Multistate Outbreak of $bla_{\text{VIM-80}}$ & $bla_{\text{GES-9}}$ 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.

CP-CRPA tested and identified through the Antimicrobial Laboratory Network, 2017-2021

- **KPC Detected**
  - KPC Detected / 56,016 Isolates
- **NDM Detected**
  - NDM Detected / 56,016 Isolates
- **VIM Detected**
  - VIM Detected / 56,016 Isolates
- **IMP Detected**
  - IMP Detected / 56,016 Isolates
- **OXA-48 Detected**
  - OXA-48 Detected / 56,016 Isolates

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**

Data are preliminary and subject to change.
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
- 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

All isolates (n=83)
- Surveillance: 33%
- Clinical: 67%

Clinical isolates (n=56)
- Respiratory: 27%
- Eye: 36%
- Urine: 18%
- Blood: 3%
- Other: 16%

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

Data are preliminary and subject to change.
Underlying conditions differed by initial specimen source (N=66)

<table>
<thead>
<tr>
<th>Underlying Condition</th>
<th>Eye culture, N=17 n(%)</th>
<th>Other clinical culture, N=23 n(%)</th>
<th>Surveillance culture, N=26 n(%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Respiratory disease</td>
<td>5 (29%)</td>
<td>9 (39%)</td>
<td>23 (88%)</td>
</tr>
<tr>
<td>Neurological disease</td>
<td>3 (18%)</td>
<td>9 (39%)</td>
<td>20 (77%)</td>
</tr>
<tr>
<td>Eye disease</td>
<td>16 (94%)</td>
<td>4 (17%)</td>
<td>4 (15%)</td>
</tr>
</tbody>
</table>

Data are preliminary and subject to change.
Indwelling devices differed by initial specimen source (N=66)

<table>
<thead>
<tr>
<th>Medical device</th>
<th>Eye culture, N=17</th>
<th>Other clinical culture, N=23</th>
<th>Surveillance culture, N=26</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n(%)</td>
<td>n(%)</td>
<td>n(%)</td>
</tr>
<tr>
<td>Tracheostomy</td>
<td>0 (0%)</td>
<td>9 (39%)</td>
<td>25 (96%)</td>
</tr>
<tr>
<td>PEG tube (feeding tube)</td>
<td>0 (0%)</td>
<td>6 (26%)</td>
<td>21 (81%)</td>
</tr>
<tr>
<td>Mechanical ventilation</td>
<td>1 (5.9%)</td>
<td>9 (39%)</td>
<td>14 (54%)</td>
</tr>
</tbody>
</table>

Data are preliminary and subject to change.
Case-patients with clinical cultures suffered vision loss and were hospitalized (N=43*)

**Eye Infections (n=17)**

<table>
<thead>
<tr>
<th>Outcome</th>
<th>N</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vision loss</td>
<td>8</td>
<td>62%</td>
</tr>
<tr>
<td>Enucleation</td>
<td>4</td>
<td>31%</td>
</tr>
</tbody>
</table>

1^outcome information available for only 13 patients  
2^not including enucleation

**Patients with any clinical culture (n= 43)**

<table>
<thead>
<tr>
<th>Outcome</th>
<th>N</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hospitalization</td>
<td>19</td>
<td>54%</td>
</tr>
<tr>
<td>Intensive Care Unit</td>
<td>6</td>
<td>17%</td>
</tr>
<tr>
<td>Death within 30 days</td>
<td>3</td>
<td>9%</td>
</tr>
</tbody>
</table>

1^information available for 35 patients  
2^three days before – 2 weeks after culture collection

*3 case-patients had clinical cultures after surveillance cultures
### Matched 1:1 Case-Control Study in CT Long-term Care Facility

<table>
<thead>
<tr>
<th>Artificial Tears</th>
<th>Cases (n=16)</th>
<th>Controls (n=16)</th>
<th>Crude OR (95% CI)</th>
<th>Adj OR (95% CI)*</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>14 (87.5%)</td>
<td>6 (37.5%)</td>
<td>5.0 (1.10, 22.82)</td>
<td>4.7 (0.98, 22.52)</td>
</tr>
</tbody>
</table>

*Adjusted for use of mechanical ventilation

Data are preliminary and subject to change.

**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

Data are preliminary and subject to change.
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.**

Data are preliminary and subject to change.
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

Opened bottles w/bacterial growth from 2 States

Bottles tested at CDC

7 bottles from 4 lots

27 isolates

_Pseudomonas aeruginosa_

ST1203 | _blaVIM-80_ | _blaGES-9_
Phylogenetic Analysis

- Phylogenetic tree from whole genome sequencing data from 61 patient isolates (circles) and 14 recovered from opened eye drop bottles (squares)
- Isolates differ from 0-24 SNPs
- SNPs called from a 6.6 Mbp clonal frame (93.69% of the reference genome)

SNP = single nucleotide polymorphism
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

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

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

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- FDA Office of Emergency Operations

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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.