Efforts and Resources for Addressing Antimicrobial Resistance

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Antimicrobial Susceptibility and Resistance: Addressing Challenges of Diagnostic Devices – FDA Public Workshop

September 13, 2017
The Antibiotic Resistance Laboratory Network

- **WEST**
  - Washington State Public Health Laboratories
    - Core Testing
    - + N. gonorrhoeae

- **CENTRAL**
  - Minnesota Department of Health Public Health Laboratory
    - Core Testing
    - + C. difficile
    - + S. pneumoniae

- **MOUNTAIN**
  - Texas Department of State Health Services Laboratory
    - Core Testing
    - + N. gonorrhoeae

- **MIDWEST**
  - Wisconsin State Laboratory of Hygiene
    - Core Testing
    - + S. pneumoniae

- **NATIONAL TUBERCULOSIS MOLECULAR SURVEILLANCE CENTER**
  - Michigan Department of Health and Human Services
    - Core Testing
    - + M. tuberculosis

- **NORTHEAST**
  - Wadsworth Center Bacteriology Laboratory
    - Core Testing

- **MID- ATLANTIC**
  - Maryland Public Health Laboratory
    - Core Testing
    - + M. tuberculosis

- **SOUTHEAST**
  - Tennessee State Public Health Laboratory
    - Core Testing
    - + N. gonorrhoeae
Addressing Serious and Urgent AR Threats

Characterize resistance mechanisms of carbapenem-R gram-negative bacteria and test for colonization. WGS of *Salmonella* to detect resistance and outbreaks.

Reference susceptibility testing of *Neisseria gonorrhoeae* to guide treatment. WGS of isolates to identify resistance mechanisms.

Confirmation of *Candida auris*, colonization testing, antimicrobial susceptibility testing.

WGS of all *Mycobacterium tuberculosis* isolates to detect resistance and to identify transmission.

Testing for antibiotic resistant *Streptococcus pneumoniae* vaccine escape strains.

WGS of *Clostridium difficile* to characterize transmission dynamics.
New Lab Capacity to Detect AR Threats

- Detecting new AR
- Delivering data to prevent infections
- Delivering data to treat infections

EXAMPLES...
VIM+ *Pseudomonas aeruginosa*

- Carbapenem-R *P. aeruginosa* are common, but few produce a carbapenemase
- Before ARLN, few VIM-producing PA cases were identified
- Since implementing the ARLN, we’ve:
  - Identified an outbreak at a FL long term acute care facility.
  - Leveraged ARLN capacity to support outbreaks in IL and FL.
  - Isolated cases in NV, TX, CA and OR. Two cases associated to healthcare abroad. No ongoing transmission identified.
Changing Susceptibility of *Neisseria gonorrhoeae*

- 2015 Treatment Recommendation: ceftriaxone + azithromycin
- Testing in ARLN increases the number of isolates tested and the turn-around time for results
- ARLN testing results are being closely monitored for increasing azithromycin resistance to determine if treatment recommendations need to be revised.
Candida auris Outbreaks

Candida auris cases in the United States

Number of Cases Reported

- 1 - <20
- 20 - <39
- 39 - <58
- 58 - 77

Location

<table>
<thead>
<tr>
<th>Location</th>
<th>Number Reported</th>
<th>Dates of collection</th>
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<tbody>
<tr>
<td>Connecticut</td>
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<tr>
<td>Florida</td>
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<tr>
<td>Illinois</td>
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</tr>
<tr>
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<td>New York</td>
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<td>May 2013, Apr 2016 - Jul 2017</td>
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<td>Oklahoma</td>
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A Pilot Program

- Antimicrobial Susceptibility Testing of New Antibiotics
  - There is often a gap between the approval of a new drug and the availability of testing methods in hospital laboratories
  - This gap can result in under use and over use of a new antibiotic
  - Testing is most important for pan or nearly pan-resistant bacteria
  - We can leverage ARLN lab capacity to place reference broth microdilution testing capabilities in regional labs and use ARLN electronic test order and report capabilities for rapid reporting
More Resistant Bacteria and Bacteria that are Resistant to More Drugs

An Example:

- 70 yo female hospitalized for an infection in her hip
- The patient recently traveled to India and was hospitalized for treatment of a hip fracture
- Infecting isolate: NDM-producing *Klebsiella pneumoniae* that was pan-resistant
- The patient developed septic shock and died

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**Notes from the Field**

Pan-Resistant New Delhi Metallo-Beta-Lactamase-Producing *Klebsiella pneumoniae*

— Washoe County, Nevada, 2016

Loi Chen, PhD; Randall Todd, MD; Julia Khalilbash, PhD; Manya Waters, PhD; Alexander Kallen, MD

