Technical Appendix


Infrastructure

In 2016, CDC established the Antibiotic Resistance Laboratory Network (AR Lab Network) to address gaps in national laboratory testing capacity. The AR Lab Network can rapidly detect antibiotic resistance in samples or isolates from healthcare, food, and the community, and inform local responses to prevent spread and protect people. In healthcare settings, the AR Lab Network works in conjunction with CDC’s Containment Strategy to rapidly identify unusual resistance and help contain its spread. In 2017, the public health laboratories of all 50 states, five large cities, and Puerto Rico began testing and characterizing clinical isolates of carbapenem-resistant Enterobacteriaceae (CRE) and *Pseudomonas aeruginosa* (CRPA). Seven state public health laboratories serve as regional labs and support all jurisdictions within their region by testing colonization screening swabs for carbapenemase-producing organisms (CPOs) and characterizing isolates of carbapenem-resistant *Acinetobacter baumannii* (CRA).

Isolate Recruitment

Each public health laboratory has worked to establish or collaborate with a network of clinical laboratories to submit isolates to the AR Lab Network for phenotypic and molecular testing. For Enterobacteriaceae, testing is focused on isolates that are resistant to ertapenem, imipenem, meropenem, or doripenem using standard antimicrobial susceptibility testing definitions (minimum inhibitory concentrations of $\geq 4 \mu g/ml$ for imipenem, meropenem, and doripenem or $\geq 2 \mu g/ml$ for ertapenem). The AR Lab Network has prioritized testing of *Klebsiella oxytoca*, *Klebsiella pneumoniae*, *Escherichia coli*, and *Enterobacter* species but encourages testing of additional genera of Enterobacteriaceae where local capacity and capabilities allow.

For *Pseudomonas aeruginosa* and *Acinetobacter baumannii*, isolates resistant to imipenem, meropenem, or doripenem, using standard antimicrobial susceptibility testing (minimum inhibitory concentrations of $\geq 8 \mu g/ml$) are targeted. *Acinetobacter baumannii* testing is done through sentinel surveillance conducted by the seven regional laboratories and includes isolates recruited from at least one clinical laboratory in each AR Lab Network jurisdiction within each region.

The size and coverage of isolate submission networks in each jurisdiction varies. Some states have near or fully comprehensive coverage because of reporting rules that require isolate submission. For those states without isolate submission requirements, CDC recommends that isolate submission be focused on populations, specific healthcare facilities, or healthcare facility types with higher rates or likelihood of resistant infections.

Note: The AR Lab Network is not a surveillance system. Within each state, isolate submissions and testing are determined by state regulations and priorities.

Isolate Testing
Data include clinical, surveillance, and outbreak isolates and specimens. State and local public health labs use a variety of methods to test for organism identification, carbapenemase production, and mechanism testing.

**Organism identification**

Organism identification methods include, but are not limited to, Vitek 2, Microscan, API20E, and MALDI-TOF (matrix-assisted laser desorption/ionization-time of flight) mass spectrometry.

**Carbapenemase production**

Laboratories use either the modified carbapenem inactivation method (mCIM) or CarbaNP as phenotypic tests to determine whether an organism is carbapenemase-producing.

**Mechanism testing**

Isolates are tested for the presence of $\text{bla}_{\text{KPC}}$, $\text{bla}_{\text{NDM}}$, $\text{bla}_{\text{VIM}}$, $\text{bla}_{\text{OXA-48}}$, and $\text{bla}_{\text{IMP}}$ carbapenemase genes using real-time PCR assays, Streck ARM-D kits, or FDA-approved diagnostics (i.e., Cepheid Gene Xpert Carba-R, or Nanosphere Verigen).

Note: During 2017 and 2018, the AR Lab Network did not routinely test for other mobile oxacillinase (OXA) genes, such as $\text{bla}_{\text{OXA-23}}$, $\text{bla}_{\text{OXA-24/40}}$, and $\text{bla}_{\text{OXA-58}}$, known to be common in CRA.

**Tiered testing structure**

The testing in the AR Lab Network is tiered. Most isolate characterization occurs in the state and local public health laboratories. Regional laboratories provide surge capacity and confirmatory testing for isolates or mechanisms not characterized at their state and local public health laboratories. CDC provides surge capacity and confirmatory testing for any specimens or molecular targets not characterized by state, local, or regional public health laboratories.

**Colonization Screening**

In accordance with manufacturer’s guidance, public health laboratories use the Gene Xpert Carba-R assay (Cepheid, Sunnyvale, CA) to detect the presence of $\text{bla}_{\text{KPC}}$, $\text{bla}_{\text{NDM}}$, $\text{bla}_{\text{VIM}}$, $\text{bla}_{\text{OXA-48-like}}$, and $\text{bla}_{\text{IMP-1}}$ carbapenemase genes in rectal swab specimens. Cepheid is currently unable to detect most variants of $\text{bla}_{\text{IMP}}$ known to be circulating in the United States. CDC provides surge capacity for regional labs during periods of validation.

**Reporting**

Laboratories in the AR Lab Network report data to CDC at least monthly. During 2017, most labs transmitted their data via email using an Excel file that had specified fields. By the end of 2018, 40 states could upload standardized CSV formatted files directly from their Laboratory Information Management Systems (LiMS) using a secure online portal.

**Data Processing**

At CDC, data have been compiled using SAS 9.4, standardized, and stored as a SAS dataset. Data are cleaned, standardized, and stored as a SAS Dataset on a monthly basis. *Klebsiella aerogenes* isolates
are classified as *Enterobacter aerogenes*. At the end of each calendar year, data are reconciled in partnership with all reporting labs to verify the number of isolates and the data associated. Each isolate is counted once; testing results from state, local, and regional laboratories and CDC’s Clinical and Environmental Microbiology laboratory are consolidated into one record.

Note: The AR&PSP includes AR Laboratory Network closed out data available as of July 2019.

**Dictionary of Terms**

- **AR**: Antimicrobial/Antibiotic Resistance
- **AR Lab Network**: Antibiotic Resistance Laboratory Network
- **Carbapenemase**: Group of beta-lactamase enzymes active against carbapenems
- **CP**: Carbapenemase gene-positive
- **CPO**: Carbapenemase-producing organism
- **CRE**: Carbapenem-resistant Enterobacteriaceae
- **CRPA**: Carbapenem-resistant *Pseudomonas aeruginosa*
- **CSV**: Comma separated value
- **FDA**: U.S. Food and Drug Administration
- **HAI**: Healthcare-associated infection
- **IMP**: Integron-encoded Metallo-beta-lactamases
- **KPC**: *Klebsiella pneumoniae* Carbapenemase
- **LIMS**: Laboratory Information Management System
- **MALDI-TOF**: Matrix-assisted laser desorption/ionization-time of flight
- **MBL**: Metallo-beta-lactamase
- **mCIM**: Modified Carbapenem Inactivation Method
- **MIC**: Minimum inhibitory concentration
- **NDM**: New Delhi Metallo-beta-lactamase
- **OXA-48**: Oxacillinase-48 beta-lactamase
- **PCR**: Polymerase chain reaction
- **PHL**: Public Health Laboratory
- **VIM**: Verona Integron-encoded Metallo-beta-lactamase
- **SAS**: Statistical Analysis Software