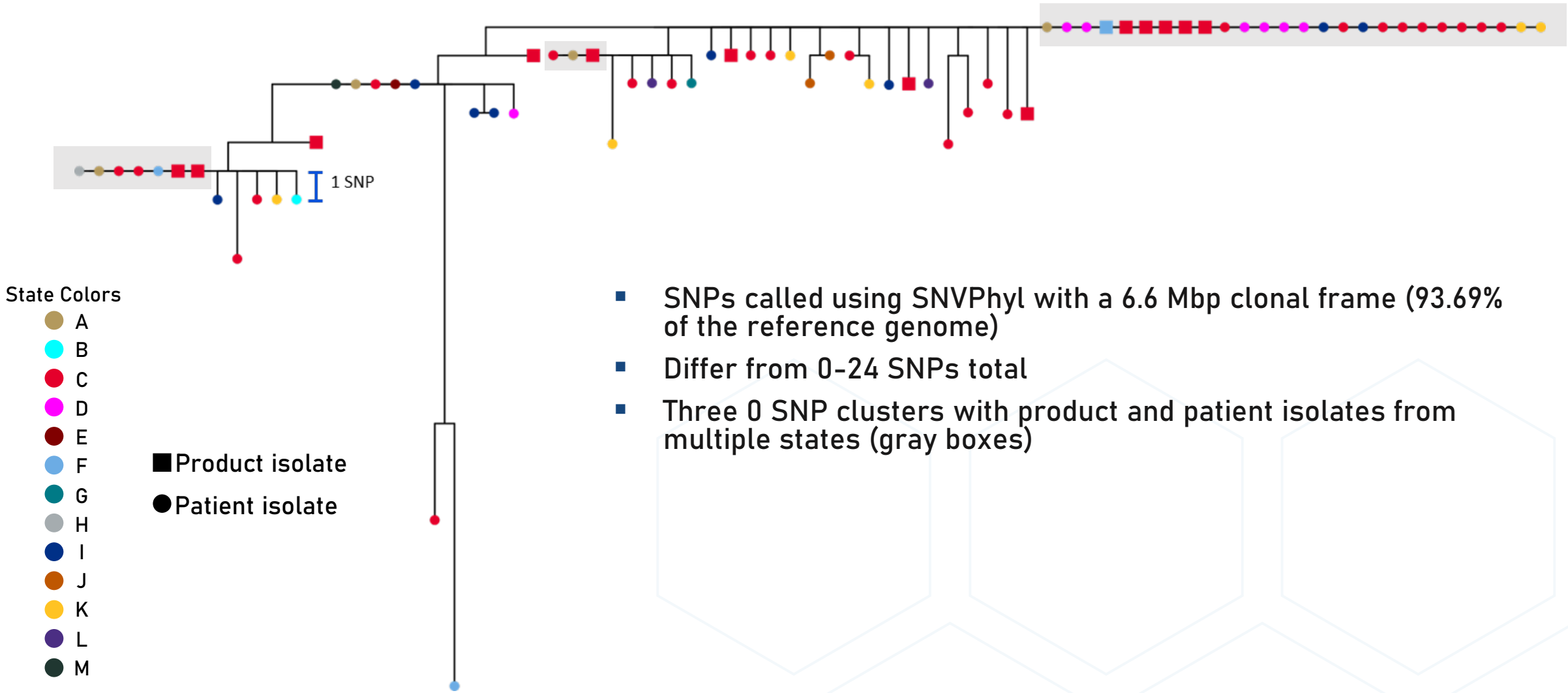
Outbreak strain identified in

7

bottles from 4 lots and 2 states

FDA testing of unopened EzriCare bottles is ongoing.

