Containing Novel Resistance

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Outline

- Introduction to novel resistance
  - Carbapenemase-producing carbapenem-resistant Enterobacteriaceae (**CP-CRE**)
  - Carbapenemase-producing non-Fermenters (**CP-NF**)
  - mcr
  - *Candida auris*
- AR Laboratory Network (ARLN) overview
- Containment guidance
- Emerging issues in carbapenem-resitant organisms
- Texas investigations

Antimicrobial Resistance (AR)

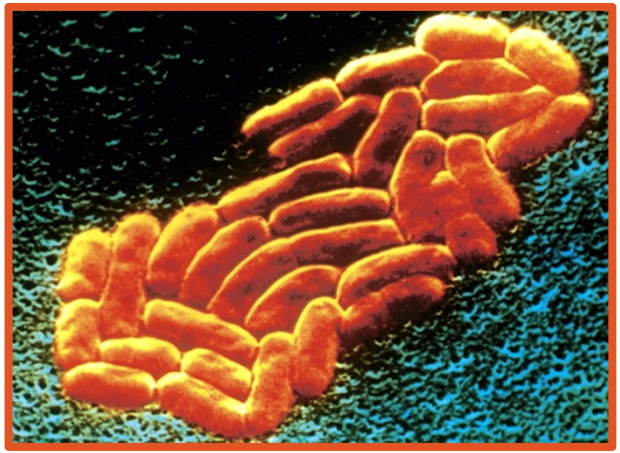
- 2013 CDC Antibiotic Resistance Threats in the United States
  - Estimated more than 2 million antibiotic-resistant infections resulting in at least 23,000 deaths in US each year
  - Urgent threat: Carbapenem-resistant Enterobacteriaceae (CRE)
  - Serious threats: ESBLs, multidrug-resistant *Pseudomonas aeruginosa,* multidrug-resistant *Acinitobacter*
- Containment of novel or targeted multidrug-resistant organisms (MDROs) is a CDC priority
- Emergence of new MDROs

Gram-Negative Rods

- Encompass large number of pathogenic and non-pathogenic bacteria
- Glucose fermenters
  - Includes gut commensals and pathogens
  - Enterobacteriaceae: e.g., *Escherichia coli, Klebsiella pneumoniae, Salmonella spp.*
- Glucose non-fermenters
  - Opportunistic pathogens
  - *Pseudomonas aeruginosa, Acinetobacter baumannii*
  - Intrinsically non-susceptible to many commonly used antimicrobials

Enterobacteriaceae

- Large family of gram negative rods with >25 recognized genera
- Normal gut flora & opportunistic pathogens
- Most common family encountered in clinical microbiology labs
  - Most common are *Klebsiella* spp., *Escherichia coli*, and *Enterobacter* spp.
  - Also *Proteus*, *Providencia*, and *Morganella*



K pneumoniae, scanning electron micrograph
http://www.ppdictionary.com/bacteria/

Carbapenems

- Many Enterobacteriaceae are very susceptible to many antibiotics including members of the penicillin family
- Some have enzymes called β-lactamases that lead to reduced susceptibility to penicillins
- 1990s - emergence and spread of extended-spectrum β-lactamases (ESBLs)
- Carbapenems: broad-spectrum “antibiotics of last resort”
  - Used to treat highly resistant infections
  - Four approved agents in US (imipenem, meropenem, doripenem, ertapenem)
- Carbapenem-resistant Enterobacteriaceae (**CRE**)
  - Often multidrug resistant; cause infections with high mortality rates

How Common are CRE in the United States?

- Among HAIs submitted to National Healthcare Safety Network (NHSN)
  - ~3-4% of Enterobacteriaceae NS to a carbapenem during 2011 to 2014*
    - In 2001, only 1.2% NS to a carbapenem
- In 2014, 7.8% of short-stay acute care hospitals doing surveillance for CAUTI or CLABSI had at least one CRE**
  - 24% of long-term acute care hospitals (LTACHs)
- Facilities reported 0-13 LabID CRE Events per month in 2015***
  - High incidence states: mean 1.5 events/month
  - Low incidence states: mean 0.08 events/month

*CDC AR Patient Safety Atlas https://www.cdc.gov/hai/surveillance/ar-patient-safety-atlas.html
**Walters, M et al. SHEA oral abstract, 2016
***Vasquez, A. et al., ID Week Poster, 2016

Annual Incidence of CRE Compared to Other MDROs

- **CRE: 2.93 per 100,000 population**
- Methicillin-resistant *Staphylococcus aureus*: 25.1 per 100,000 population
- *Clostridium difficile*: 147.3 per 100,000 population

Source: CDC Emerging Infections Program

Carbapenem Resistance Mechanisms

- Carbapenemases
  - Enzymes that breakdown carbapenems
- Non-carbapenemase-producing carbapenem-resistant Enterobacteriaceae **(non-CP-CRE)**
  - Extended – spectrum cephalosporinase + porin loss
    - Extended-spectrum β-lactamases (ESBLs)
    - AmpC
  - 1986-1990 in NNIS 2.3% of *Enterobacter* NS to imipenem
    - Appear to have remained relatively stable
- Carbapenemase-producing CRE **(CP-CRE)**

Carbapenemases

- Enzymes that degrade carbapenem antibiotics
- Usually found on plasmids, which can lead to rapid spread
- 5 enzymes of primary public health concern
  - *K. pneumoniae* carbapenemase (KPC)
  - New Delhi Metallo-β-lactamase (NDM)
  - Verona Integron Mediated Metallo-β-lactamase (VIM)
  - Imipenemase (IMP)
  - OXA-48-type
- Other carbapenemases less frequently encountered
  - Chromosomally encoded (e.g., SME in *Serratia*)
  - No spread beyond country of origin (e.g., SPM, GIM, SIM)

Why Are Plasmid-Encoded Carbapenemases a Public Health Priority?

- Cause infections associated with high mortality rates
- Resistance is highly transmissible
  - Between organisms – plasmids
  - Between patients
- Treatment options are limited
  - Pan-resistant strains identified
  - Could be decades before new agents are available to treat
- Potential for spread into the community
  - *E. coli* common cause of community infection
- Has spread rapidly (CP-CRE) throughout US and world

CP-CRE Examples

- Potential for swift, epidemic spread
- Can dramatically increase proportion of resistant isolates
- Examples
  - Israel: KPC outbreak
    - 11% carbapenem resistant in 2006
    - 22% carbapenem resistant in 2007
  - Greece: Dissemination of VIM
    - <1% carbapenem resistant in 2001
    - 20%-50% carbapenem resistant in 2006

Schwaber and Carmeli, JAMA. 2008;300(24):2911-2913. doi:10.1001/jama.2008.896
Vatopoulos, EuroSurveillance, Volume 13, Issue 4, 24 January 2008

The US Carbapenemase: KPC

ANTIMICROBIAL AGENTS AND CHEMOTHERAPY, Apr. 2001, p. 1151–1161 Vol. 45, No. 4
0066-4804/01/$04.00+0 DOI: 10.1128/AAC.45.4.1151–1161.2001

Novel Carbapenem-Hydrolyzing β-Lactamase, KPC-1, from a Carbapenem-Resistant Strain of *Klebsiella pneumoniae*

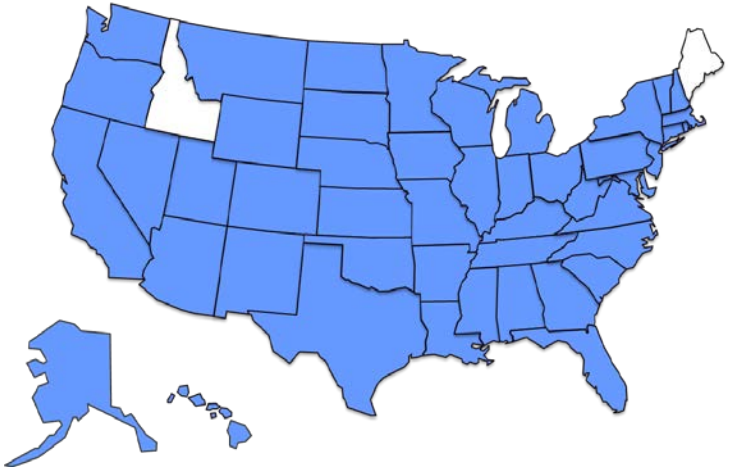
HESNA YIGIT,[1] ANNE MARIE QUEENAN,[2] GREGORY J. ANDERSON,[1]
ANTONIO DOMENECH-SANCHEZ,[3] JAMES W. BIDDLE,[1] CHRISTINE D. STEWARD,[1]
SEBASTIAN ALBERTI,[4] KAREN BUSH,[2] AND FRED C. TENOVER[1]*

- Isolate collected in 1996 during an ICU surveillance project from NC

Why Are Plasmid-Encoded Carbapenemases a Public Health Priority?

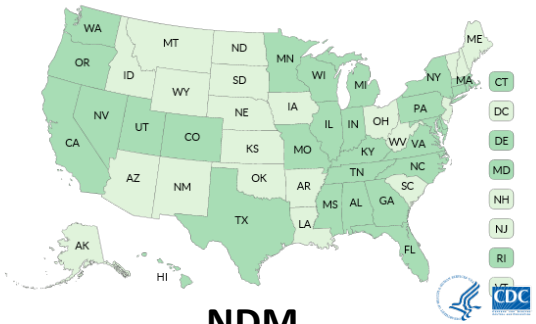
States with KPC-CRE Reported to CDC

2001

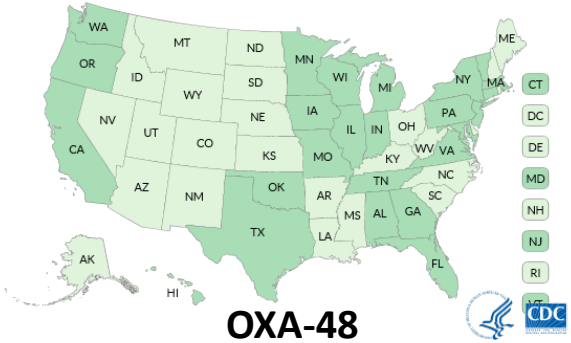


2016

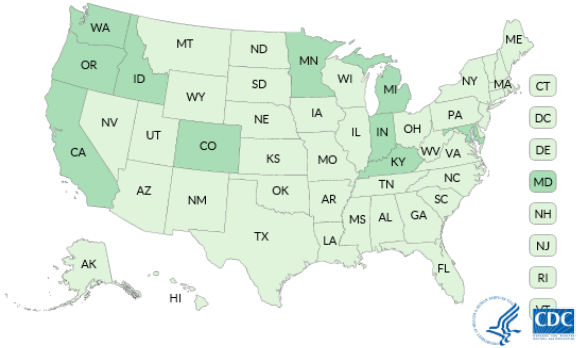
CP-CRE reported to the Centers for Disease Control and Prevention (CDC) as of January 2017



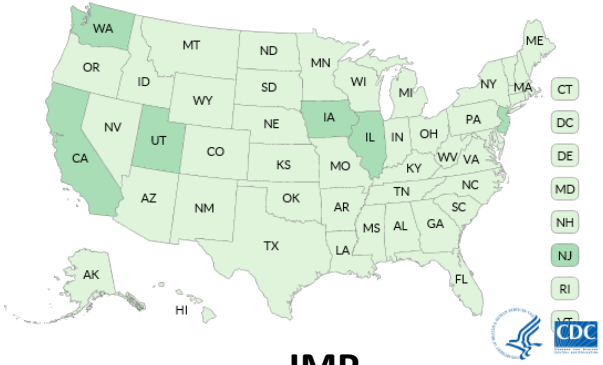
NDM



OXA-48



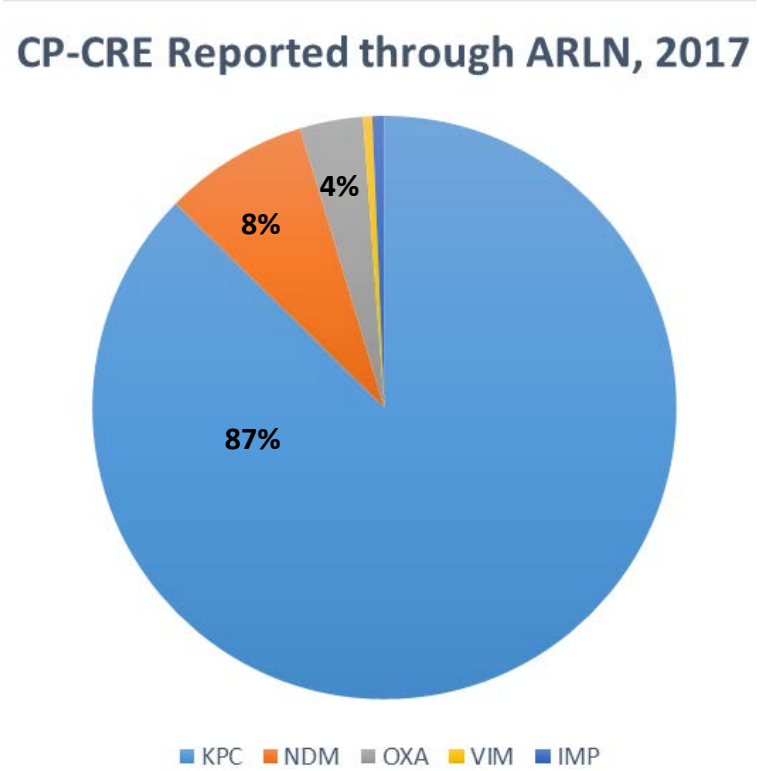
VIM



IMP

https://www.cdc.gov/hai/organisms/cre/trackingcre.html

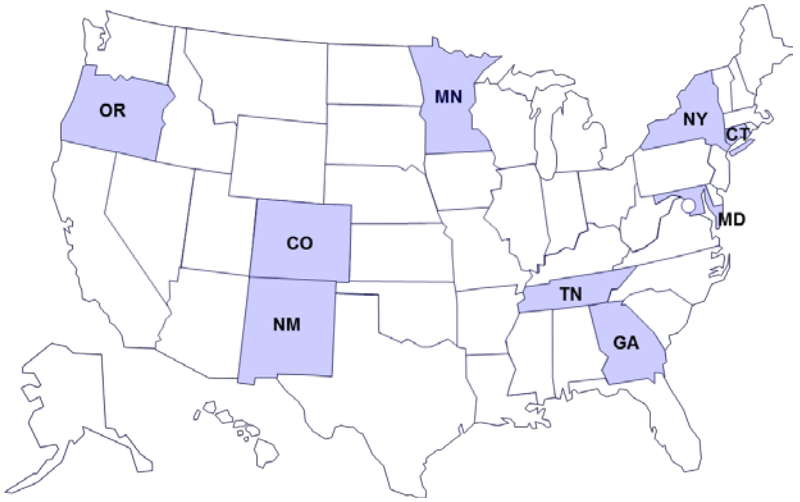
Carbapenemases In the U.S.



Data are preliminary and subject to change

CRE Surveillance

- Emerging Infections Program (EIP) Multi-site Gram-negative Surveillance Initiative (MuGSI)
- Population-based surveillance in nine metropolitan areas
- 15.1 million persons under surveillance in 2017



EIP MuGSI Surveillance

- Proportion of carbapenemase-producing isolates in CRE varies regionally
  - From 15.4% (Oregon) to 76.5% (Maryland)
  - Overall 47.9%

- Location of culture collection: 66.1 % outside of short-stay acute care hospitals

- 75.1% of cases had acute care hospitalization in prior year

Guh et al. JAMA, 2015;314(14):1479-1487.

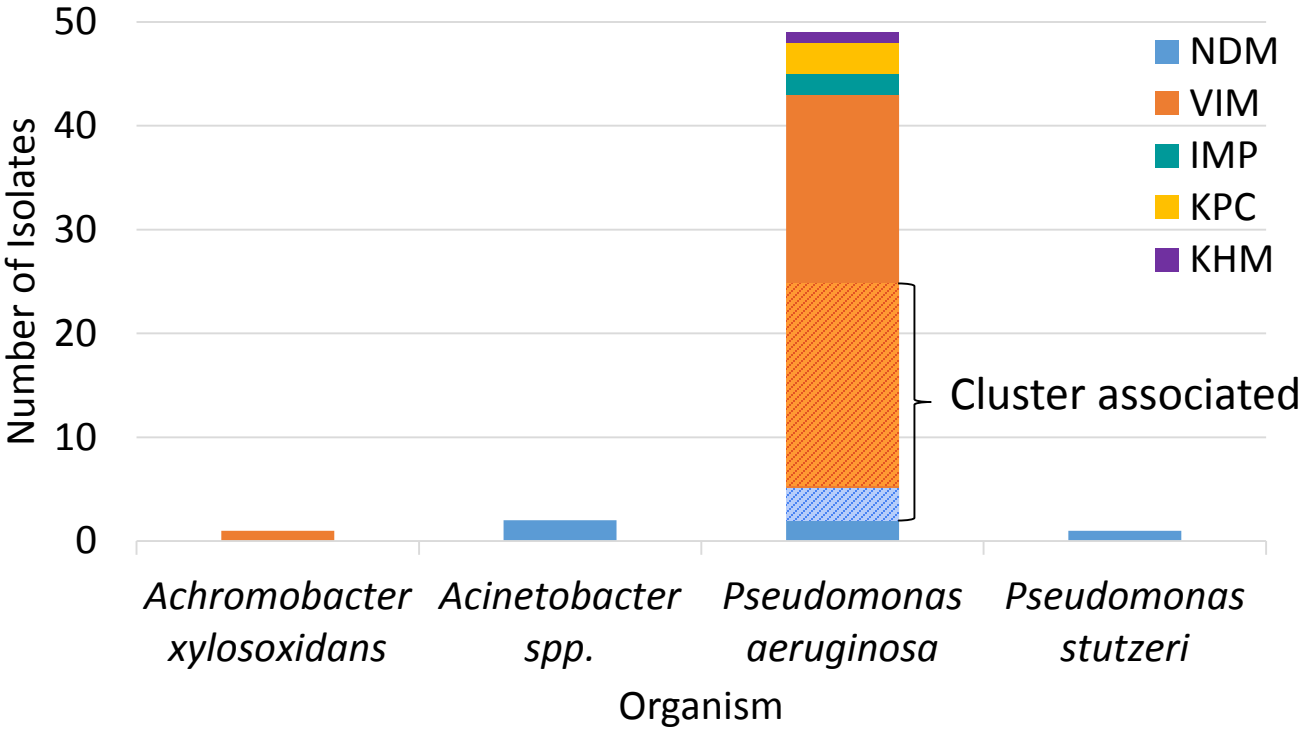
Carbapenemase-Producing Non-Fermenters

Carbapenem-Resistant Non-Fermenters

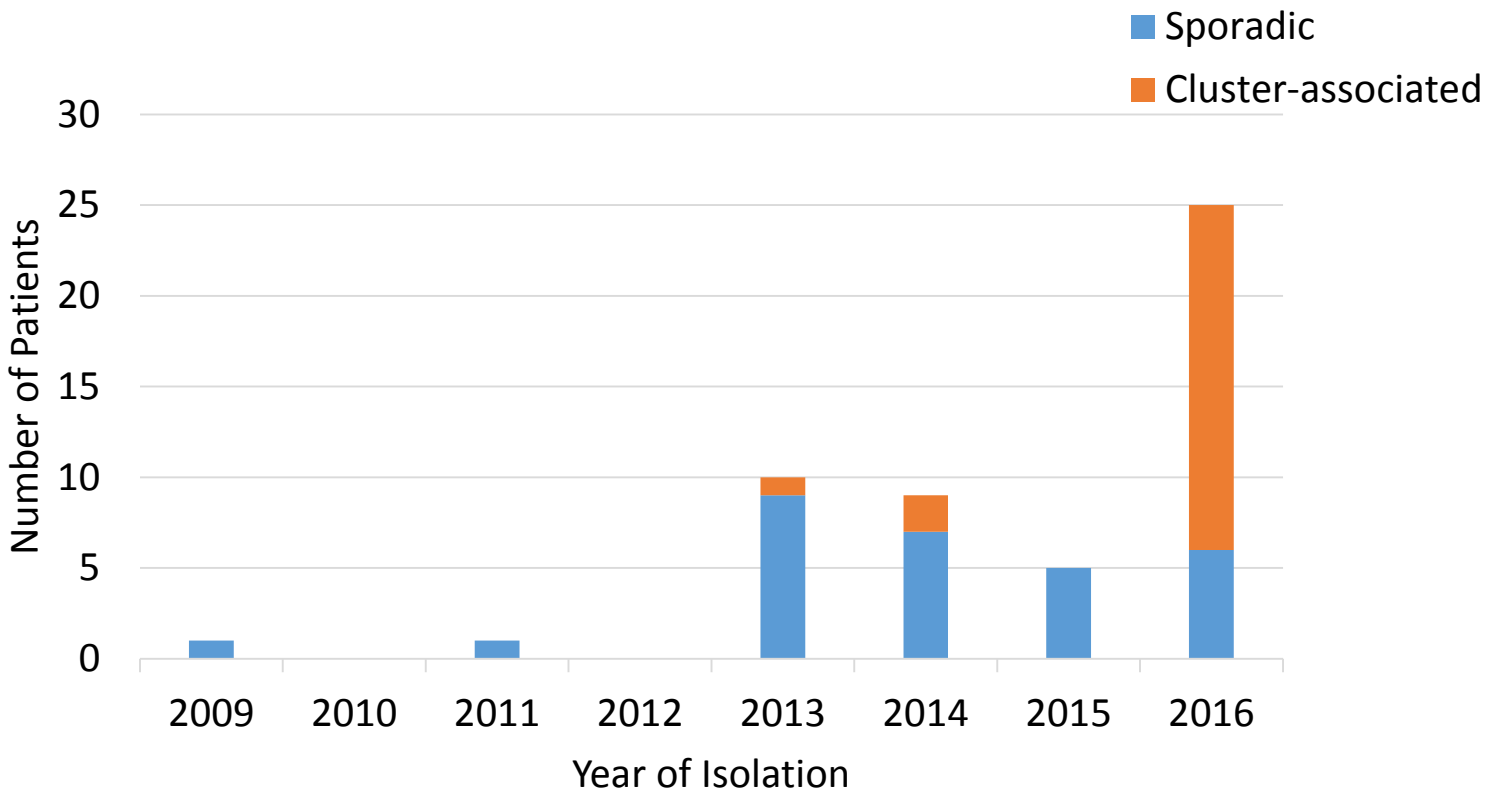
- Carbapenemase-producing non-fermenters (**CP-NF**)
- Can have chromosomal or plasmid-mediated carbapenem resistance
- Carbapenem-resistant *Pseudomonas aeruginosa (***CR-PA**)
  - Brazil 1998-2012: 39% of CRPA produced carbapenemase
  - Europe 2009-2011: 20% of CRPA produced carbapenemase
  - Denmark 2011: 7% of CRPA produced carbapenemase
  - U.S. 2015: 2% of CRPA tested produced carbapenemase
- VIM is most commonly reported worldwide
  - IMP, KPC, and NDM also reported in U.S

Hansen, F., *Microbial Drug Resistance*, 2014, 20(1):22-29
Rizek, C., *Annals of Clinical Microbiology,* 2014, 13: 43
Castanheira, M., *J. Antimicrob Chemother*, 2014, 69: 1804-1014

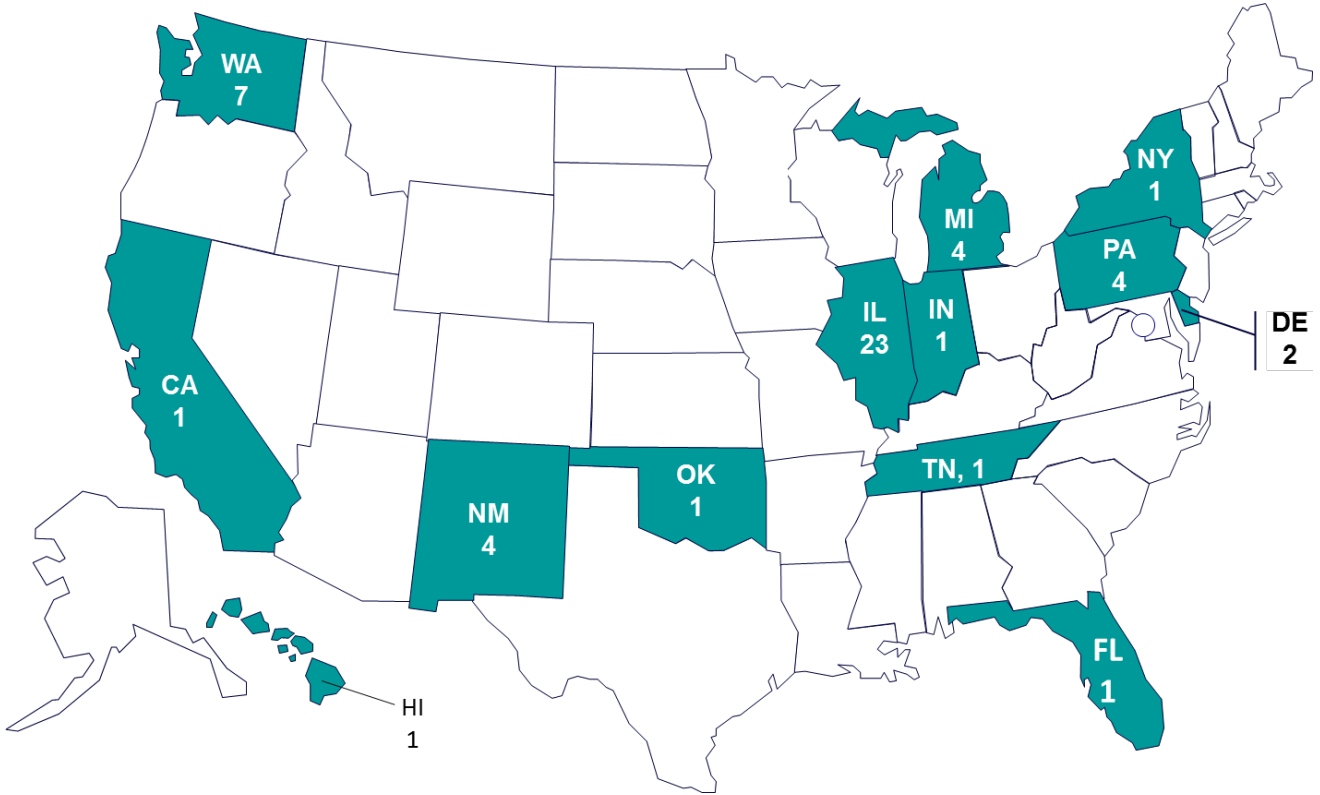
CP-NF Isolates Reported to CDC, by Organism and Mechanism, January 2009-December 2016, N=53



Patients with CP-NF Isolates Reported to CDC, by Year, N=51



Patients with CP-NF Reported to CDC, by State, January 2009-December 2016, N=51



CP-NF: Considerations for Public Health Response

- Carbapenemase-producing non-fermenters are rare in the U.S.
  - VIM *Pseudomonas* most frequently reported
  - Other carbapenemases, including KPC, less frequently identified
  - Unknown proportion associated with travel

- Responses should consider different attributes of these organisms
  - *Acinetobacter*: Environment can plan substantial role in transmission
  - *Pseudomonas*: Water bug, moist environments

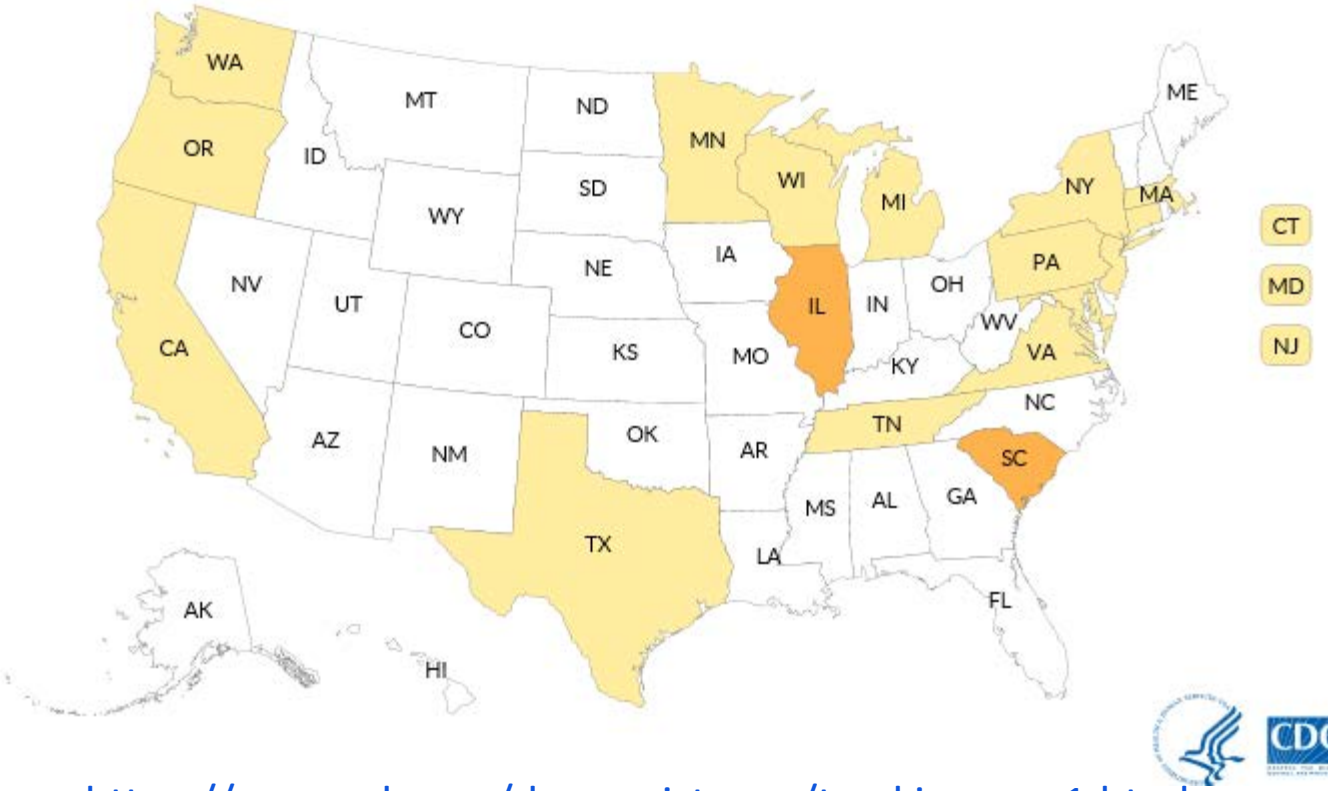
Colistin Resistance and mcr

Colistin and emergence of *mcr* in the U.S.

- Mobile colistin resistance (mcr)
  - First reported in 2015 isolates from China*
  - Now identified in isolates from across globe**
- Mobile resistance to Polymyxin class of antibiotics (colistin, polymyxin B)
- Antibiotic used to treat serious, highly resistant infections
- 26 cases (24 mcr-1 and 2 mcr-3) identified as of August 31, 2017
- 14 *E. coli (*including 1 STEC*),* 10 *Salmonella,* 2 *Klebsiella pneumonia*
  - Only one CP-CRE (NDM)

*Liu et al. Lancet ID, 2015; 26(2):161-168-1487.
**Skov et al. Euro Surveillance; 21 (9): 30155.

Colistin and emergence of *mcr* in the U.S.



https://www.cdc.gov/drugresistance/tracking-mcr1.html

Key Findings from *mcr* Investigations

- 22/26 had international travel in year prior
  - Bahrain, Cambodia (n=2), China (n=2), Columbia, Dominican Republic (n=6), Jamaica/St. Vincent/Bahamas, Lebanon, Mexico (n=2), Portugal, Thailand, Vietnam (n=3)
- 11/26 had known inpatient healthcare exposure in year prior (3 unknown)
  - Currently investigating 1 potential transmission in healthcare
- Concern for spread in healthcare settings
- https://emergency.cdc.gov/han/han00390.asp

Candida auris

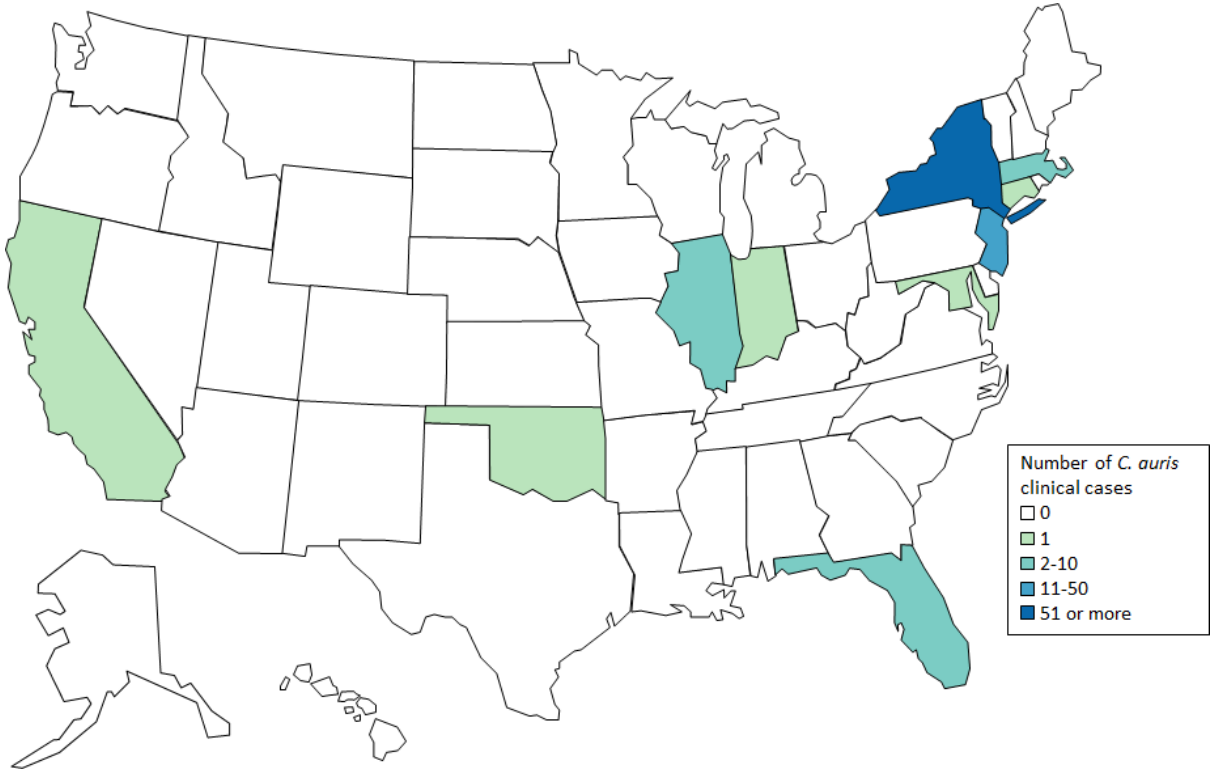
Recent Emerging Threat: *Candida auris* (*C. auris*)

- Fungus that causes invasive infections, high mortality, can be resistant to multiple antifungal drugs
- Unlike most other Candida species:
  - Colonizes intact skin and readily contaminates environmental surfaces for long periods (e.g., bedrails, bedside tables, chairs)
  - Often misidentified by clinical labs (e.g. *C. haemulonii)*, requires special lab methods and training (MALDI-TOF)
  - Appears to be supplanting other *Candida spp.* in facilities where found more frequently

Recent Emerging Threat: *Candida auris* (C. auris)

- 153 cases as of 8/31/2017 (126 confirmed; 27 probable)
- 10 states
- Majority of clinical isolates were from blood
- Resistance (n=127)
  - 91% to fluconazole
  - 29% to amphotericin B
  - 6% to echinocandins
- Majority from skilled nursing facilities (SNFs) or LTACHs

Recent Emerging Threat: *Candida auris* (C. auris)



https://www.cdc.gov/fungal/diseases/candidiasis/tracking-c-auris.html

Recent Emerging Threat: *Candida auris* (C. auris)

- *Candida auris* Recommendations for Healthcare Facilities and Laboratories
  - https://www.cdc.gov/fungal/diseases/candidiasis/recommendations.html
- Suspect *C. auris* when isolate identified as:
  - *Candida haemulonii, Candida duobushaemulonii* by Vitek 2 YST
  - *Rhodotorula glutinis* by API 20C (when red color not present)
  - *Candida sake* by API 20C
  - *Candida catenulata, Candida haemulonii* by BD Phoenix
  - *Candida parapsilosis*, Candida famata, Candida guilliermondii*,* or *Candida lusitaniae** by MicroScan
  - *Candida spp.* not identified by a valid identification method

*if no hyphae/pseudohyphae present on cornmeal agar

Recent Emerging Threat: *Candida auris* (C. auris)

- Identification algorithm: https://www.cdc.gov/fungal/diseases/candidiasis/pdf/Testing-algorithm-by-Method-temp.pdf

- Reporting: candidaauris@cdc.gov

Detection of Targeted MDROs

Detection

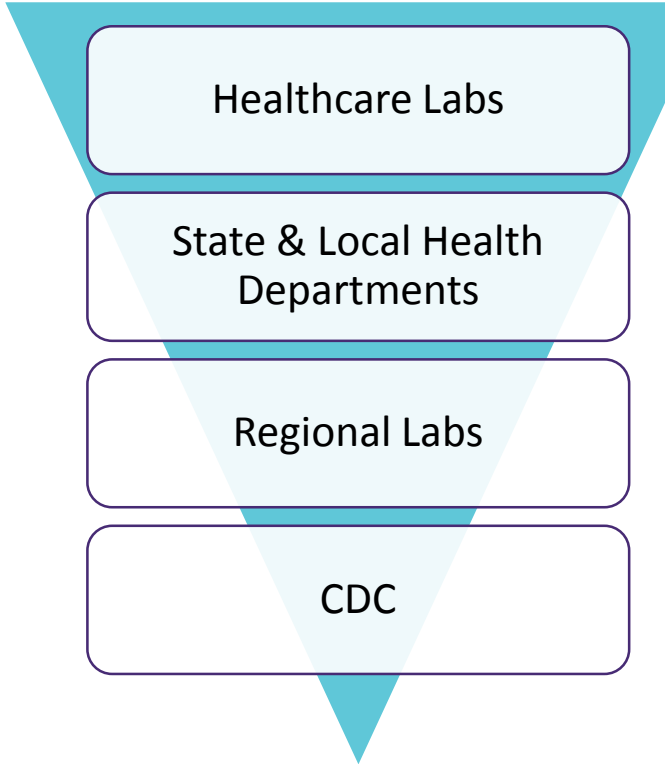
- Problem: restricted capacity to detect and respond to emerging resistance if CDC is the only sentinel surveillance program for AR
- Limited state capacity for AR testing
- In clinical labs, data is not often connected to public health action

Solution: CDC's AR Laboratory Network (ARLN)

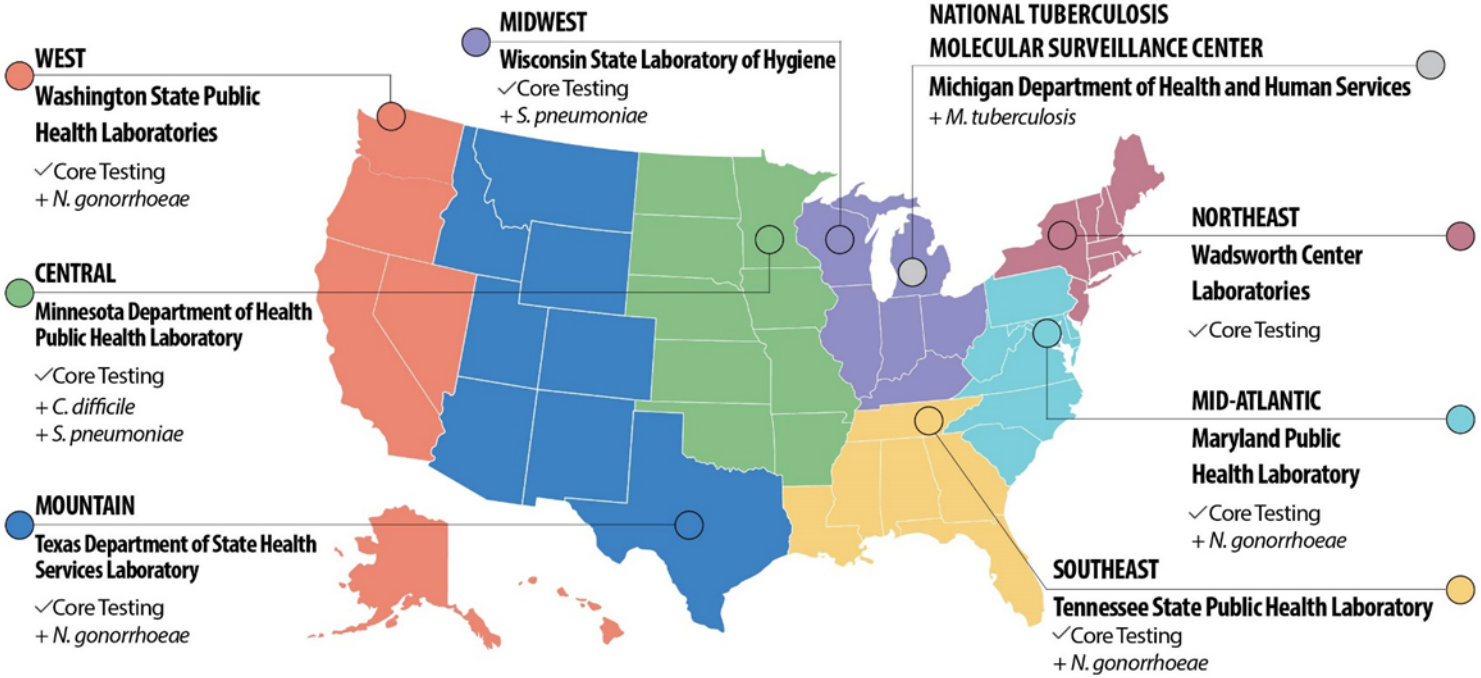
- Transform the national lab infrastructure with regional laboratories and local labs with gold-standard methods and technology
  - species identification and confirmatory antimicrobial susceptibility testing
  - phenotypic screening for carbapenemase production
  - carbapenemase mechanism testing
- Enhanced testing capacity in all 50 states and five local jurisdictions
- Faster detection for rapid and improved public health response
- Communication channels to engage clinical laboratory partners
- Real-time, actionable data to combat AR threats

AR Solutions at Every Level

- The ARLN ensures more consistent and improved communication, coordination, and tracking at all levels every time.
- When resistance threats are detected within healthcare facilities or state/local labs, regional labs can provide support to characterize, support response, and track these discoveries.
- Flexibility in surveillance testing to focus on the next emerging threat.
- CDC's ARLN team and Programs provide logistics support, subject matter expertise, and tailored solutions.



ARLN Regional Labs and TB Center



ARLN Regional Lab Core Testing

- CRE/CRPA Isolate Characterization
- Targeted surveillance
  - Carbapenem-R Acinetobacter spp.
  - ESBL-producing Enterobacteriaceae
  - Isolate testing for mcr-mediated colistin resistance

Outbreak Response CRE Colonization

Confirms CRE
Submits to HAI Coordinator

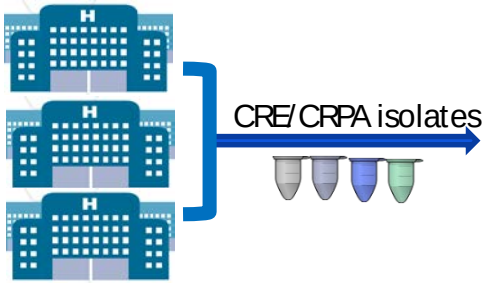
Identifies Patient Contacts
Coordinates Swab Collection

CRE Colonization Screening from Rectal Swabs

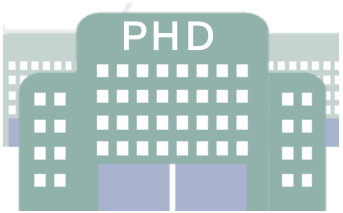
Results to Facility, Epidemiologist, and Lab in 2 Days

ARLN: Laboratory Support for Containment

Hospitals/Clinical Laboratories

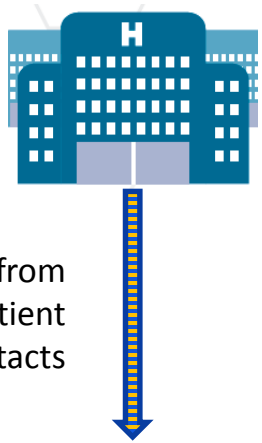


Public Health Laboratories
50 States
5 Local Health Departments



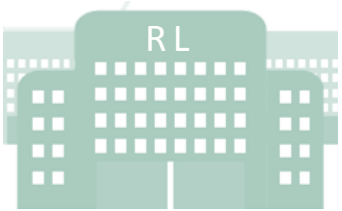
May include:
- Species identification
- Confirmatory AST
- Phenotypic screening for carbapenemase production
- Carbapenemase mechanism testing

Colonization screening in ARLN



Rectal swabs from CP-CRE+ patient contacts

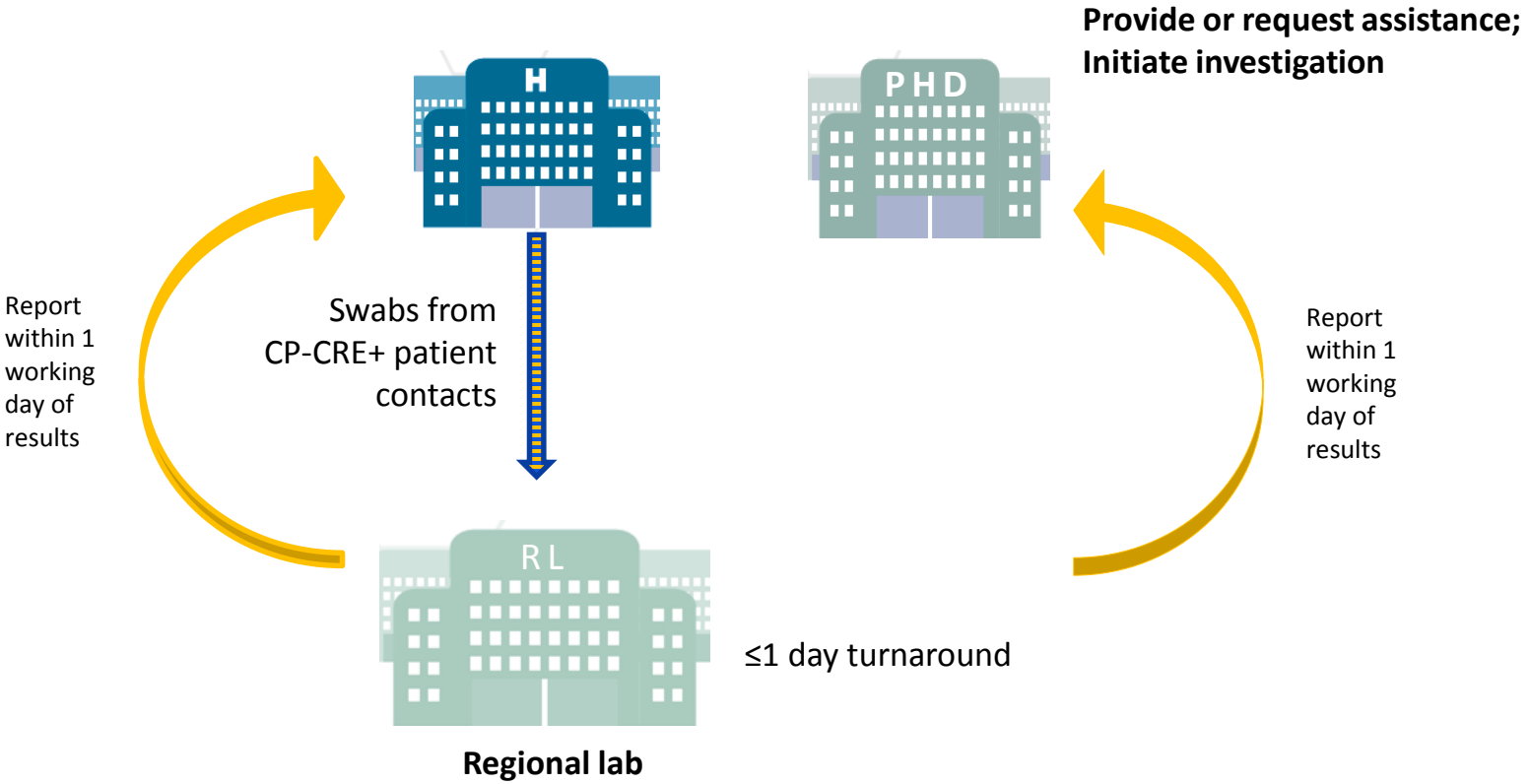
Swabs positioned regionally for rapid deployment to facilities where screening taking place



Regional lab

Rapid PCR-based detection from swab (Cepheid)

Colonization screening in ARLN



Texas Regional Lab Capabilities

Test TYPE	Method
Bacterial Species Identification	- Matrix assisted laser desorption ionization-time of flight mass spectrometry (MALDI-TOF) - API 20 is MALDI-TOF result not definitive - Conventional biochemicals
Antimicrobial Susceptibility Testing (AST)	- Disk Diffusion - Etest - Broth Microdilution (coming soon)
Carbapenemase Production Testing	mCIM, CarbaNP
Mechanisms of Resistance Testing	- Cepheid panel - CDC PCR protocol: KPC/NDM, OXA-48 like, VIM, mcr-1/mcr-2
Whole Genome Sequencing	Illumina MiSeq

*Provided by TX regional lab

CRE by the Numbers

January – July 2017 CRE data reported as of September 5, 2017

2,207 isolates tested

645 confirmed as carbapenemase-producers

3 *mcr*-1 cases confirmed by the AR Lab Network

89 AR Lab Network alerts, informing local epi response

26 public health labs reporting

Containment of Targeted MDROs

Containment Strategy

- Goal: slow spread of novel or rare multidrug-resistant organisms or mechanisms
- Systematic, aggressive response to single cases of high concern antimicrobial resistance
  - Focus on stopping transmission
- Response activities have tiered approach based on organism/mechanism attributes
- Complements existing guidance
  - CRE Toolkit
  - VRSA Investigation Guide

https://www.cdc.gov/hai/outbreaks/mdro/index.html

Response Tiers

- Tier 1
  - resistance mechanisms novel to the United States (i.e., not or only very rarely identified in the United States) or
  - organisms for which no current treatment options exist (pan-resistant)
  - organisms and resistance mechanisms for which experience in the United States is extremely limited and a more extensive evaluation might better define the risk for transmission
- Tier 2
- Tier 3

Response Tiers

- Tier 1
- Tier 2
  - MDROs primarily found in healthcare settings but not found regularly in the region; these organisms might be found more commonly in other areas in the United States
- Tier 3

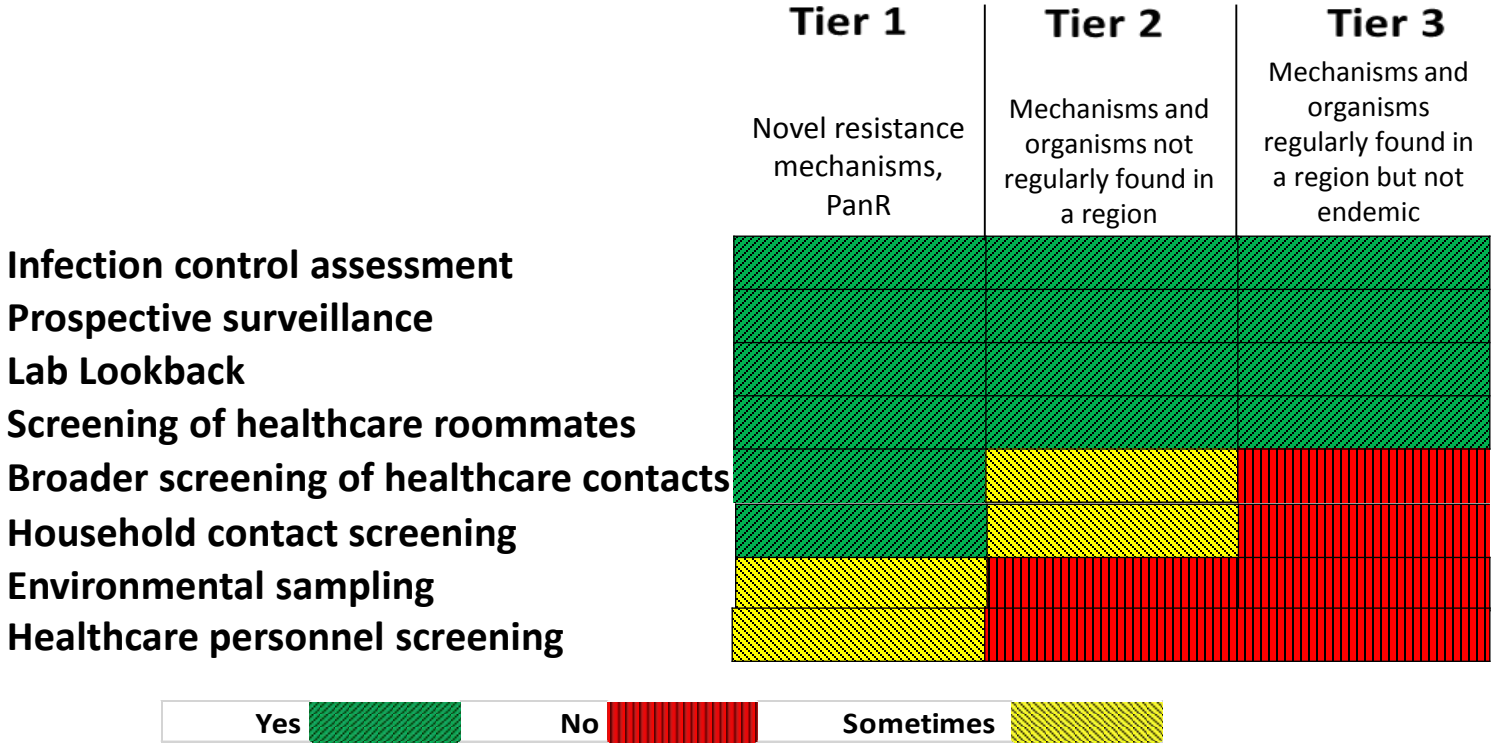
Response Tiers

- Tier 1
- Tier 2
- Tier 3
  - MDROs targeted by the facility/region that are already established in the United States and have been identified before in the region but are not thought to be endemic

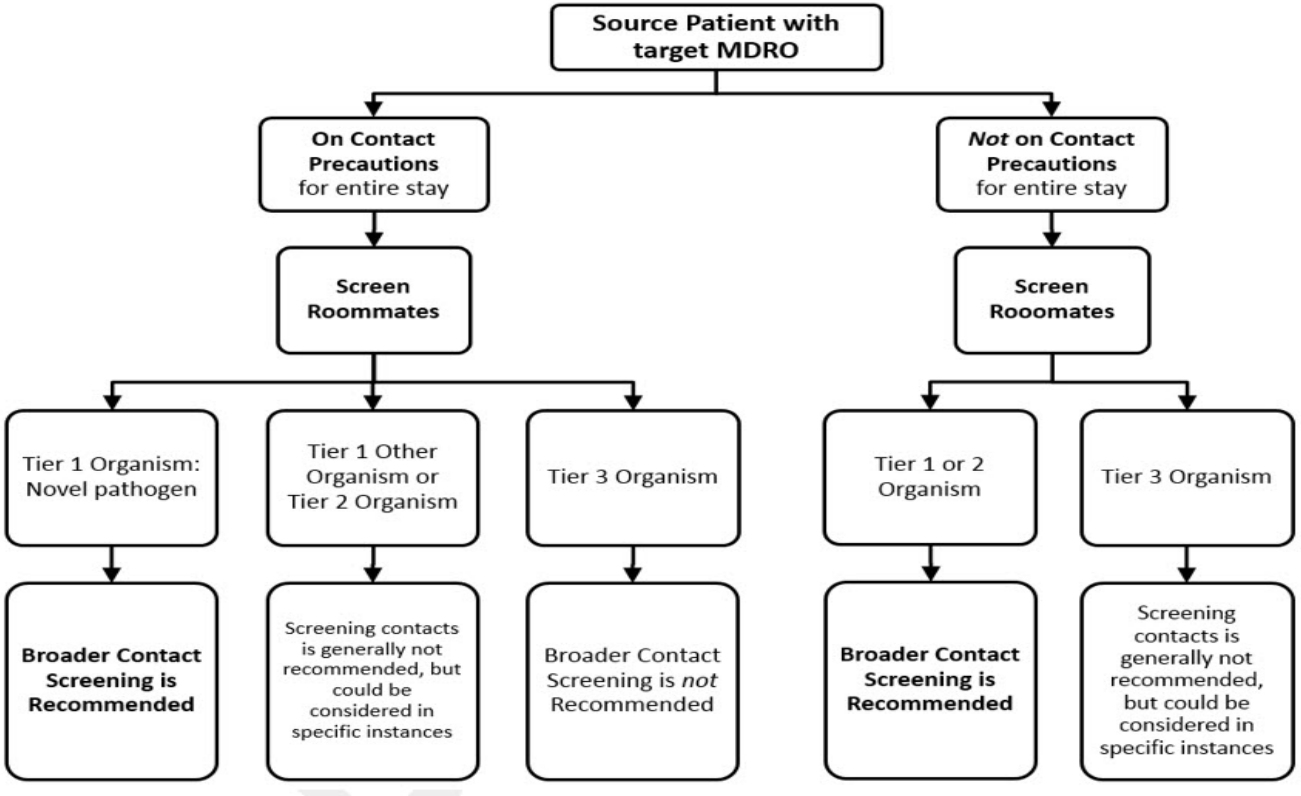
Targeted Pathogens for Containment

- *Candida auris (*tier 1)
- *mcr*-1 producing Enterobacteriaceae (tier 2)
- Vancomycin-resistant *Staphylococcus aureus* (tier 1)
- Pan-resistant isolates (tier 1)
- Carbapenemase-producing carbapenem-resistant Enterobacteriaceae (particularly non-KPC) (tier 2)
- Carbapenemase-producing *Pseudomonas* sp. (tier 2)
- Carbapenem-resistant Enterobacteriaceae producing *Klebsiella pneumoniae* carbapenemase (tier 3)
- Other isolates might be important in some areas

Containment Response Elements



Approach to screening healthcare contacts



https://www.cdc.gov/hai/outbreaks/mdro/index.html

Infection Control Considerations

- Notify patients of their results
- Educate and inform healthcare personnel and visitors
- Ensure adequate supplies are available and appropriate infection control practices in place
  - hand hygiene
  - transmission-based precautions
  - environmental cleaning
- Flag patient record
- Ensure patient's status and infection control precautions are communicated at transfer
- If MDRO present at admission, notify transferring facility

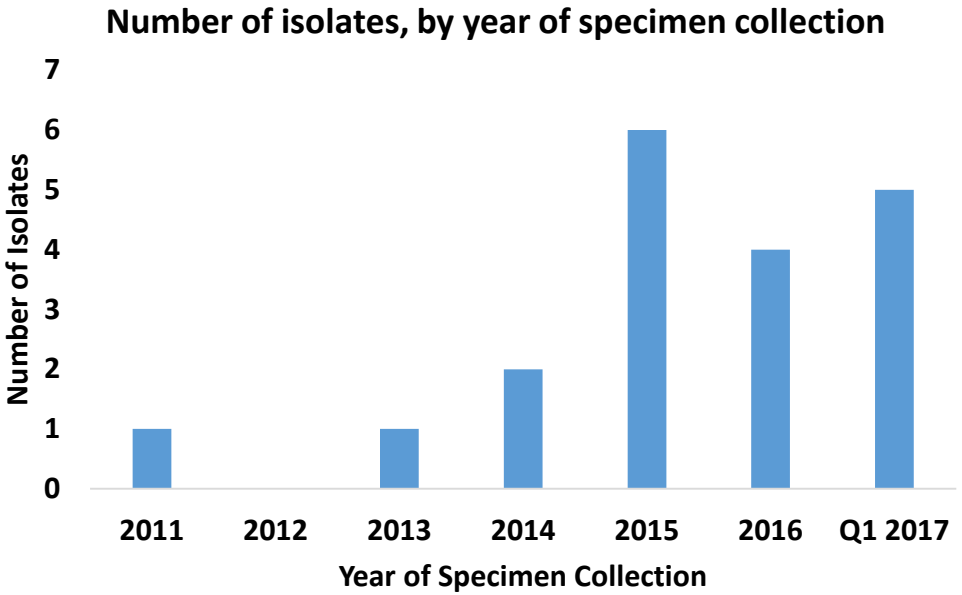
Emerging Issues in Epidemiology of CP-Organisms

Emerging Issues in Epidemiology of CP-Organisms

#1: Increase of non-KPC carbapenemases reported in Enterobacteriaceae other than *Klebsiella*, *Enterobacter*, and *E. coli*

Number of isolates, by organism

Organism	Number of Isolates
Proteus mirabilis	5
Providencia rettgeri	5
Morganella morganii	4
Citrobacter freundii	3
Serratia marcescens	3
Salmonella seftenberg	1
Providencia stuartii	1
Grand Total	22



Emerging Epidemiologic Trends

- **#2: Increased detection of IMP, VIM, and OXA-48**

Emerging Issues in Epidemiology of CP-Organisms

#3: CP-CRE in U.S. patients without healthcare or international travel

- Colorado: 6/10 recent NDM community-associated*
  - 2 had recent international travel
- Source currently unknown
  - CP-CRE found in community sources in U.S.
    - OXA-48 in municipal water that failed fecal coliform testing[$]
    - IMP-27 in environmental samples on pig farm[#]

*Janelle, S., et al., MMWR Morb Mortal Wkly Rep 2016;65:1414–1415. DOI: http://dx.doi.org/10.15585/mmwr.mm6549a6.
[$] Tanner, W.D., poster presentation
[#]Mollenkopf, D.F., Antimicrob Agents Chemother 61:e01298-16. DOI: https://doi.org/10.1128/AAC.01298-16.

Emerging Issues in Epidemiology of CP-Organisms

#4: New modes of transmission: sink drains and hoppers

- Hospital sink drains and hoppers can become colonized with CP-CRE and contaminate the patient environment
- Characteristic outbreak “signature”
  - Single mechanism in multiple genus and species
  - Cases persist despite infection control interventions for person to person transmission and environmental cleaning
- Lab work ongoing to describe extent of spread and to evaluate ways to prevent (e.g., lids on hoppers)
- Keep patient supplies away from sink splash zone

Antimicrobial Resistance In Texas

Texas CP-CRE and Carbapenemase-Producing *Pseudomonas aeruginosa* (CP-PA)

- 347 isolates submitted from TX to regional lab for characterization reported to CDC as of 8/31/2017
  - 97 CP-CRE identified (96 KPC, 1 OXA-48)
  - 13 CP-PA identified (6 VIM-*Pseudomonas, 2* IMP-*Pseudomonas, 5 no gene currently identified*)

Number CP of isolates, by organism

Organism	Number of Isolates
Klebsiella pneumoniae	92
Enterobacter cloacae	2
Enterobacter cloacae complex	1
Escherichia coli	2
Pseudomonas aeruginosa	13
Grand Total	**110**

TX CP-PA

- VIM-PA
  - 8 cases identified in 4 facilities in 2016 and 2017
  - Cases primarily in West Texas/Panhandle
  - 1 patient screened as a result
  - No additional cases identified from screening

- 4 MDR-*Pseudomonas* cases among pediatric patients at burn hospital
  - 2 patients identified with IMP-PA
  - Investigation suggests importation and transmission

TX mcr-1, and OXA-48

- mcr-1 from ESBL E. coli in urine from a 49 yo without international travel
  - 20th U.S. case (1st in TX)
  - Admitted to ACH, LTACH, and IRF

- First OXA-48 identified in *E. coli* from a wound culture at a rehab facility
  - Screened 3 healthcare contacts in close proximity to patient's room (all negative)

Summary

- Containment of MDROs is complex
- Guidance available
  - https://www.cdc.gov/hai/outbreaks/mdro/index.html
- Coordination between lab and epi is critical
- TX organisms for containment
  - Carbapenemase-producing PA (**VIM** and IMP)
  - CP-CRE (OXA-48 and NDM)
  - mcr-1
  - *C. auris*
  - Be on the lookout for others (*e.g.*IMP and VIM producing-CRE*)*

Thank you

For more information, contact CDC
1-800-CDC-INFO (232-4636)
TTY: 1-888-232-6348 www.cdc.gov