On August 25, 2016, the Washoe County Health District in Reno, Nevada, notified of a patient at an acute-care hospital with carbapenem-resistant Enterobacteriaceae (CRE) that was resistant to all available antimicrobial drugs. The specific CRE, *Klebsiella pneumoniae*, was isolated from a wound specimen collected on August 19, 2016. After CRE was identified, the patient was placed in a single room under contact precautions. The patient had a history of recent hospitalization outside the United States. Therefore, based on CDC guidance (1), the isolate was sent to CDC for testing to determine the mechanism of antimicrobial resistance, which confirmed the presence of New Delhi metallo-beta-lactamase (NDM). The patient was a female Washoe County resident in her 70s who arrived in the United States in early August 2016 after an extended visit to India. She was admitted to the acute care hospital on August 18 with a primary diagnosis of systemic inflammatory response syndrome, likely resulting from an infected right hip seroma. During the 2 years preceding this U.S. hospitalization, the patient had multiple hospitalizations in India related to a right femur fracture and subsequent osteomyelitis of the right femur and hip. The patient had been in India in June 2016, with susceptibility testing in the United States indicating that the infection in India had been in June 2016.
Verification of an Automated, Digital Dispensing Platform for At-Will Broth Microdilution-Based Antimicrobial Susceptibility Testing

Kenneth P. Smith, James E. Kirby
Department of Pathology, Beth Israel Deaconess Medical Center, Boston, Massachusetts, USA

With rapid emergence of multidrug-resistant bacteria, there is often a need to perform susceptibility testing using or newer antimicrobial agents. Such testing can often be performed only by using labor-intensive, time-consuming, and lies outside the capacity of most clinical labs, necessitating reference laboratory testing and thereby delay of susceptibility data. To address the compelling clinical need for microbiology laboratories to perform this testing, we explored a novel, automated, at-will broth microdilution-based susceptibility testing platform. Specifically, we utilized inkjet printer technology in the HP D300 digital dispensing system to dispense, directly from stock solution plate, the 2-fold serial dilution series required for broth microdilution testing. This technology was compared to absorbance readings and data analysis to determine MICs. Performance was verified by testing members of the E. coli strain and cefoxitin-resistant E. coli for susceptibility to ampicillin, cefazolin, ciprofloxacin, colistin, gentamicin, meropenem, and tetracycline, using the results obtained with a broth microdilution reference standard. In precision studies, essential and categorical errors were 96.8% and 98.3%, respectively. Furthermore, significantly fewer D300-based measurements were required than from the modal MIC, suggesting enhanced reproducibility. In accuracy studies performed using a panel of clinical isolates, rates of essential and categorical agreement and very major, major, and minor errors were 94%, 3.4%, and 0%, respectively. Based on these promising initial results, it is anticipated that the D300-based method will be capable of being implemented in institutional-based clinical microbiology laboratories to perform at-will broth microdilution testing of antimicrobial susceptibility testing gap.
On Demand MIC Panels

- Easy method to place reference BMD capacity in ARLN labs

Applications
- Testing susceptibility of pan-R pathogens to new drugs
- Collect AST data for breakpoint decisions

Can leverage ARLN cloud based electronic test order and result for faster turn-around times
ARLN - Summary

- Regional labs with comprehensive phenotypic and genotypic testing capacity for urgent and serious AR pathogens

- The goals of testing are to detect new AR, to prevent infections, and to improve treatment of infections

- The testing menu is flexible and can be adapted in response to changing AR threats
CDC & FDA Antibiotic Resistance Isolate Bank

New innovations can support earlier diagnoses and more effective treatment options that can slow antibiotic resistance.

- CDC uses bacteria samples (isolates) from health departments, labs, and outbreak and surveillance activities.
- CDC analyzes and sequences the bacteria’s resistance and makes the data and sample available.
- **Researchers** can use the bacteria and data to challenge, develop new diagnostic tests and antibiotics.
- **Laboratorians** can validate lab tests to improve patient care.

**BY THE NUMBERS**
- CDC curated 14 panels from its 450,000+ isolate collection
- 55,000 isolates shared since July 2015
- 571 unique customers
- 637 orders processed
The isolates helped us challenge our diagnostic tests to ensure they can detect a variety of resistance targets. We also used the panels to validate automated sensitivity instruments when we adopted new breakpoints.

– Diagnostic Developer
For more information on CDC AR Investments

www.cdc.gov/arinvestments
Thank You
jpatel1@cdc.gov

For more information, contact CDC
1-800-CDC-INFO (232-4636)

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.