Laboratory Submissions for Enhanced Antibiotic Resistance Surveillance

Overview: Problem

- Limited state capacity to detect and respond to known and emerging forms of resistance
- CDC previously was the only site for surveillance of emerging resistance
  - Very dependent on an informed clinician and laboratory at healthcare facility to recognize and send off specimens of unusual resistance
- AR mechanism testing primarily performed at commercial and academic institutions which are not connected to a surveillance network
- Culture independent diagnostic testing (CIDT) in clinical labs limits ability to detect resistance for public health purposes

Overview: Solution

- CDC’s Antibiotic Resistance Laboratory Network (ARLN) increases the ability to detect, respond to, and prevent antimicrobial threats
  - Establishes 7 regional labs
  - Each bolstering gold-standards for antimicrobial resistance (AR) detection and reporting technology
  - Greatly improves the ability to track resistance using real-time, actionable data
  - Allows collection of AR isolates for the CDC and FDA AR Isolate Bank as well as various CDC whole genome sequencing (WGS) projects
    - Will advance the development of diagnostic testing and new antimicrobials
  - Based on preexisting regionalization established by PulseNet
- Supported by CDC’s Epidemiology and Laboratory Capacity (ELC) for Infectious Diseases

Controlling Novel or Targeted Multidrug-resistant Organisms (MDROs)

- Identifying if transmission/dissemination is occurring
- Identifying affected patients
- Ensuring appropriate control measures are promptly initiated/implemented to contain potential spread
- Characterizing the organism or mechanism in order to guide further response actions, patient management and future responses

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<thead>
<tr>
<th>Tier</th>
<th>Organisms</th>
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</thead>
<tbody>
<tr>
<td>1</td>
<td>Resistance mechanisms novel to the United States (e.g., VRS)</td>
</tr>
<tr>
<td>2</td>
<td>MDROs primarily found in healthcare settings but not believed to be found in the region (e.g., CRE with novel mechanisms like CP-1A)</td>
</tr>
<tr>
<td>3</td>
<td>MDROs targeted by the facility/region that are already established in the U.S. (e.g., KPC)</td>
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CARB Action Plan Outlines Milestones to Improve Laboratory Capacity

Sub-Objective 2.1.1: Create a regional public health laboratory network that uses standardized testing platforms to expand the availability of reference testing services, characterize emerging resistance patterns and bacterial strains obtained from outbreaks and other sources, and facilitate rapid data analysis and dissemination of information.
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Emerging MDROs Tested under ARLN

- All Local, State, and Regional Labs
  - Carbapenem-resistant *Enterobacteriaceae* (CRE)
  - Carbapenem-resistant *Pseudomonas aeruginosa* (CRPA) and *Acinetobacter* spp.
  - Extended Spectrum Beta-Lactamase (ESBL)-producing *Enterobacteriaceae* – colistin mcr-1 resistance
  - *Candida* spp.
  - *Salmonella* spp.
- Select Labs Only
  - *Clostridium difficile*
  - WGS for all *Mycobacterium tuberculosis* isolates
  - *Neisseria gonorrhoeae*
  - *Streptococcus pneumoniae*

Emerging Carbapenem Resistance Mechanisms

- **Mechanism Type**
  - Carbapenemase Production – Biggest Threat
  - Extended Spectrum Beta Lactamase + porin mutations
  - AmpC + porin mutations
  - Intrinsics resistances
    - Imipenem (*Proteus, Providencia, Morganella, and Serratia*)
- **Mechanism Transferrance**
  - Chromosomal (Vertical Transmission)
    - Stays within species lineage
    - Can handicap/damage bacterial function
  - Integron/plasmid mediated (Horizontal Transmission)
    - Carbapenemases
    - Can jump species
    - Not usually associated with reduced bacterial functionality
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## Carbapenemases

1. **Klebsiella pneumoniae carbapenemase (KPC)**
   - Most common carbapenemase in the United States
   - Confers resistance to all β-lactam agents

2. **New Delhi Metallo-β-lactamase (NDM)**
   - First detected in 2009; rapid global spread, primarily among Enterobacteriaceae
   - Previously associated with travel, now with domestic transmission

3. **OXA-48-like enzymes**
   - Inefficient carbapenemases, don't hydrolyze cephalosporins well
   - Commonly travel with other β-lactamases

4. **Verona Integron-encoded Metallo-β-lactamase (VIM)**
   - Relatively slow global spread; mostly in *P. aeruginosa*

5. **Active on Imipenem Metallo-β-lactamase (IMP)**
   - Relatively slow global spread; mostly in *P. aeruginosa*

