Wisconsin State Laboratory of Hygiene

UNIVERSITY OF WISCONSIN–MADISON

The Antibiotic Resistance Laboratory Network (ARLN)

Wisconsin Clinical Laboratory Network Webinar

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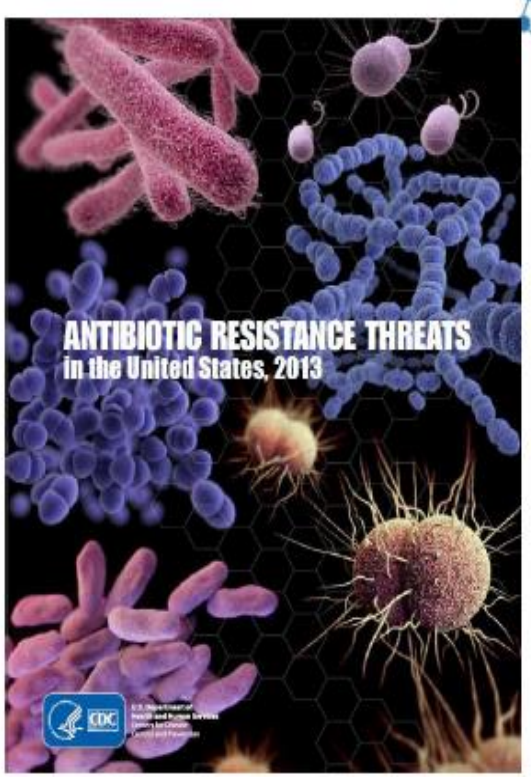
Objectives

- Explain what ARLN is and what your role will be in this national network
- Discuss how you can utilize ARLN resources and partnerships to report and confirm unusual resistance and refer multi-drug resistant organisms for further studies
- Describe the impact of culture independent diagnostic testing (CIDT) on the detection of antibiotic resistance at local, state and national levels

Antimicrobial Resistance- U.S.

Antibiotic Resistance in the United States

- Sickens >2 million people per year
- Kills at least 23,000 people each year
  - Plus 15,000 each year from *C. difficile*
- >$20B/year in healthcare costs
- Threatens modern medicine
  - If we lose antibiotics, we lose the ability to treat patients with sepsis, cancer, provide organ transplants, and save victims of burns and trauma
- Need to act now or even drugs of last resort will soon be ineffective



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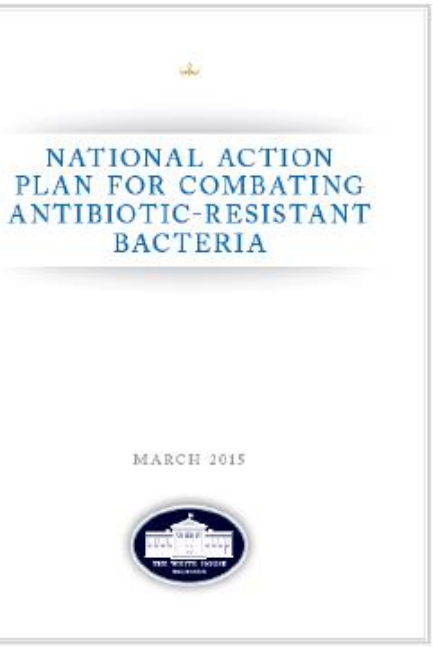
National Action Plan

Combating AR: National Action Plan & The Antibiotic Resistance Solutions Initiative

- National Action Plan for CARB called for a CDC response to:
  - Detect and respond to resistant pathogens
  - Prevent spread of resistant infections
  - Encourage innovation for new strategies
- CDC answered with the AR Solutions Initiative, requesting $264M to respond comprehensively
- FY16: $160M appropriation will address AR with an ambitious, transformative approach, implementing CARB activities by 2020— **including support to increase lab capacity**



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National Strategy Identifies Five Core Actions

1) Slow the development of resistant bacteria and prevent their spread

2) Strengthen National One-Health efforts to combat resistance

3) Advance development and use of rapid and innovative diagnostic tests

4) Accelerate basic and applied research and development for new antibiotics, other therapeutics, and vaccines

5) Improve international collaboration and capacities for AR prevention, surveillance, control and AR R&D

Antibiotic Resistance Solutions Initiative

- 2016---$160M for CDC to fight antibiotic resistant-bacteria
  - Largest portion to 50 state health depts, six largest local HDs, and Puerto Rico
  - Additional $40M in 2017
- Opportunity to expand capacity to detect and respond to AR threats
  - State and local public health
  - Academic partners
  - Healthcare partners
  - Veterinary partners

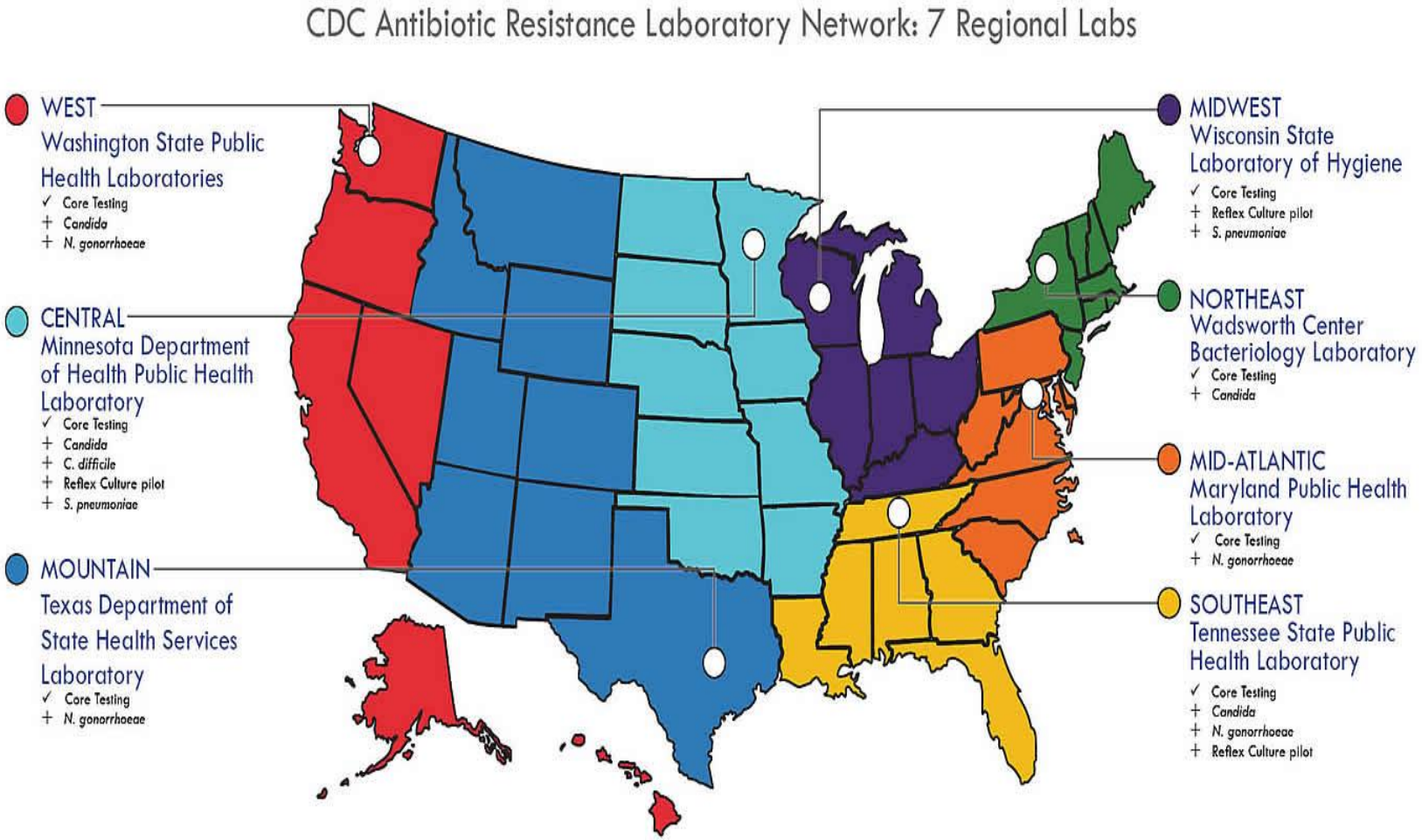
ARLN- Regional Approach

CDC's AR Laboratory Network (ARLN)

The ARLN transforms much of the current national AR lab landscape by boosting local capacity and technology to detect, support response to, and prevent AR threats and create new innovations to combat AR.

- Establishes 7 Regional Labs with:
  - Comprehensive lab capacity for 7+ antibiotic-resistant pathogens identified by CDC's *AR Threat Report* as "urgent" or "serious" threats
  - Local gold standard labs with cutting-edge technology
  - Faster outbreak detection and response support, better tracking of resistance
  - Real-time, actionable data to prevent and combat future AR threats
- Lab regions are based on an existing regionalization scheme established by PulseNet
- Supported by CDC's Epidemiology and Laboratory Capacity (ELC) for Infectious Diseases through FY16 funding from Congress

ARLN Regional Map



ARLN Key Partners

- Healthcare Labs
- State & Local Health Departments
- Regional Labs
- CDC

Healthcare Lab Role

- Work with state health department to establish and understand isolate and specimen submission criteria
- Utilize available CDC and state public health lab resources for isolate and specimen submission
- Monitor resistance results
  - Outbreak detection in patient population
  - Informed treatment

State and Local PH Lab Role

- Work with healthcare labs in jurisdiction to establish and communicate isolate and specimen submission criteria
- Partner with state and local health department epidemiologists
- Perform WGS of all *Salmonella* isolates
- Perform CRE confirmation and characterization testing for labs in jurisdiction
  - CDC training, guidelines and resources

Regional Lab Role

- Working with local and state PHL's
  - Surge testing, training, specimen repository
- Tracking changes in resistance for already hard-to-treat pathogens
  - CRE, GC, *S. pneumoniae*, *Candida* spp.
- Sentinel surveillance sites for new and unusual resistant organisms
  - VRSA, MCR, *Acinetobacter* spp., *P. aeruginosa*
- Piloting strategies to collect critical public health data in the era of CIDT
  - *C. difficile*, *Salmonella*, Enterotoxigenic *E. coli*

CDC Role

- Develop testing methods, training and guidance
- Perform WGS on unusual resistant isolates
- Collect data from state and regional labs; identify data gaps
- Report critical findings to US and International partners
- Identify trends in resistance
- Update the AR Isolate Bank (new resistant organisms available for research)
- Request threat assessments
- Provide strategic prevention recommendations

ARLN Core Activities

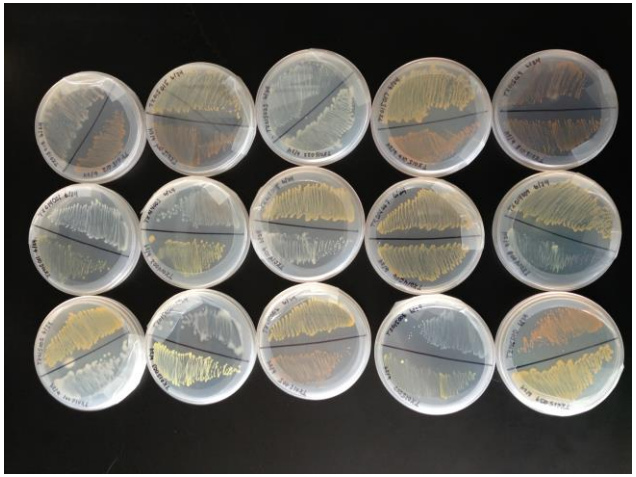
- Detection of CRE colonization
  - GeneXpert CARBA-R
- Threat Assessment on new or known threats-----MRSA, VRE, VRSA, MCR
- Isolate collection for use in CDC's AR Isolate Bank and WGS projects

Additional ARLN Regional Lab Activities

- Consulate and serve as a resource
  - For state prevention programs, personnel at state CRE labs, other labs in the ARLN
- Communicate with CDC
  - Send results, participate in regular meetings, submit month reports with findings
- Training and proficiency
  - Participate in annual trainings and proficiency testing isolates for new assays. Provide training to state and local CRE laboratories in the region

Additional ARLN Regional Lab Activities

- Isolate collection from clinical labs
  - Work with CDC to establish collection of nationally representative isolates