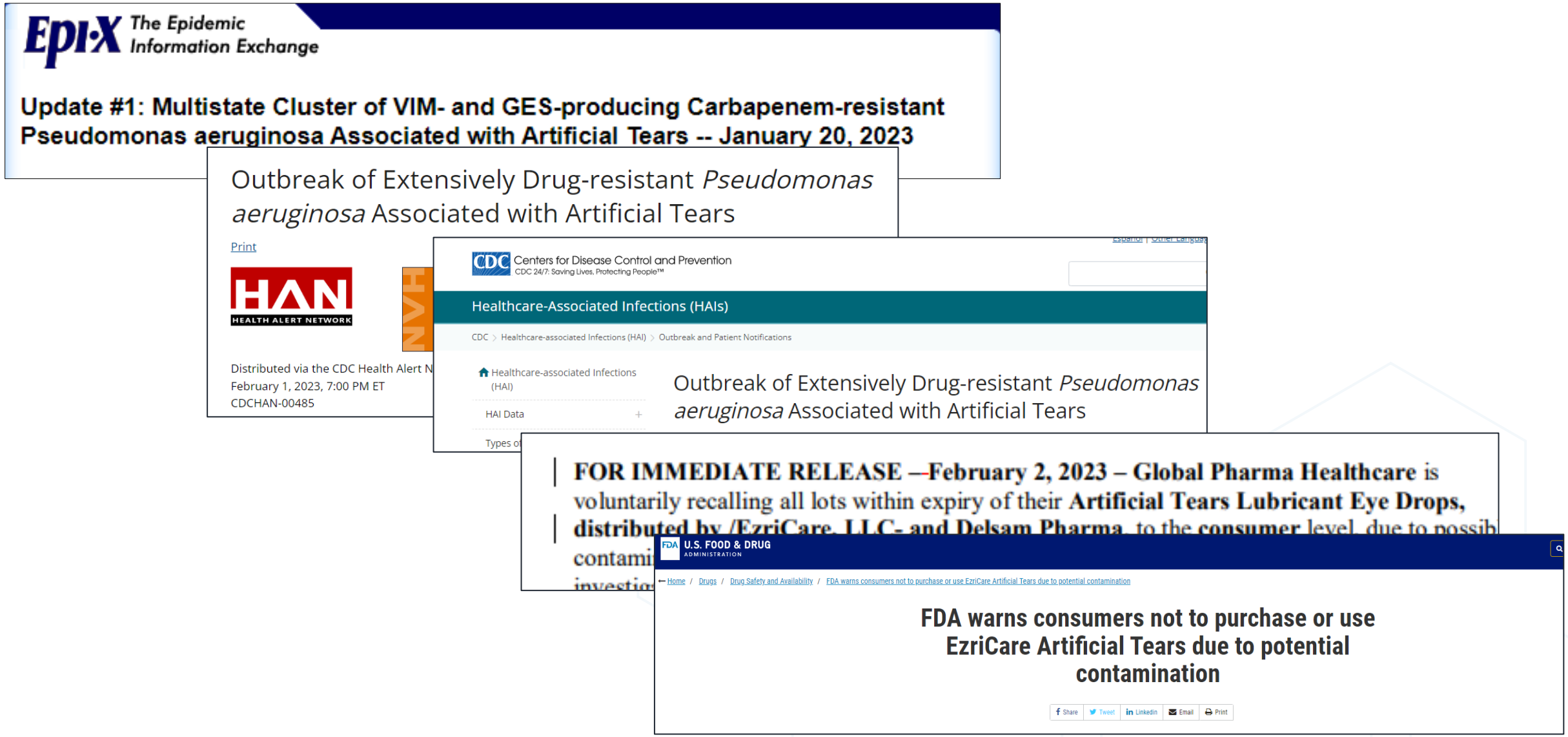
Isolates from Patients and Opened Product are Closely Related



- SNPs called using SNVPhyl with a 6.6 Mbp clonal frame (93.69% of the reference genome)
- Differ from 0-24 SNPs total
- Three 0 SNP clusters with product and patient isolates from multiple states (gray boxes)

