

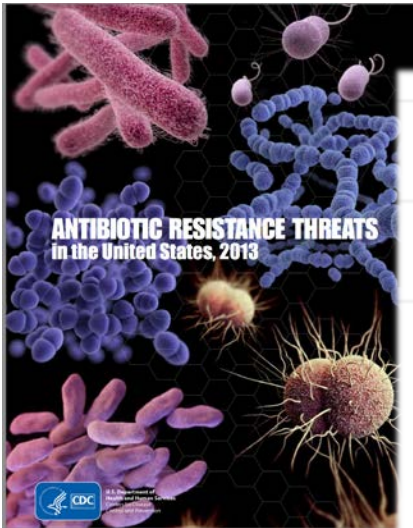


**Department
of Health**

**Wadsworth
Center**

Antibiotic Resistance Laboratory Network Northeast Update and Expanded Drug Susceptibility Testing

**Elizabeth Nazarian
Northeast Regional AR Lab Network Lead
Wadsworth Center, NYSDOH**



Urgent Threats

- *Clostridium difficile*
- Carbapenem-resistant Enterobacteriaceae (CRE) ←
- Drug-resistant *Neisseria gonorrhoeae*

Serious Threats

- Multidrug-resistant *Acinetobacter* ←
- Drug-resistant *Campylobacter*
- Fluconazole-resistant *Candida* (a fungus) ←
- Extended spectrum β -lactamase producing Enterobacteriaceae (ESBLs)
- Vancomycin-resistant *Enterococcus* (VRE)
- Multidrug-resistant *Pseudomonas aeruginosa* ←
- Drug-resistant Non-typhoidal *Salmonella*
- Drug-resistant *Salmonella* Typhi
- Drug-resistant *Shigella*
- Methicillin-resistant *Staphylococcus aureus* (MRSA)
- Drug-resistant *Streptococcus pneumoniae*
- Drug-resistant tuberculosis

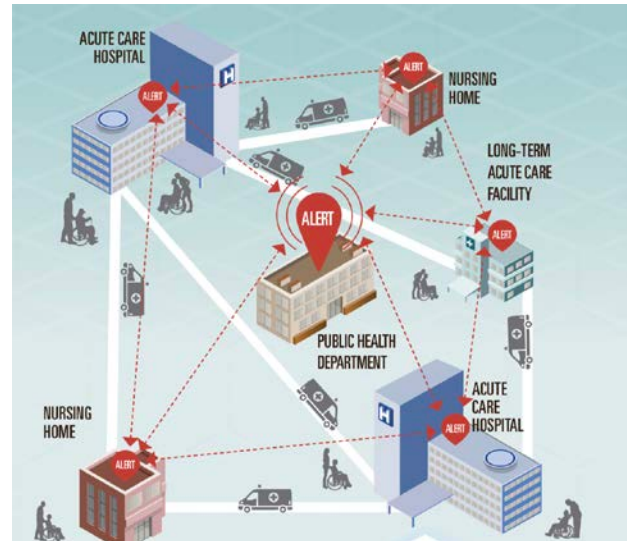
Concerning Threats

- Vancomycin-resistant *Staphylococcus aureus* (VRSA)
- Erythromycin-resistant Group A *Streptococcus*
- Clindamycin-resistant Group B *Streptococcus*

Updated AR Threats Report Fall anticipated 2019

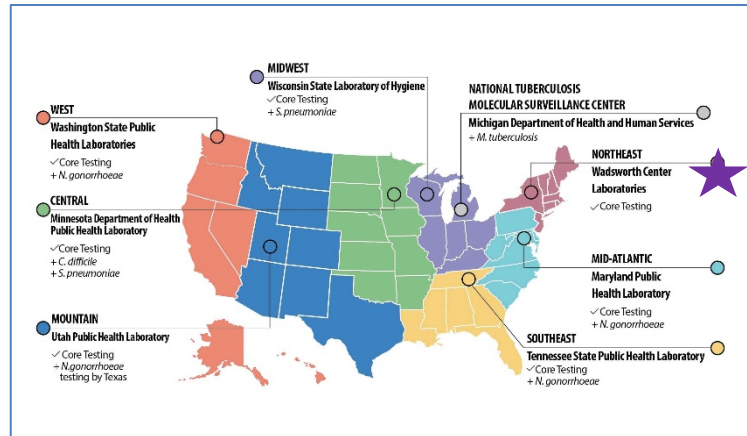
AR Lab Network

- Provides gold standard methods and diagnostics in all 50 states, 5 large cities, and Puerto Rico, and includes 7 Regional labs with expanded testing capabilities
- Testing complements CDC's Containment Strategy to help identify, respond and contain the urgent and serious threats and keep new threats from spreading
- **In 2018, the AR Lab Network tested 14,054 CRE and 10,279 CRPA.**
- **40% CRE and 3.5% CRPA were found to contain one of the 5 main carbapenemases**



Wadsworth Center Northeast Regional Laboratory

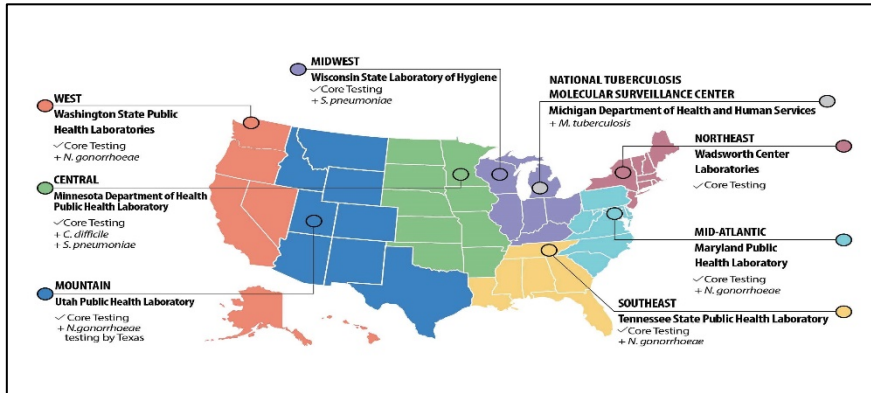
7 Regional Labs






Core Testing :

- CRO Colonization testing
- CRE/CRPA Isolate Characterization
- Confirmation/Detection Discordant or Novel mechanisms
- Emerging threats (*mcr* genes and MDR *Acinetobacter* spp.)
- Pan-resistance
- *Candida* susceptibility (Mycology Laboratory)
- *Candida auris* identification and screening (Mycology Laboratory)

AR Lab Network Laboratories



CRE 
Carbapenem-Resistant
Enterobacteriaceae 


CRPA 
Carbapenem-Resistant
Pseudomonas aeruginosa

Acquired
Carbapenemase
genes:

*bla*_{KPC}
*bla*_{NDM}

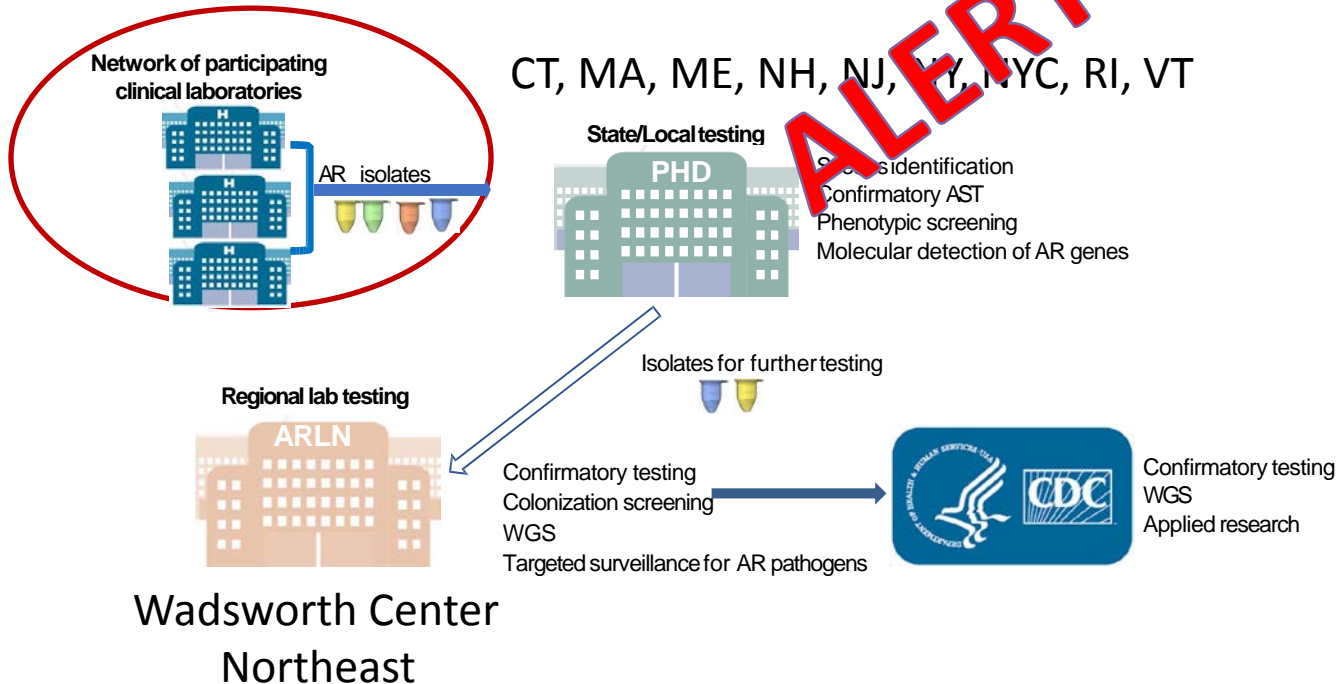
*bla*_{VIM}
*bla*_{IMP}
*bla*_{OXA-48}

(CP= carbapenemase producing)

CP-CRE
CP-CRPA 

AR Lab Network Testing Approach

Tiered Testing

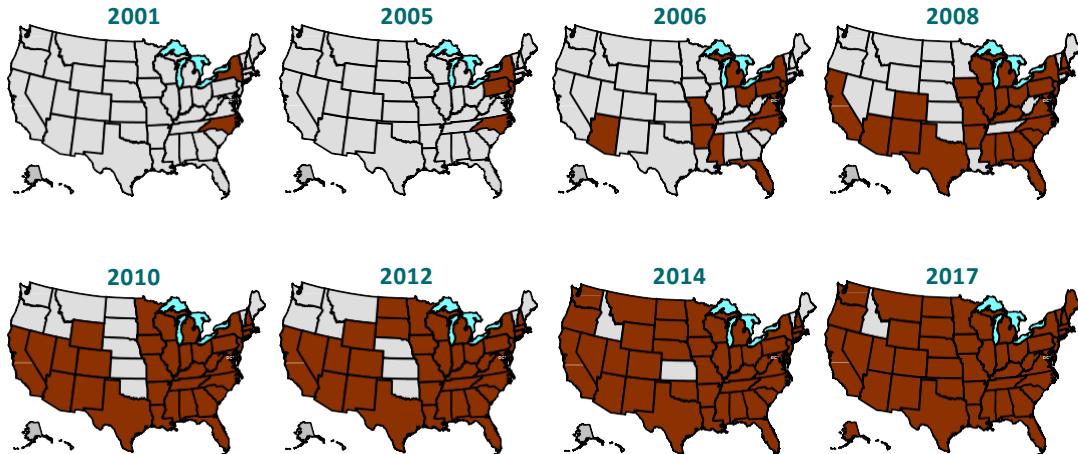


ALERT

Wadsworth Center
Northeast

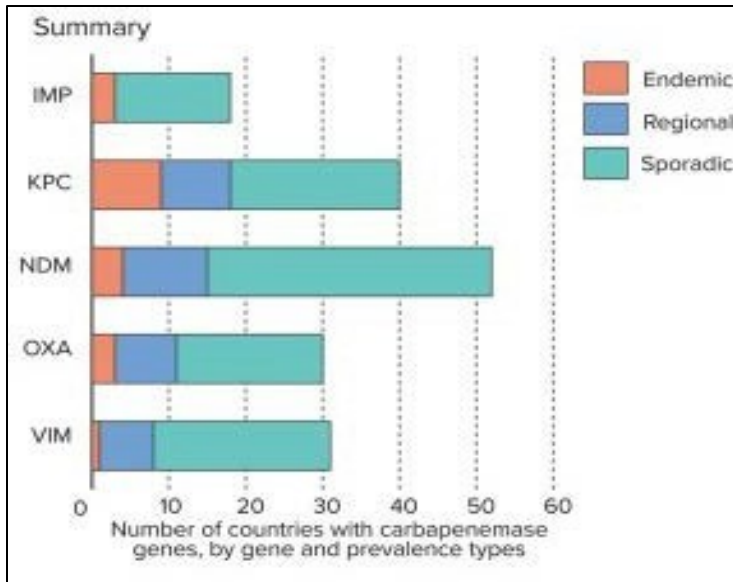
Rapid Spread of Carbapenemase-Producing (CP) Enterobacteriaceae in the United States

KPC-CRE found in the US spread from 2 states in 2001 to 49 states, DC, and PR in 16 years



 States with *Klebsiella pneumoniae* carbapenemase (KPC)-producing Carbapenem-resistant Enterobacteriaceae (CRE) confirmed by CDC

Prevalence Worldwide Carbapenemase Genes (KPC, NDM, OXA, VIM, IMP)



Logan et al., J Infect Dis. 2017. Feb 15

Regional Laboratory Testing Updates...

- CRAB - Detection of OXA-23, -24/40, -58 Multiplex in Isolates and Rectal Swabs – April 22, 2019



93 Alerts from 5 Jurisdictions

- OXA-23 (88)
- OXA-24/40 (5)

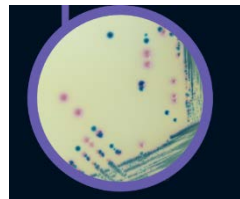
Regional Laboratory Testing Updates...

- Limitations with IMP variant detection by Cepheid Carba-R (IMP-1 only)



EMAG®

- Validation of CDC IMP assay for Isolates and Rectal Swabs
- Validation of CDC MCR-1/MCR-2 assay for Isolates and Rectal Swabs
- Validation of mSuperCARBA™ CHROMagar for efficient and enhanced isolate recovery from positive colonization screenings
- 84% isolate recovery



Regional Laboratory Testing Updates...

Whole-genome sequencing (WGS)

- Identify all AR genes in genome
 - Database includes over 5,500 unique genes
- Identify emerging and novel AR mechanisms
- Identify AR genes to the variant level (*bla*_{KPC-2} vs *bla*_{KPC-5})

- Outbreak investigations
 - Identify transmission events between patients

Antibiotic Resistance WGS at Wadsworth: Pipeline Overview

Illumina Sequencing Reads



de novo assembly & quality control



Are the bacteria
similar?
(Multilocus Sequence
Typing)

MLST

What antibiotic
resistance genes are
present?

Gene Variant

Where are the
antibiotic resistance
genes located?
Plasmid?

Total analyzed with pipeline: >800

Supplemental Reporting through LIMS

Antimicrobial Resistance Gene Analysis - Whole-Genome Sequencing *

Gene(s) Identified:

blaNDM-1

Gene Variant

Multilocus Sequence Typing Analysis*

MLST ST:

1399

MLST

* The performance characteristics of this test were determined by the Wadsworth Center. It has not been cleared or approved by the U.S. Food and Drug Administration.

END OF REPORT

A Look at the DATA.....

AR Lab Network –Northeast Regional Laboratory 2018 Testing

CRE Isolate Submission

- 834 Tested
- 542 identified as CP-CRE (65%)
 - 479 KPC
 - 46 NDM
 - 21 OXA-48 like
 - 1 KPC/NDM
 - 1 NDM/OXA-48

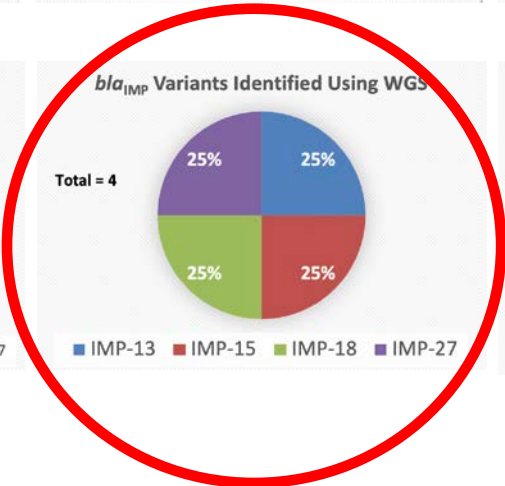
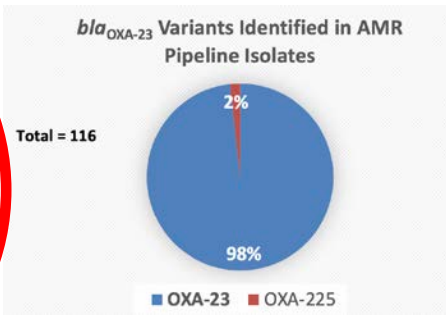
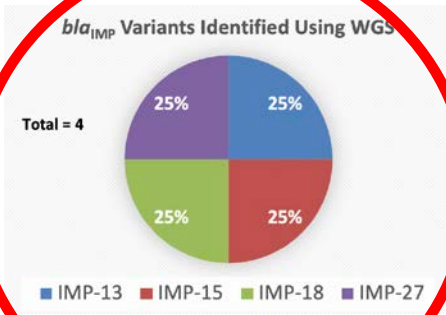
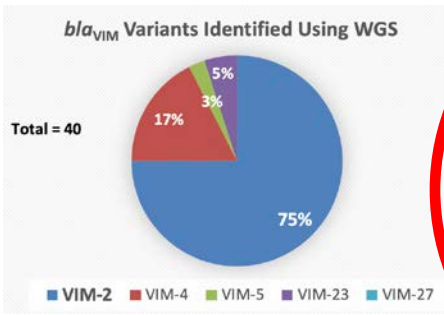
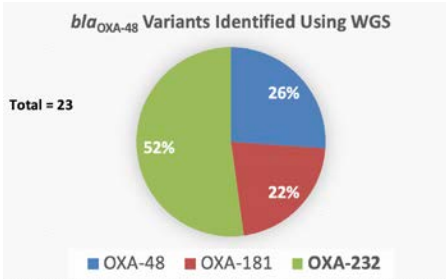
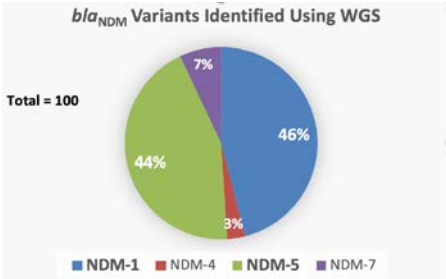
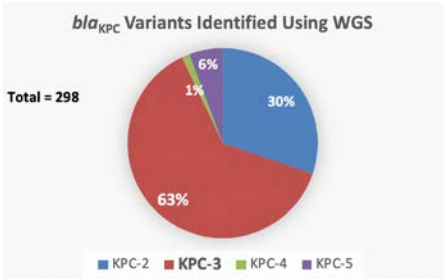
CRPA Isolate Submission

- 1418 Tested
- 55 identified as CP-CRPA (~4%)
 - 29 VIM
 - 15 KPC
 - 3 OXA-2/OXA50 like
 - 2 NDM
 - 2 IMP
 - 1 IMP/NDM

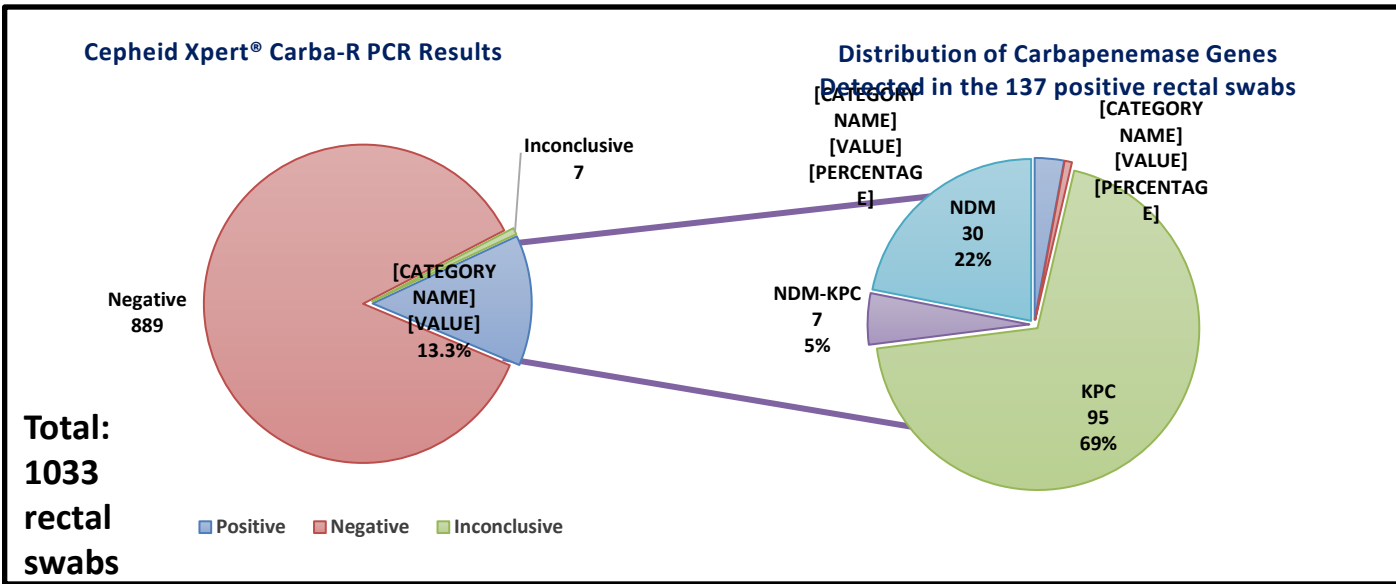


CRE/CRPA Colonization Screening

- 615 Rectal Swabs
- 4 States and NYC
- 70 Health care facilities



Northeast Region AR Lab Network CRE colonization screenings, 2017-2019



2019 - >1300 rectal swabs tested


DATA

CDC's AR Lab Network closes the gap between local capabilities and the data needed to combat AR in healthcare and the community.



NORTHEAST REGION

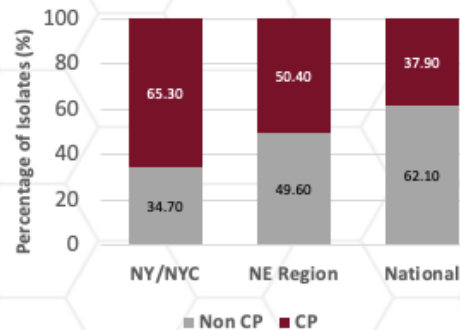

 Department
of Health

 Wadsworth
Center

CRE and CRPA Isolate Testing, 2018*

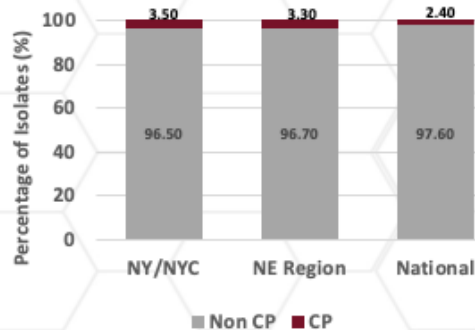
CRE isolates tested NY and NYC: 1088

% CP&-CRE: 65.3



CRPA isolates tested NY and NYC: 1418

% CP&-CRPA: 3.5



*As of May 2019; data subject to change

^a Graphs adjusted for number of isolates tested

[&] CP is defined as PCR-positive for at least one of the carbapenemase genes tested

Expanded Antimicrobial Susceptibility Testing (ExAST) for *Enterobacteriaceae* producing a metallo-beta-lactamase (MBL)

- NDM most prevalent MBL in *Enterobacteriaceae*
- Multidrug resistant due to additional AR genes
- Resistant to newer, more recently approved drugs for CRE:
 - Ceftazidime-avibactam
 - Meropenem-vaborbactam
 - Plazomicin
 - Imipenem-relebactam

(Mostly effective against KPC-producing CRE)



Expanded Antimicrobial Susceptibility Testing (ExAST) for *Enterobacteriaceae* producing a metallo-beta-lactamase (MBL)

New Antimicrobials Submitted to FDA or in Phase 3 Trials:

- Cefidericol
- Aztreonam-avibactam
- Cefepime-taniborbactam

(Show efficacy for treatment of NDM-producing CRE)

**Recommended Treatment: Aztreonam-avibactam
(Aztreonam + Ceftazidime-Avibactam)**

How is AST performed for Aztreonam-avibactam?

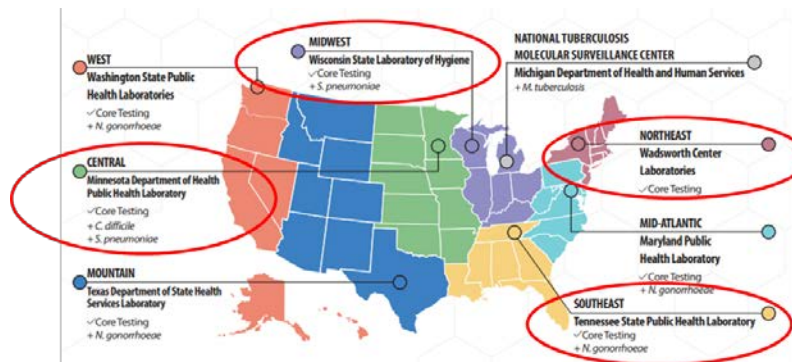
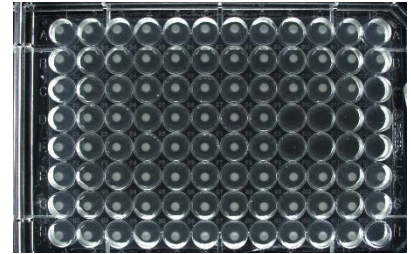
HP Printing technology repurposed for dispensing antibiotics instead of ink



- HP D300e allows for in-house creation of BMD panels with novel antibiotics
- The combinations are **not yet included in commercially available BMD panels**
 - Aztreonam
 - Ceftazidime-Avibactam
 - **Aztreonam-Avibactam**
 - Aztreonam-Ceftazidime-Avibactam

ExAST

- Multi-site Pilot Validation
- Northeast and Mid-Atlantic Regions
- ExAST Validation sign-off February 28, 2019
- Testing requests received March 2019
- 18 isolates tested to date



“What you need to know to Access Expanded Antimicrobial Susceptibility Testing (ExAST) for Hard-to-Treat Infections at Wadsworth Center”

What isolates can be submitted?

Enterobacteriaceae..

- Test non-susceptible to all beta-lactams including ceftazidime-avibactam or meropenem-vaborbactam
- OR**
- Confirmed NDM, VIM or IMP by a molecular method



What is the testing process?

Isolate Confirmation



- *Enterobacteriaceae* – MALDI-TOF MS
- Non-susceptible to beta-lactams – GNX2F
- Carbapenemase production – mCIM
- Carbapenemase gene-coded resistance – Real-time PCR



ExAST Panel

- Aztreonam
- Ceftazidime-Avibactam
- Aztreonam-Avibactam
- Aztreonam-Ceftazidime-Avibactam

Final Report

3 days



How is Testing Requested?

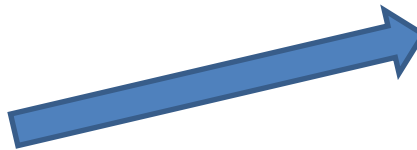


- Healthcare Providers, Clinical Laboratories, State Public Health Laboratories and Epidemiologists

- Pre-authorization/Approval Required**

ARLNCORENY@health.ny.gov

- ExAST Fact Sheet
- Pre-authorization Approval Form
- NYS Specific Requisition
- Guidance for Isolate Submission



Expanded Antimicrobial Susceptibility Testing for Hard-to-Treat Infections

Antimicrobial susceptibility testing for Enterobacteriaceae producing a metallo-beta-lactamase (MBL)

Clinicians, hospital laboratories, and public health labs can request expanded antimicrobial susceptibility testing (AST) from CDC's Antibiotic Resistance Lab Network (ARL Lab Network) to find new, effective treatment options for their patients' most resistant infections.

- Enterobacteriaceae are resistant to new drugs for carbapenem-resistant Enterobacteriaceae (CRE) treatment, specifically ceftazidime-avibactam and meropenem-avibactam. However, these bacteria may be susceptible to the combination therapy ceftazidime + avibactam + acrivimycin.
- Susceptibility testing is CLIA-compliant and results will be reported for ceftazidime + avibactam, acrivimycin, and combinations + avibactam to help determine ability of combination therapy.
- CDC plans to expand testing as more antimicrobial treatment options become available for other hard-to-treat bacterial infections.
- There is no cost for this service.

*Ceftazidime + avibactam + acrivimycin is a combination drug recommended by the CDC for the treatment of certain infections caused by CRE-producing Enterobacteriaceae.

- 1 What isolates can I submit?**
Hospital laboratories and clinicians are encouraged to submit Enterobacteriaceae isolates that:
 - Are from susceptible to all beta-lactams, including either ceftazidime-avibactam or meropenem-avibactam. These isolates may be MBL-producing isolates with true effective treatment options.**OR**
 - Enterobacteriaceae with NDH4, VIM, or IMP genes confirmed by a molecular test.
- 2 What is the testing process?**
 - All non-urged sites (all business days) receive isolates for therapy decisions.
 - Isolates will be tested to confirm carbapenem resistance, carbapenem production, and to identify carbapenemase gene-coded resistance.
 - Isolates that meet the inclusion criteria will be tested for susceptibility to ceftazidime + avibactam, acrivimycin and avibactam + acrivimycin.
- 3 How do I request the test and receive results?**
 - Physicians, providers, hospital laboratories, and public health labs should email their request to request testing and instructions for submitting the bacterial isolate.
 - Provide preliminary AST testing results and confirm that the testing's infectious disease department has been notified and/or infectious disease physician has been consulted.
 - The regional lab uses and contact information on the right.

AS PART OF THE ARL LAB NETWORK, YOUR STATE & REGIONAL LAB WORK TO:
 DETECT RESISTANT SPECIES & NEW THREATS | PERFORM SUSCEPTIBILITY TESTING TO TRACK RESISTANCE | HELP RESPOND TO OUTBREAKS

www.cdc.gov/DrugResistanceresolutionsinitiative/AR-Lab-Network

Pre-authorization Form

Section 1

At Lab Network's Expanded Antimicrobial Susceptibility Testing (EAST) for Hard to Treat Infections Program

 **Department of Health**
Wadsworth Center
130 New Scotland Avenue, Albany, NY 12242
608.402.0200 ext. 3333
Phone: (518) 462-4177
Fax: (518) 485-3775

Clear Form

EAST Pre-authorization Form
Instructions: Please provide the following information to ensure the antibiotic is available to be used in WADSWORTH@health.ny.gov with subject line: "EAST Request: # [request guidance for isolate submission URL]".

Section 1: Patient/Order Information:

Patient Name: _____
Specimen Collection Date: _____
City/State: _____ Specimen Source: _____
Specify ID# (submitting facility or laboratory accession ID number): _____

Section 2: Submission Contact Information
All information must be provided.

Test results (if available) must be sent with the report of department have been notified of or consulted (see, including to facilities: antibiotic tests, including meropenem-vaborbactam, MBL) producer with laboratory test (e.g. eCIM, MBL)

Section 3: Submission Criteria (check all that apply)

A copy of initial AST (raw data preferred) and molecular test results (if available) must be sent with the isolate.

- Infectious disease physician and/or facility's infection control department have been notified of or consulted on test request
- Enterobacteriaceae tests non-susceptible to all beta-lactams, including ceftazidime-avibactam
- Enterobacteriaceae tests non-susceptible to all beta-lactams, including meropenem-vaborbactam
- Enterobacteriaceae confirmed as a metallo- β -lactamase (MBL) producer with laboratory test (e.g. eCIM, MBL Test)

Enterobacteriaceae with: NDM gene IMP gene VIM gene

State Public Health Laboratory: _____

Point of Contact Name: _____

Phone Number: _____

Fax Number (results may be returned by secure fax): _____

Email (results may be returned by encrypted email): _____

ExAST Specific Requisition

Patient Demographics				*denotes required information			
Last Name *		First Name *		MI	DOB *		Sex <input type="checkbox"/> Male <input type="checkbox"/> Female
Street Address			City		State		Zip Code
NYS County of Residence *		NYS DOH Outbreak Number		CDESS Case Number		Submitter's Reference Number	
Submitter (Laboratory report will be sent to)				*denotes required information			
Name and Address *				Laboratory PFI			
Name				Contact Person			
Address				Telephone Number (____) _____ - _____ ext. _____			
City		State		Zip			
Specimen Information				*denotes required information			
Specimen is: <input checked="" type="checkbox"/> Isolate <input type="checkbox"/> Primary Specimen <input type="checkbox"/> Autopsy Specimen				Collection Date * ____/____/____ MM / DD / YYYY			
Source / Specimen Type *				Time Collected (if applicable for test) ____:____:____ (HH:MM)			
Laboratory Examination Requested				www.wadsworth.org/IDtesting			
<input checked="" type="checkbox"/> Bacterial <input type="checkbox"/> Fungal <input type="checkbox"/> Mycobacterial <input type="checkbox"/> Parasitic <input type="checkbox"/> Serology <input type="checkbox"/> Viral							
Suspected Organism / Agent							
<input type="checkbox"/> Identification / Confirmation		<input type="checkbox"/> Susceptibility (specify antimicrobial(s))		<input type="checkbox"/> TB Fast Track www.wadsworth.org/mycobac/asttrack.htm		<input type="checkbox"/> Serology (specify test and define onset date)	
<input type="checkbox"/> Viral Encephalitis Panel www.wadsworth.org/divisions/infdis/enceph/form.htm		<input checked="" type="checkbox"/> Other (specify) AMR-Expanded AST (Aztreonam-Avibactam)					
Submitting lab findings: Smear/Stain/Other results				Comments Provide copy of AST Results			
Specimen submitted on/in: Media		Preservative		Tissue cell line			
Relevant Exposure: <input type="checkbox"/> Contact known case <input type="checkbox"/> Food/water <input type="checkbox"/> Nosocomial							
<input type="checkbox"/> Travel Location & Dates		<input type="checkbox"/> Animal Type		<input type="checkbox"/> Arthropod Type			

Infectious Diseases Requisition

New York State Department of Health
615 Broadway
New York, NY 10037
Phone: (516) 402-1000
Fax: (516) 402-1000
www.health.ny.gov

Requisition ID: 123456789
Requisition Date: 10/10/2011

Abstract Demographic

Submitter: [Name] [Address] [City] [State] [Zip] [Phone] [Fax] [Email]

Specimen: [Type] [Quantity] [Container]

Source: [Location] [Date] [Time]

Specimen Information

Specimen is: Isolate Primary Specimen Autopsy Specimen

Collection Date: ____/____/____
MM / DD / YYYY

Source / Specimen Type: _____

Time Collected: ____:____:____
(HH:MM)

Laboratory Examination Requested

Bacterial Fungal Mycobacterial Parasitic Serology Viral

Suspected Organism / Agent

Identification / Confirmation

TB Fast Track www.wadsworth.org/mycobac/asttrack.htm

Viral Encephalitis Panel
www.wadsworth.org/divisions/infdis/enceph/form.htm

Other (specify) AMR-Expanded AST (Aztreonam-Avibactam)

Submitting lab findings: Smear/Stain/Other results

Specimen submitted on/in: Media Preservative Tissue cell line

Relevant Exposure: Contact known case Food/water Nosocomial

Travel Location & Dates Animal Type Arthropod Type

ExAST Testing

Example # 1:

- Physician request via State Epidemiologist
Escherichia coli, NDM from Urine

Resistant to all drugs tested by Clinical Laboratory

Expanded Broth Microdilution Susceptibility

Ceftazidime/avibactam MIC:	Resistant; >64/4 ug/ml
Aztreonam MIC:	Resistant; 64 ug/ml
Aztreonam/avibactam MIC:	Not interpretable; 8/4 ug/ml

[Note]

For aztreonam-avibactam, a minimum inhibitory concentration (MIC) is reported without an interpretation because clinical breakpoints for this drug combination have not been established. This drug demonstrates in vitro activity against metallo- β -lactamase (MBL) producing Enterobacteriaceae. Its clinical efficacy is under evaluation in clinical trials. Surveillance data indicate that MICs of MBL-producing Enterobacteriaceae (n=580) range from $\leq 0.015/4$ to 8/4 ug/ml.

ALERT



Example # 2:

- Clinical laboratory request via State Epidemiologist
Klebsiella pneumoniae, nearly Pan-resistant
from Tracheal Aspirate
- Resistant to all drugs tested by Clinical Laboratory including ceftazidime-avibactam and meropenem-vaborbactam (Cefepime susceptible)
- Carbapenemase-production and molecular testing for carbapenemase genes not performed by Clinical laboratory

Example # 2:

- Isolate forwarded for CP-CRE testing at Regional Laboratory

Klebsiella pneumoniae
NDM/OXA-48



Expanded Broth Microdilution Susceptibility	
Ceftazidime/avibactam MIC:	Resistant; >64/4 ug/ml
Aztreonam MIC:	Resistant; >64 ug/ml
Aztreonam/avibactam MIC:	Not interpretable; 1/4 ug/ml

NOTES:

[1] For aztreonam-avibactam, a MIC is reported without an interpretation because clinical breakpoints for the drug combination have not been established. This drug demonstrates in vitro activity against metallo- β -lactamase (MBL) producing Enterobacteriaceae. In a large surveillance study, the MICs of 580 MBL-producing Enterobacteriaceae ranged from $\leq 0.015/4$ to $8/4$ $\mu\text{g}/\text{mL}$ with a mode of $0.125/4$ $\mu\text{g}/\text{mL}$. The clinical efficacy of this drug combination for treating infections is unknown and under evaluation in a clinical trial. Because of limited treatment options, the 2018 Sanford Guide recommends the combination of ceftazidime-avibactam + aztreonam as a last resort for the treatment of serious infections caused by MBL-producing Enterobacteriaceae (Note: the agent in this regimen that is active against MBL-producing bacteria is aztreonam-avibactam). Please see the Sanford Guide for additional information if the ceftazidime-avibactam + aztreonam drug combination is considered for treatment.



ALERT



Escherichia coli

Source	Carbapenemase	WGS	AZT/AVI MIC
Blood	NDM	NDM-5 CTX-M-15	0.06/4
Urine	NDM	NDM-5 TEM-1	8/4
Urine	NDM/OXA-48	NDM-5 OXA-48	8/4
Sputum	NDM/OXA-48	NDM-5 OXA-181	2/4
Blood	NDM	NDM-5 CTX-M-15 TEM-1	4/4
Perirectal	NDM	NDM-1 TEM-1	0.12/4
Perirectal	NDM	Pending	8/4

Klebsiella pneumoniae

Source	Carbapenemase	WGS	AZT/AVI MIC
Tracheal Aspirate	NDM/OXA-48	NDM-5 OXA-232 CTX-M-15 SHV-11 TEM-1	1/4
Blood	NDM	NDM-1 CTX-M-15 SHV-11 TEM-1	0.25/4
Urine	NDM	NDM-9 CTX-M-15 SHV-11 TEM-1	0.25/4
Perirectal	NDM	NDM-5 CTX-M-15 SHV-11 TEM-1	0.25/4

Enterobacter cloacae


Source	Carbapenemase	WGS	AZT/AVI MIC
Urine	NDM	NDM-1	0.06/4
Blood	NDM	NDM-1 CTX-M-15 TEM-1	0.5/4
Urine	NDM	NDM-1 TEM-1	1/4
Blood	NDM	Pending	2/4

Morganella morganii

Source	Carbapenemase	WGS	AZT/AVI MIC
Tracheal Aspirate	NDM/KPC	NDM-7 KPC-2 TEM-1	0.5/4

ARLNCORENY@health.ny.gov

<https://wadsworth.org/antimicrobial-resistance-laboratory-network>



ARLABnetwork

Antimicrobial Resistance Laboratory Network

[Home](#) » [Public Health Programs](#) » [Infectious Diseases](#) » Antimicrobial Resistance Laboratory Network

AR Lab Network Regional Lab testing takes place in both the [Bacteriology Laboratory](#) and the [Mycology Laboratory \(Candida\)](#)

Northeast Regional Isolate Submission (CT, ME, MA, NH, NJ, RI, VT and NYC)

- Submit discordant CRE/CRPA after initial testing, pan-resistant CRE/CRPA, MDR *Acinetobacter baumannii*, emerging antibiotic-resistant bacteria including *mcr-1* and *mcr-2* containing bacteria.
- Complete the [Infectious Diseases Requisition Form](#). (Please fill in "AMR ID" in the other section.)

New York State Isolate Submission

- NYS CRE/CRPA isolate submission should include CRE, CRPA, pan-resistant CRE/CRPA, MDR *Acinetobacter baumannii*, emerging antibiotic-resistant bacteria including *mcr-1* and *mcr-2* containing bacteria.
- Complete the [Infectious Diseases Requisition Form](#). (Please fill in "AMR ID" in the other section.)

Infectious Diseases

- Laboratory Response Network
- Electronic Test Request/Reporting
- Antimicrobial Resistance Laboratory Network
- Arbovirology
- Bacteriology
- Biodefense

Acknowledgements



Wadsworth Center AR Team
AR Fellows
Wadsworth Center Core Facilities

NYS BHAI, NYS MARO, BCDC Epidemiology

Center for Disease Control and
Prevention: ARX, DHQP

Association of Public Health Labs:
Nikki Marchan, Kelly Wroblewski

Clinical Laboratories
Sentinel Laboratories
State/City Public Health Labs
State/City HAI Epi/Teams

Therapeutic Options for CRE Infections

Drug Status	Drug	Activity for MDROs		
		KPC	NDM	OXA-48 Like
Drugs of Last Resort	Colistin	?	?	?
	Tigecycline	✓	✓	✓
Recently Approved	Ceftazidime-avibactam	✓	✗	✓
	Meropenem-vaborbactam	✓	✗	✗
	Eravacycline	✓	✓	✓
	Plazomycin	✓	?	✓
	Imipenem-relebactam	✓	✗	?
Recently Submitted to FDA or Phase 3	Cefidericol	✓	✓	✓
	Aztreonam-avibactam	✓	✓	✓
	Cefepime-taniborbactam	✓	✓	✓