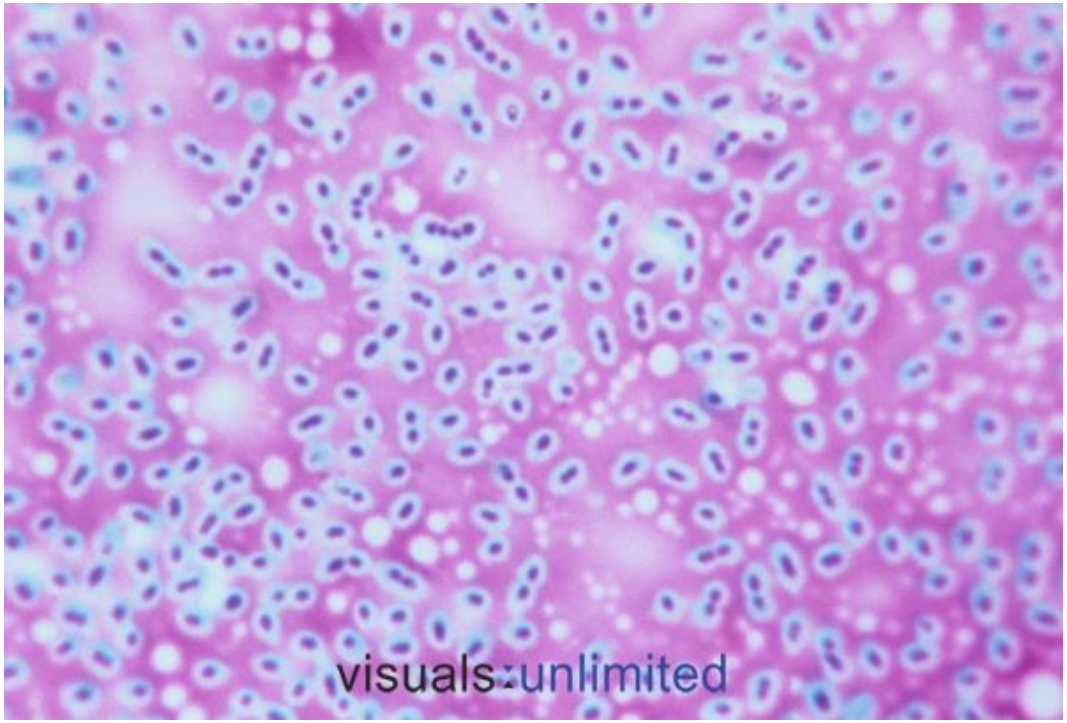


- Partner with state prevention programs for outbreak testing

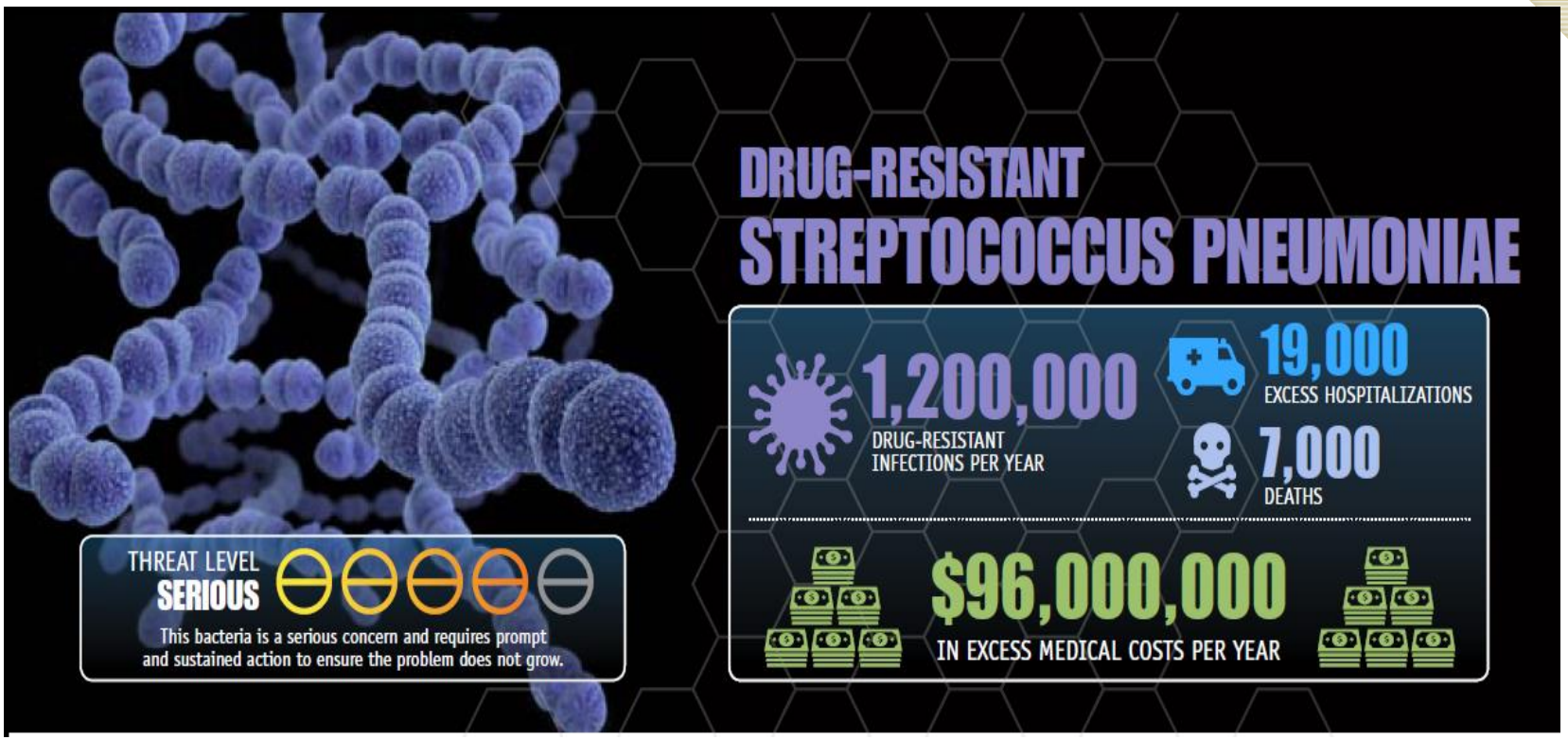
ARLN Testing in Select Regional Labs

- Fungal AST of *Candida* species to identify emerging resistance
  - *C. auris, C. glabrata*
- *C. difficile* special projects
- *N. gonorrhoeae* AST
- Reflex culture pilot (WSLH)
  - *Salmonella*
  - Enterotoxigenic *E. coli*
- AST and serotyping of MDR *S. pneumoniae* (WSLH)

S. pneumoniae ARLN Activities



Minnesota and Wisconsin State Public Health Labs



Drug	USA %S	WI %S
Penicillin	94.8	96.3
Erythromycin	68.3	71.2
Levofloxacin	99.6	98.0

S. pneumoniae ARLN Activities

- Each lab will test 500 *S. pneumoniae*
  - Priority to states not included in Active Bacterial Core surveillance (ABC) and states in south/southeast region
- Criteria for submission
  - Isolates from sterile body sites (invasive)
    - Priority for isolates from children <5 years
  - MDR phenotype—invasive or non-invasive
    - Resistant to ≥3 drug classes
  - For Wisconsin, WDPH approval required

S. Pneumoniae ARLN Tests

- Identification
  - Conventional methods-----Gram stain, optochin test, bile solubility, catalase
  - MALDI-TOF
  - lytA real-time PCR
- Serotyping
  - Conventional PCR and/or real-time PCR
  - Quellung method
- Broth microdilution MICs---Sensititre

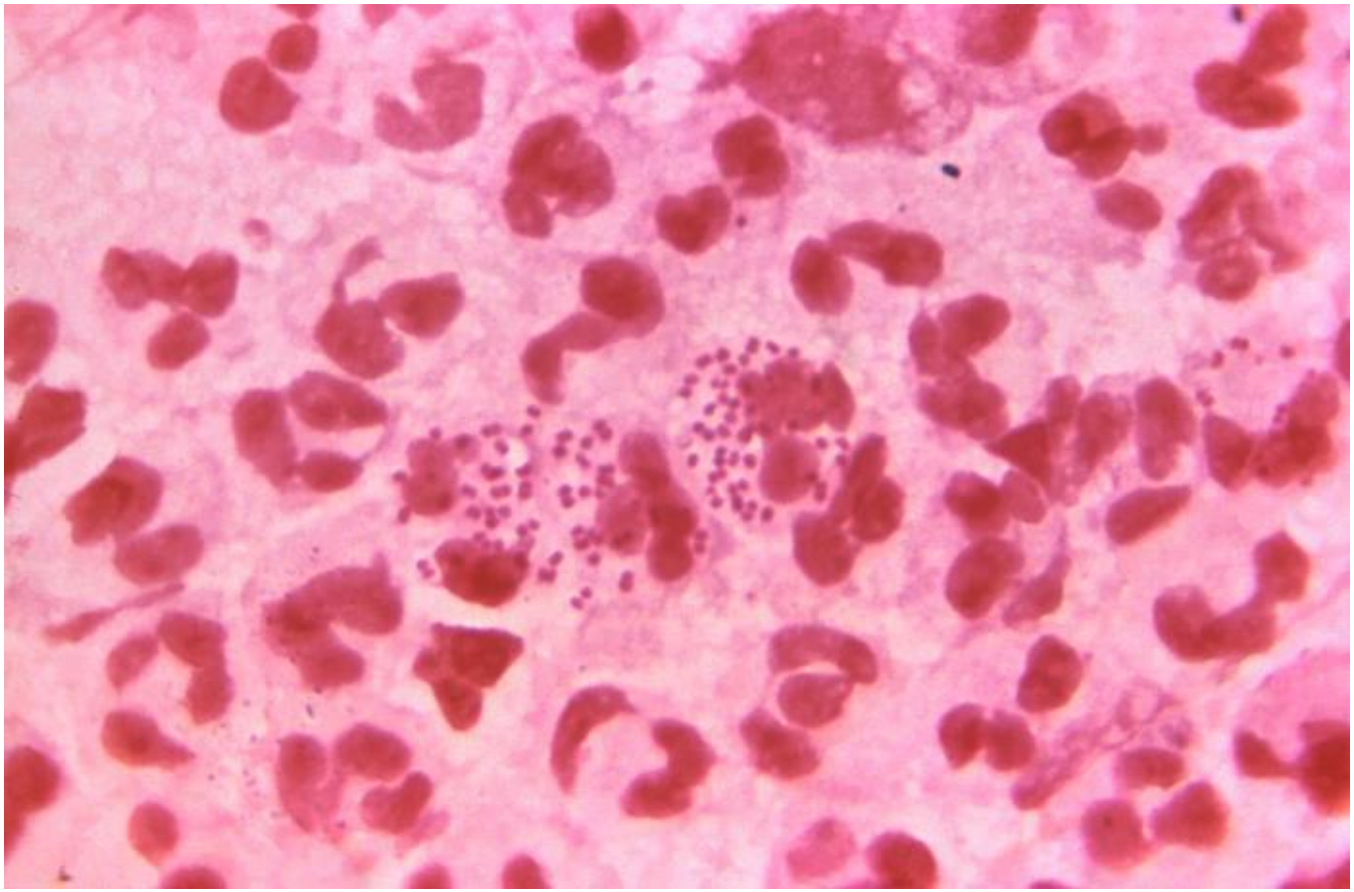
S. pneumoniae Reporting

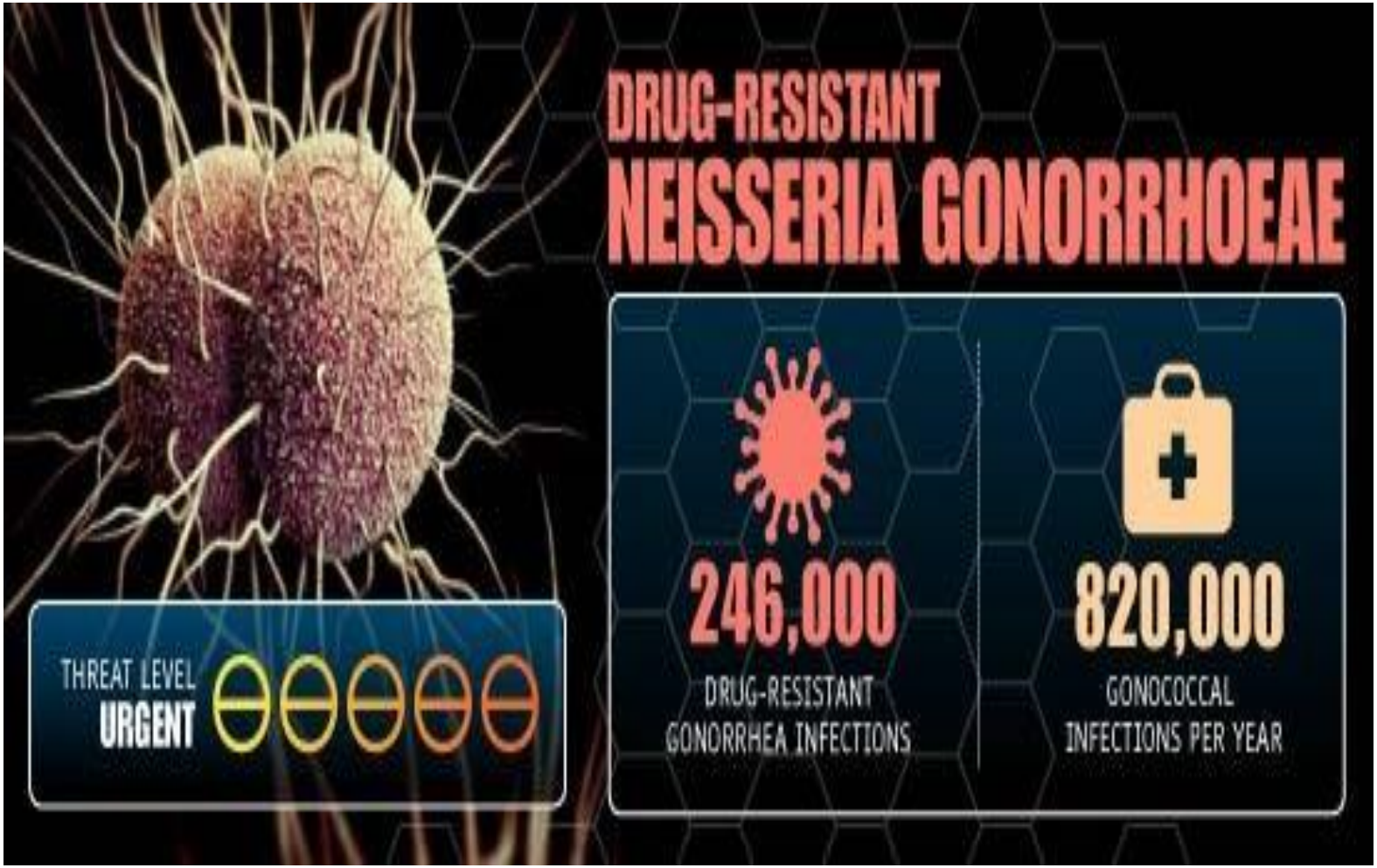
- Serotype reports back to the submitting institutions
- Possible reporting methods
  - Fax
  - Encrypted e-mail
  - Electronic lab reporting (ELR)
    - Electronic test ordering and reporting (ETOR
    - AIMS

S. pneumoniae Reporting

- Reports to CDC
  - AST results on a monthly basis
  - Serotypes having non-susceptibility to a beta lactam drug (non-meningitis breakpoints)
  - Novel antibiotic resistance (e.g. Linezolid, Vanco)

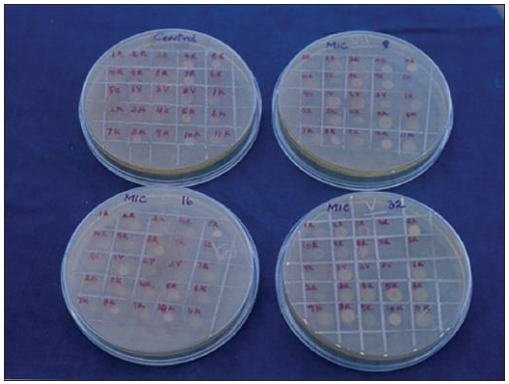
Neisseria gonorrhoeae



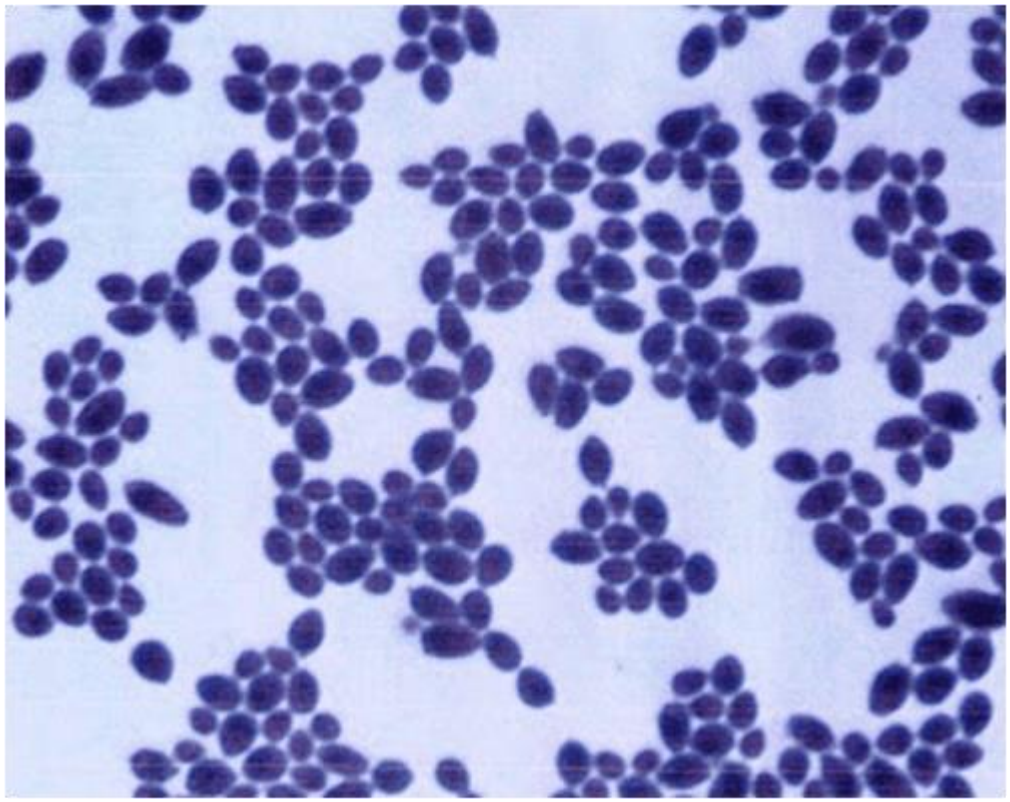

DRUG-RESISTANT
NEISSERIA GONORRHOEAE
THREAT LEVEL
URGENT
246,000
DRUG-RESISTANT
GONORRHEA INFECTIONS
820,000
GONOCOCCAL
INFECTIONS PER YEAR

Neisseria gonorrhoeae ARLN Activities

- Enhance resistance surveillance to test 20,000 isolates annually
- Isolates from STD surveillance clinic sites and rapid detection and response programs
- Agar dilution and ß-lactamase testing



Candida species



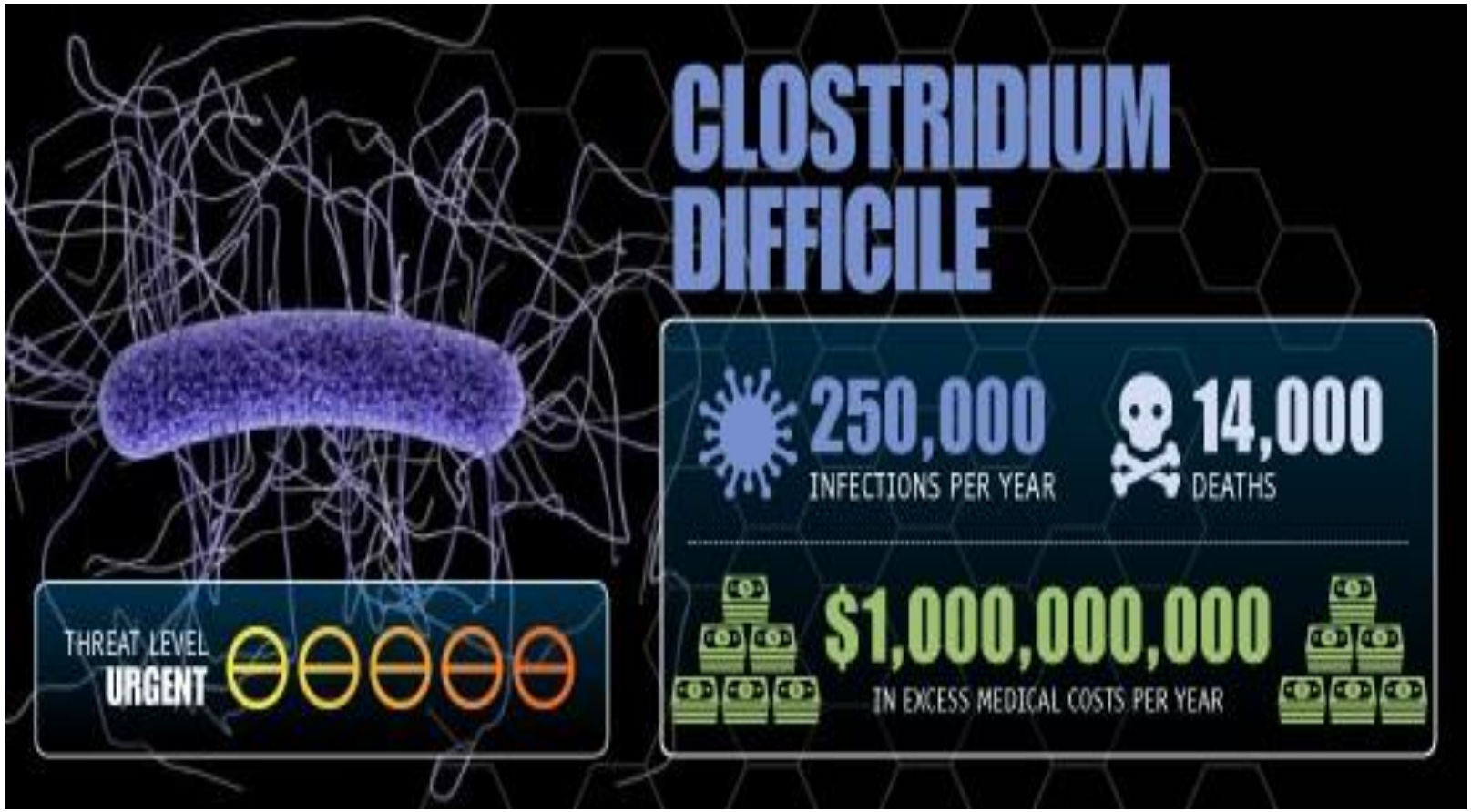
Candida Susceptibility Testing

- Surveillance for multidrug-resistant yeast
- Candida auris
  - Emerging MDR yeast
  - Invasive healthcare-associated infections with high mortality
  - Since 2009 occurrences in 9 countries on 4 continents
  - Healthcare outbreaks reported in 2 countries

Candida auris

- Requires special methods for identification
  - Could be misidentified with biochemical methods
    - Vitek, API systems cannot differentiate it
      - *C. haemulonii*
      - *C. famata*
      - *Saccharomyces cerevisiae*
  - MALDI-TOF can differentiate *C. auris*, but not included in database of all systems
  - Sequencing the D1-D2 region of the 28s rDNA gene can identify
- Some clinical labs do not identify all *Candida* to the species level

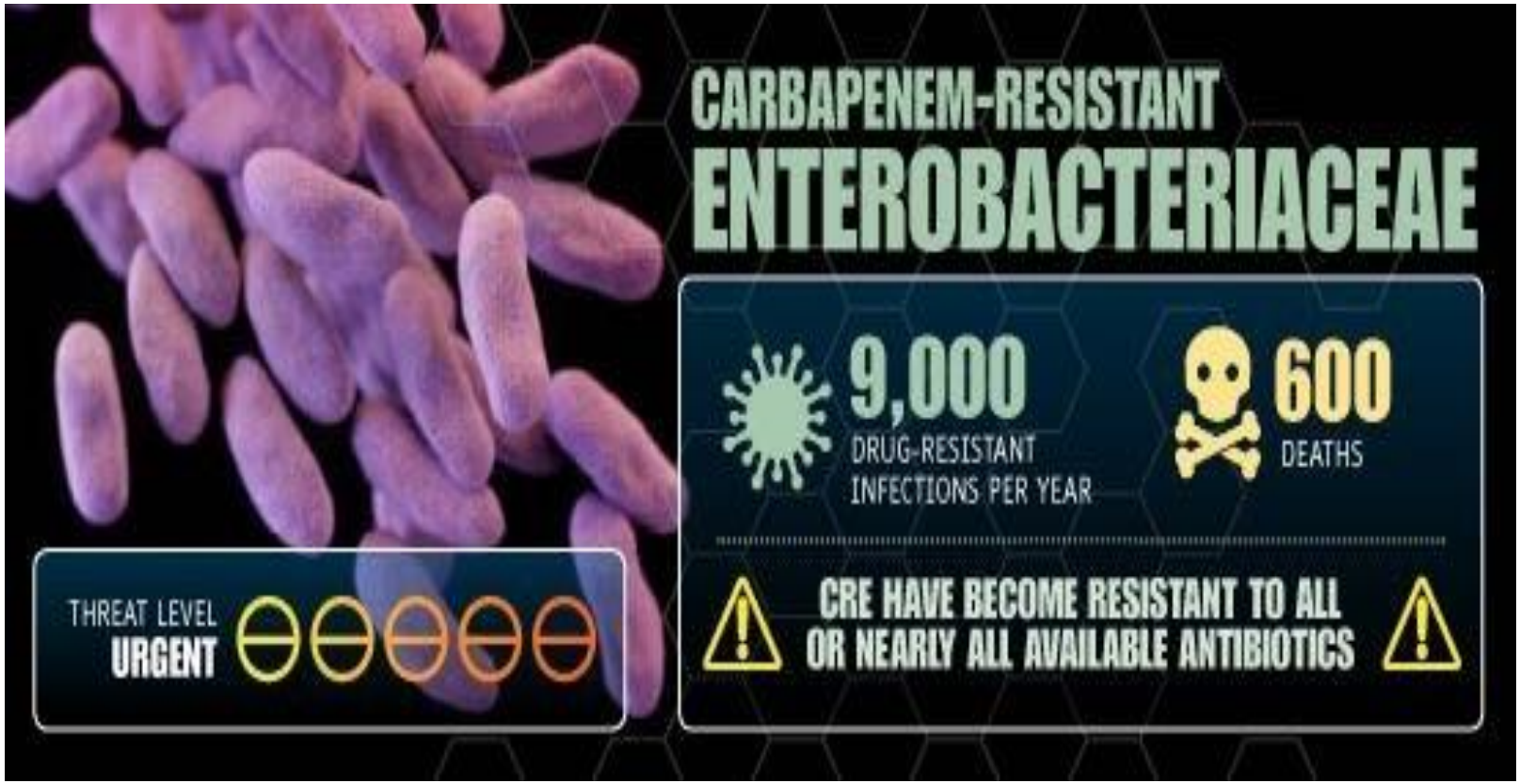
Clostridium difficile



Clostridium difficile

- Minnesota Department of Health Laboratory
- Perform CDC-directed and coordinated public health assessment of emerging or changing epidemiology of *C. difficile*
- Implement culture capacity and advanced molecular detection (AMD) testing in order to identify existing and novel virulence and antimicrobial resistance markers at the nucleic acid sequence level
- Initially, little ARLN impact on all but MN and CDC labs

Carbapenem-Resistant Enterobacteriaceae (CRE)

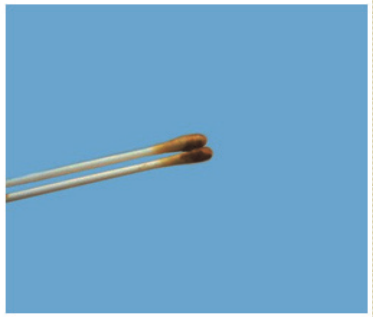


Carbapenem-Resistant Enterobacteriaceae (CRE)

- Continued detection of known CR mechanisms:
  - KPC
  - NDM
  - OXA-48
  - IMP
  - VIM
  - MCR
- WSLH PFGE subtyping for cluster detection
  - Notification of WDPH Healthcare Acquired Infections Program when clusters detected

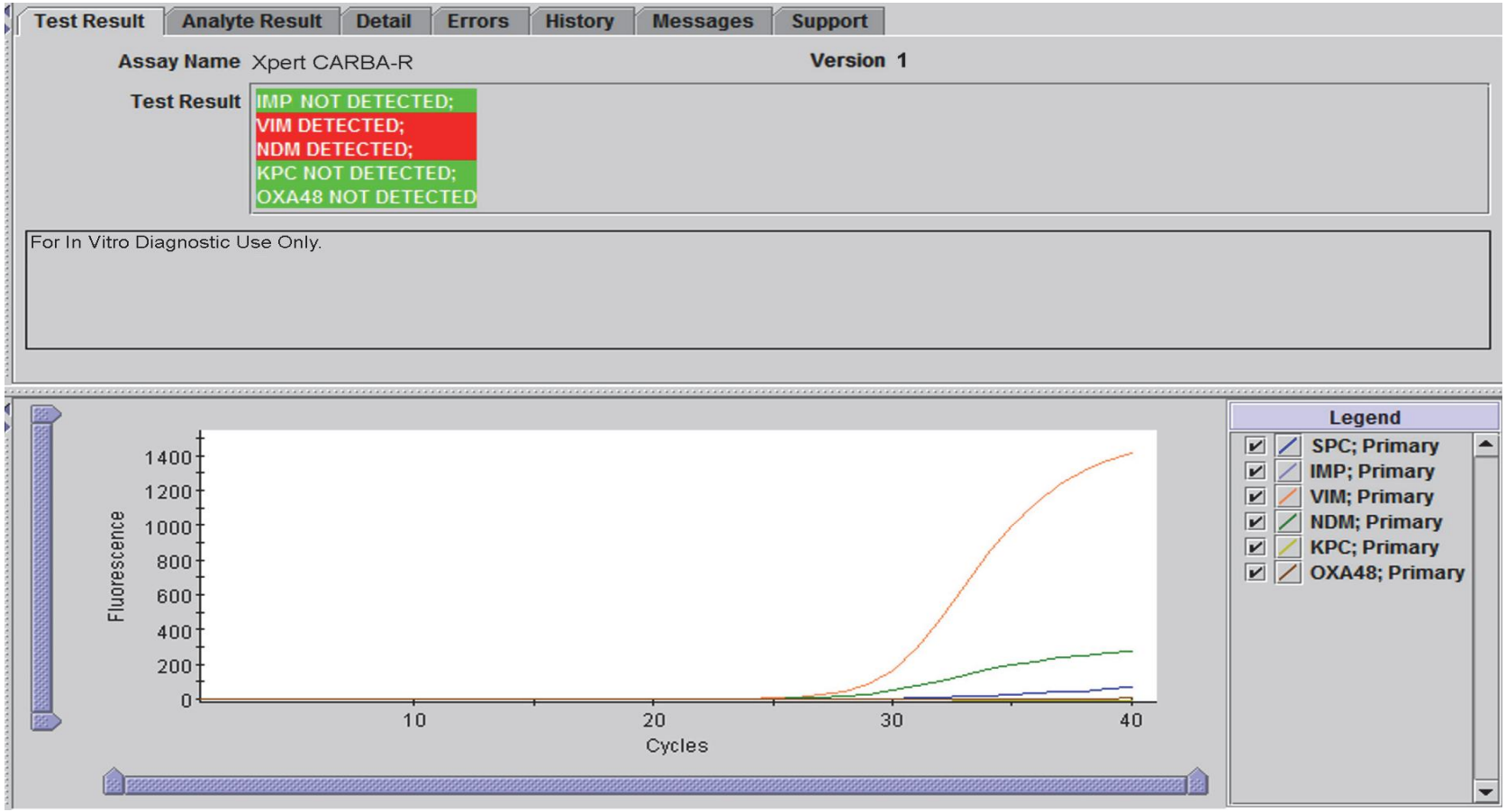
CRE Colonization Screening

- Rectal swab screening of contacts to confirmed CRE case patients
- Approval of state epidemiologists required prior to testing (both state jurisdiction and regional approval)
- Dual rectal swab collection
  - Direct MacConkey Plate Culture method
  - Cepheid GeneXpert CARBA-R PCR assay
- Prompt submission to Regional ARLN Lab
- Results reported within two days of receipt



CRE PCR Testing

- GeneXpert CARBA-R

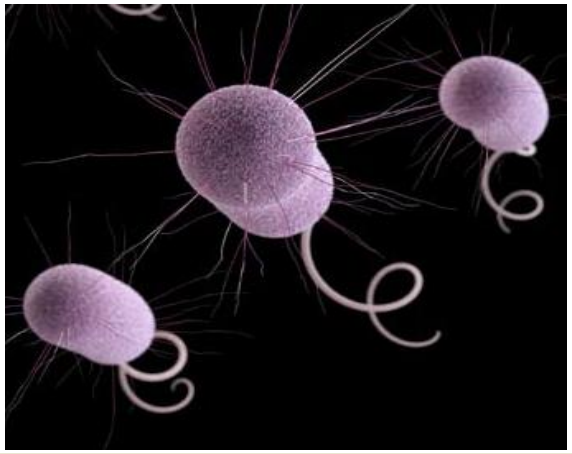


Direct MacConkey Plating

- Rectal swab plated directly to MAC plate with meropenem disk (if OXA-48 suspected, ertapenem disk is used)
- Colonies within zone of inhibition screened for CRE
  - GeneXpert CARBA-R
  - CarbaNP or CIM
  - In-house PCR assay
- CRE identified to genus and species
  - MALDI-TOF

Other GN MDR Organisms of Interest to ARLN

- Carbapenem-Resistant *P. aeruginosa* (CRPA)
  - Of the estimated 51,000 healthcare-associated *P. aeruginosa* infections in the U.S. each year, 13% are MDR
  - Estimated 440 deaths per year in the U.S.
- Submit any suspect Carbapenem- resistant *P. aeruginosa* to WSLH



Carbapenem-Resistant *P. aeruginosa* (CRPA)

- Harbor Verona Integron-encoded Metallo-betalactamase (VIM)
- Submission criteria for CRPA:
  - Susceptible to Aztreonam
  - Non-susceptible to Imipenem, Meropenem or Doripenem (Ertapenem NA- No CLSI guidelines)
  - Non-susceptible to Ceftazidime
  - Non-susceptible to Pipericillin/Tazobactam

Other GN MDR Organisms of Interest to ARLN

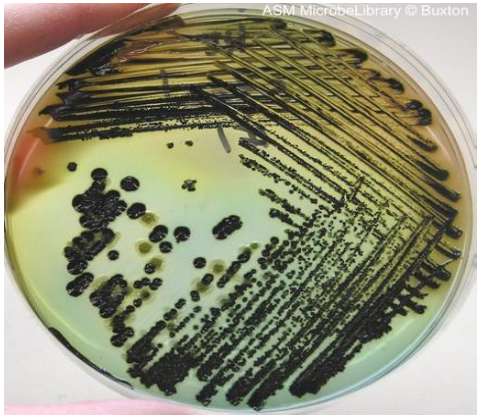
- MDR *Acinetobacter* spp.
  - Of the 12,000 healthcare-associated *Acinetobacter* spp. infections in the U.S. each year, 63% are MDR
  - Estimated 500 deaths per year in the U.S.
- Submit any *Acinetobacter* spp. to WSLH that is resistant to three or more classes of antibiotics (=MDR)

Salmonella and ETEC Reflex Culture Pilot Program

- For Wisconsin clinical laboratories, nothing will change
  - Continue to submit all positive stool specimens determined to be positive by a CIDT (or the isolate if recovered in-house)
  - Submit as reported; **PLEASE DO NOT BATCH**
- WSLH will partner with one other state PHL to culture all *Salmonella* and ETEC positive stool specimens from that state

Salmonella Reflex Culture

- Isolation of *Salmonella* from CIDT-positive stool specimens



- Performance of WGS to identify nucleic acid sequences encoding resistance

ETEC Reflex Culture

- Isolation of ETEC colonies from CIDT-positive stool specimens

- Real-time PCR identification of ETEC colonies (Presence of LT and ST targets)

Impact of CIDT on AST

- Many healthcare labs are implementing CIDT for the detection of pathogenic organisms and discontinuing culture techniques
- Pathogenic organisms no longer isolated leads to loss of antimicrobial resistance data and detection of MDR or unusual resistance
- MDR *N. gonorrhoeae* example of CIDT impact
  - >320,000 reported cases in the U.S./ yr (>800,000 estimated)
  - 30% resistant to at least one antibiotic
  - CDC establishment of GISP to track

Impact of CIDT on AST-ARLN

- Key to ARLN program is cooperation and partnership with healthcare laboratories
- Healthcare systems are at the front line of antimicrobial resistance
- Submission of isolates and specimens from patients with confirmed or suspected MDR or unusual resistance to state PHL and ARLN regional labs will aid in detection and subsequent prevention

Impact of CIDT on AST- WSLH

- WSLH requests submission of specimens of public health significance for surveillance
- Clinicians may desire AST on isolates at WSLH
  - Only CLSI recommended antimicrobial reporting
  - Limited to the antimicrobials on hand and validated methods in use at WSLH
  - Order on WSLH requisition form (Micro Form A)
  - Fee for service for reported AST
  - WSLH may also return isolates for testing at submitting healthcare laboratory upon request

Reporting

- Continue to follow internal infection preventionist guidelines and state statute
- Discuss unusual results with state public health laboratory and division of health- healthcare acquired infections coordinators
- Reporting to submitting healthcare labs will be timely; depend upon ARLN program and test method used
- Reporting will be secure and electronic
- Monthly routine reporting to CDC ARLN Program; prompt reporting of novel resistance

Summary

- The ARLN is part of a national effort to combat antimicrobial resistance
- The ARLN will require active participation and effective communication among agencies at the local, state, regional and national levels in order to be effective
- Widespread use of CIDT in the absence of culture threatens surveillance for AR in the U.S.; ARLN is providing resources to state PHL and Regional Labs to address this impact

Summary

- Resources are available to facilitate both the reporting of unusual antimicrobial resistant organisms and the referral of such organisms for further studies
  - Healthcare laboratories should forward any unusually resistant organism to either their state PHL or ARLN Regional Laboratory for further studies
  - Reach out to the WDPH, WSLH or ARLN with any questions regarding AR organisms

Contact Information- WSLH

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Contact Information- CDC

- ARLN Web Page:

http://www.cdc.gov/drugresistance/solutions-initiative/ar-lab-networks.html

- ARLN Program email

arln@cdc.gov

Questions?