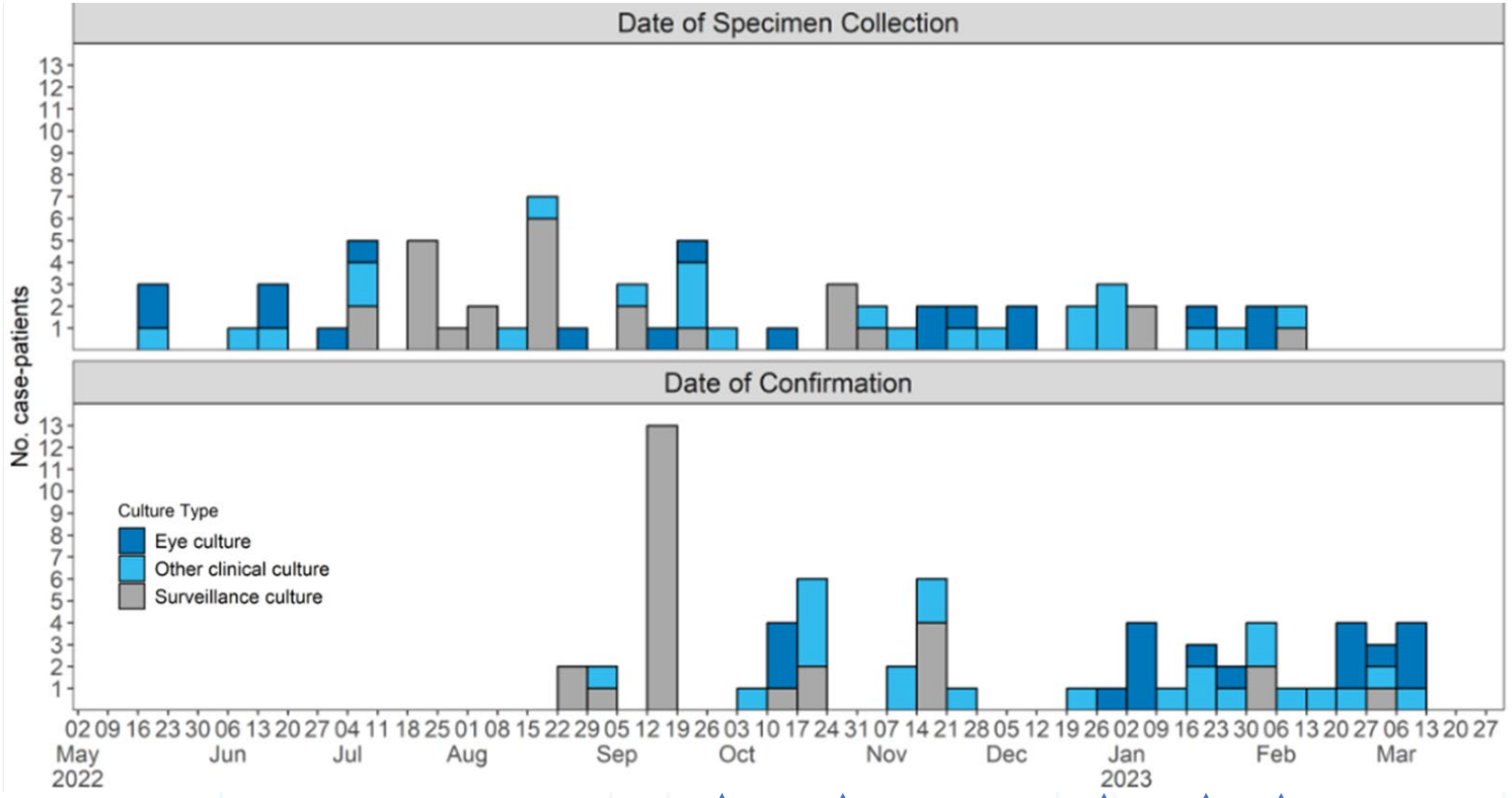
*SNP: single nucleotide polymorphism; **SNV: single nucleotide variant

Public Health Communications



Investigation Timeline

- Starting in May 2022, there were 1-9 clinical cases/month through Feb 2023
- Case confirmation lagged specimen collection
  - Time for isolates to be identified and sequenced
  - Many cases, especially from eye infections, identified retrospectively after clinical and public health alerts
- Patients with culture collected after recall used EzriCare prior to recall or had epidemiologic links to known cases
- Ongoing monitoring for cases



Identify same strain across 3 outbreaks Sept 28—Oct 6

EpiX #1 Call for cases Oct 27

Ophthalmology Clinic alert Dec 29

EpiX #2 Alert re: EzriCare Jan 20

HAN, Feb 1 Recall, Feb 2

Summary

- CDC, in collaboration with CDC-supported AR Lab Network and HAI/AR programs identified a large multistate outbreak of extensively drug-resistant *P. aeruginosa* linked to artificial tears
  - Benefit of national, coordinated effort between public health laboratories and HAI/AR programs to rapidly identify and investigate cases
  - HAI/AR programs' infection control support and AR Lab Network screening capacity helped mitigate secondary transmission
- Epidemiology and laboratory investigation used multiple lines of evidence to identify a preservative-free brand of artificial tears as outbreak source, leading to product recall
- Transmission of extensively drug resistant organisms through widely distributed, over-the-counter product presents new challenges for containment

Looking Ahead

- Control of pathogens traditionally associated with healthcare, such as resistant *P. aeruginosa* and Enterobacterales, further challenged by exposures and reservoirs outside of healthcare
- Whole-genome sequencing of resistant healthcare pathogens can be a critical tool for addressing antimicrobial resistance threats
  - Potential to identify outbreaks, including those dispersed across multiple facilities or geographic areas
  - Detect and track new or high concern strains
- Need to sustain pandemic investments in public health epidemiology and infection control capacity to use this information to prevent transmission and infections

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