## Expected Capacities of ARLN

<table>
<thead>
<tr>
<th>Public Health Priority</th>
<th>Current Lab Capacity</th>
<th>With the ARLN</th>
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<tbody>
<tr>
<td>Gonorrhea Testing</td>
<td>6,000 isolates per year by all state health departments</td>
<td>20,000 isolates per year by four regional labs</td>
</tr>
<tr>
<td>CRE Characterization</td>
<td>8 states conduct testing through the EIP</td>
<td>All 50 states conduct characterization testing, regional labs to confirm especially unusual resistance</td>
</tr>
<tr>
<td>Salmonella WGS</td>
<td>1/20 isolates tested through WGS</td>
<td>100% isolates tested through WGS</td>
</tr>
<tr>
<td>CRE Outbreak Lab Support</td>
<td>Upon request Provided by CDC to states</td>
<td>Sustained capacity Provided by all regional labs and CDC</td>
</tr>
<tr>
<td>Detecting new resistance threats, like mcr-1 and C. auris</td>
<td>Reported ad hoc Often detected first in academia</td>
<td>Sentinel surveillance Sustained, adaptable capacity to identify and address new AR threats</td>
</tr>
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## Overview: Louisiana

- The Louisiana Public Health Laboratory (PHL) received funding through the CDC’s ELC agreement to work with CDC’s ARLN
  - Aim is to rapidly detect antibiotic resistance and inform local responses to prevent spread and protect people.
  - Will test for CRE and CRPA
  - Ensure more consistent communication, coordination, and tracking at all levels.
  - Detect new resistance and provide better big-picture trend tracking.
  - 3 microbiologists with specialized training in AR at LA-PHL
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Submitting Isolates for CRE testing

- Submit at no cost to your facility
- Current scheme is aimed at ACHs
- 1st Step: Identify a confirmed case of CRE using the state definition:
  - *E. coli*, *Klebsiella* spp., or *Enterobacter* spp. that is resistant to any carbapenem (minimum inhibitory concentrations of ≥4 mcg/ml for meropenem, imipenem, and doripenem or ≥ 2 mcg/ml for ertapenem)
  OR
- production of a carbapenemase (e.g., KPC, NDM, VIM, IMP, OXA-48) demonstrated by a recognized test (e.g., polymerase chain reaction, modified Hodge test (MHT), Carba NP, or metallo-β-lactamase testing (e.g., MBL E-test or other screening method). For bacteria with intrinsic imipenem non-susceptibility (i.e., *Morganella morganii*, *Proteus* spp., *Providencia* spp., *Serratia* spp.), non-susceptibility to carbapenems other than imipenem is required

- 2nd Step: Within one day of results of CRE positive, identify Epi-linked contacts (roommates, healthcare workers, etc.) and send an email to ARLN.Health@TN.gov and CC HAI@LA.gov requesting swab kits for colonization testing
- 3rd Step: Send original isolate for screening to the Louisiana PHL if one of the following organisms: *Enterobacter* spp., *Klebsiella oxytoca*, *Klebsiella pneumoniae*, or *Escherichia coli*
- 4th Step: Tennessee ARLN Lab will send a packet with swabs for AST and shipping information with FedEx, packaging for transport guide, and specimen collection guide
- 5th Step: Louisiana HAI Epidemiologist (Andrea Salinas) will notify submitting facilities of results from both the Tennessee ARLN Lab and the Louisiana PHL

Submitting Isolates for CRE Colonization Testing

- Cepheid Testing for CRE performed on rectal or fecal swabs
  - Acceptable specimens
  - Unacceptable specimens

Submitting Isolates for CRE Colonization Testing

- Initiate infection control practices and contact precautions
- Swabs from CR patient contacts
- PCR-based detection ≤ 1 day turnaround
- Regional lab colonization testing
- Provide or request assistance; initiate investigation
- Report within 1 working day of results
- State testing
- Swabs from CR patient contacts
- State HAI coordinator
- PCR-based detection ≤ 1 day turnaround
- Regional lab colonization testing
- Report within 1 working day of results
- ARLN
- PHD
- H
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Submitting Isolates for CRPA Testing

- Similar to CRE Submission just described
- 1st Step: Identify a confirmed case of CRPA using the state definition:
  - All *Pseudomonas aeruginosa* resistant to imipenem, meropenem, or doripenem ($\geq 8 \mu g/mL$) by standard AST methods (exclude mucoid isolates)
- 2nd Step: Submit to Louisiana PHL
  - If novel resistance is observed, isolates will be sent from LA-PHL to Tennessee ARLN Lab
- 3rd Step: Louisiana HAI Epidemiologist (Andrea Salinas) will notify submitting facility of results from both LA-PHL and Tennessee ARLN Lab

Submitting Isolates for CRPA and CRE Testing

Submitting Isolates for Candida testing

- Similar to CRE and CRPA isolate submission just described
- 1st Step: Identify a patient with suspected *Candida auris*
  - *C. auris* is routinely misidentified in routine laboratory tests. *C. haemulonii* results should be strongly suspected of being *C. auris* especially when collected from sterile body sites.
- 2nd Step: Identify epidemiologically linked contacts and roommates
- 3rd Step: Send an email to ARLN.Health@TN.gov and CC HAI@LA.gov to receive isolate submission guidelines
- 4th Step: Follow the interim and follow-up infection control guidance given by ARLN and the Louisiana HAI-AR Program
- 5th Step: Louisiana HAI Epidemiologist (Andrea Salinas) will notify submitting facilities of results from both the Tennessee ARLN Lab and the Louisiana PHL
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References

- CDC’s ELC Grantees' Meeting Presentations and Information Sheets
- CDC’s Antimicrobial Resistance Webpages: