National Center for Emerging and Zoonotic Infectious Diseases



Emerging Infectious Disease in the U.S.

Maroya Walters, PhD, ScM

Division of Healthcare Quality Promotion

Centers for Disease Control and Prevention

November 15, 2017

No Disclosures

With so many emerging diseases, why focus on antibiotic resistance?

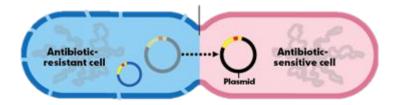
- Antibiotic resistant (AR) germs avoid the effects of the drugs designed to kill them
 - Life-saving treatments depend on antibiotics that work
- AR affects all communities
- AR is not stoppable but its spread can be slowed
 - Easiest to control when problem is small/ emerging
 - New CDC initiatives designed to contain spread of AR

Resistant germs can be anywhere and can affect every aspect of human life



Historical Perspective

- Approximately 30 years ago, new resistance mechanism identified called Extended Spectrum β-Lactamases
 - Degrade penicillins and cephalosporins
 - Move between strains on mobile genetic element called plasmid
 - Plasmids carried resistance to multiple antibiotics



Historical Perspective

- Approximately 30 years ago, new resistance mechanism identified called Extended Spectrum β-Lactamases
 - Degrade penicillins and cephalosporins
 - Move between strains on mobile genetic element called plasmid
 - Plasmids carried resistance to multiple antibiotics
- No coordinated response or guidance for ESBL control
 - Now, ~20% of isolates from HAIs are resistant to cephalosporins
 - ESBLs are prevalent in the community

Overview

- Three high priority emergent organisms or resistance mechanisms
 - Carbapenemase producing organisms
 - mcr-1
 - Candida auris
- New tools and approach to controlling emerging resistant organisms

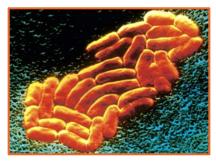
Emerging MDROs – Carbpanemease Producing Organisms

Gram-Negative Rods

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

Enterobacteriaceae

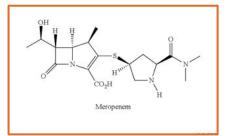
- Large family of gram negative rods with >25 recognized genera
- Most common family encountered in clinical microbiology labs
 - Most common are *Klebsiella* spp., *Escherichia coli*, and *Enterobacter* spp.
 - Also Proteus, Providencia, and Morganella
- Many are susceptible to many antibiotics including members of the penicillin family
 - Some have β-lactamases that lead to reduced susceptibility to penicillins



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

Carbapenems

- Broad spectrum "antibiotics of last resort" for highly resistant infections
- Increasingly important due to emergence and spread of extended-spectrum βlactamases (ESBLs) beginning in the 1990s
- Four approved carbapenems in US (imipenem, meropenem, doripenem, ertapenem)
 - Ertapenem less active against some bacteria, does not cover Pseudomonas



Carbapenem-Resistant Enterobacteriaceae (CRE)

- A.K.A. "Nightmare bacteria"
- Often multidrug resistant
- Cause infections with high mortality rates
- Multiple resistance mechanisms, two main types
 - Carbapenemase-producing CRE (CP-CRE)
 - Non carbapenemase-producing CRE (non CP-CRE)



Non-Carbapenemase Producing CRE (non CP-CRE)

- Often a combination of mechanisms contributes to resistance
- Chromosomal mutations such as porin loss combined with plasmid mediated mechanisms like Extended Spectrum β-lactamase (ESBL) or AmpC
- Can pass resistance vertically but not horizontally
- Often incur fitness defect

Carbapenemase-Producing CRE (CP-CRE)

- Carbapenemases are enzymes that digest carbapenems
 - Found in glucose non-fermenters in addition to Enterobacteriaceae
- Plasmid encoded
 - Can pass resistance vertically and horizontally
 - No/minimal fitness defect
- 5 carbapenemases of primary public health concern
 - K. pneumoniae carbapenemase (KPC)
 - New Delhi Metallo-β-lactamase (NDM)
 - Oxacillinase (OXA-48-type)
 - Verona Integron Mediated Metallo-β-lactamase (VIM)
 - Imipenemase (IMP)
- Potential for epidemic spread



Spread of Carbapenemases Can Rapidly Increase Percent Resistant

- Examples of Spread
 - Israel: KPC outbreak
 - 11% carbapenem resistant in 2006
 - 22% carbapenem resistant in 2007
 - Greece: Dissemination of VIM
 - <1% carbapenem resistant in 2001</p>
 - 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 Experience: KPC

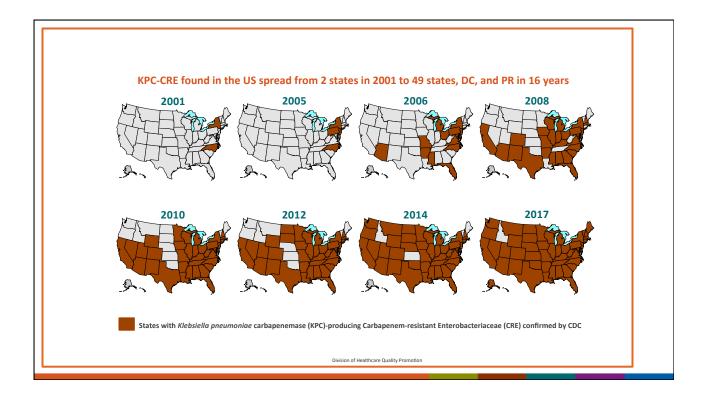
ANTIMICROBIAL AGENTS AND CHEMOTSBERALY, Apr. 2001, p. 1151–1161 0066-480401[361-004] DOI: 10.1128/AAC.45.4.1151–1161.2001 Copyright © 2001, American Society for Microbiology. All Rights Reserved.

Vol. 45, No. 4

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

HESNA YIGIT, ANNE MARIE QUEENAN, GREGORY J. ANDERSON, ANTONIO DOMENECH-SANCHEZ, JAMES W. BIDDLE, CHRISTINE D. STEWARD, SEBASTIAN ALBERTI, KAREN BUSH, AND FRED C. TENOVER 18

Isolate collected in 1996 during an ICU surveillance project from NC



How Common are CRE in U.S. Hospitals?

- 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 carbapenem¹
- In 2014, 7.8% of SSACH and 24% of LTACHs doing surveillance for CAUTI or CLABSI had at least one CRE infection²
- Facilities reported 0-13 LabID CRE Events per month in 2015³
 - High incidence states: mean 1.5 events/month
 - Low incidence states: mean 0.08 events/month

¹Weiner, L. et al., Infect Control Hosp Epidemiol 2016;1–14 ²Walters, M.. et al., SHEA, 2016 ³Vasquez, A. et al., ID Week, 2016

CRE Population-Based Surveillance

- Emerging Infections Program Multisite Gram-negative Surveillance Initiative (MuGSI)
 - 8 U.S. sites
 - CRE from urine and normally sterile sites
- Incidence 2.93 per 100,000 population across 8 metropolitan sites⁴



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

MuGSI: CRE Epidemiology

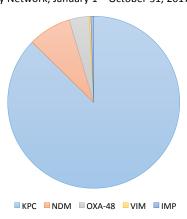
- 87% of cases from urine
- 33% from short stay acute care
- 75% had history of hospitalization in year prior
- 72% had indwelling device ≤2 days prior to culture
- 65% of case-patients hospitalized
 - 56% discharged to long term care facility

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

What Proportion of CRE are Carbapenemase Producers?

- Between January 1 and October 31, 2017, 3169 CRE were tested at state laboratories across the U.S.
 - 955 (30%) were carbapenemaseproducers
 - 120 (13%) carbapenemases were non-KPC (e.g., NDM, VIM, IMP, OXA-48)
 - 28/59 (47%) with information available had healthcare outside the U.S. in 12 months prior

CP-CRE Reported through Antimicrobial Resistance Laboratory Network, January 1 – October 31, 2017



Data are preliminary and subject to change

Patients with non KPC CP-CRE reported to CDC as of June 2017

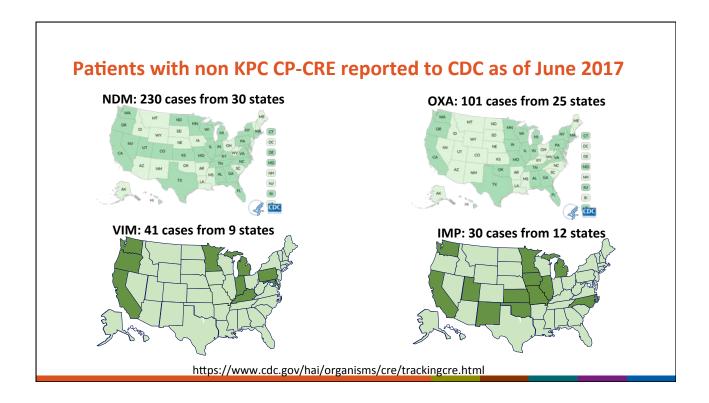
NDM: 230 cases from 30 states



OXA: 101 cases from 25 states



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



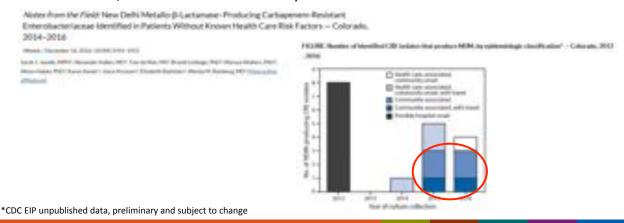
Is CP-CRE Limited to Healthcare Settings?

- EIP CRE surveillance: 10% of cases in persons without recent healthcare exposure
 - Primarily E. coli and Enterobacter in women presenting with UTI*
 - Some are CP-CRE

*CDC EIP unpublished data, preliminary and subject to change

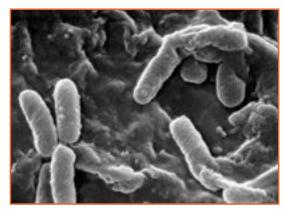
Is CP-CRE Limited to Healthcare Settings?

- EIP CRE surveillance: 10% of cases in persons without recent healthcare exposure
 - Primarily E. coli and Enterobacter in women presenting with UTI*
- Colorado: 6/10 recent NDM community-associated



Carbapenemases in Glucose Non-Fermenters

- Primarily in Pseudomonas, also Acinetobacter and Achromobacter
- Carbapenemase-producing
 Pseudomonas common in some parts of the world
 - Brazil 1998-2012: 39% of CRPA
 - Europe 2009-2011: 20% of CRPA
 - Denmark 2011: 7% of CRPA

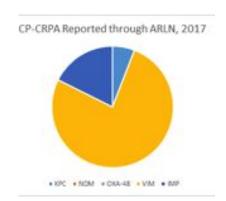


Scanning Electron Micrograph of P. aeruginosa, CDC

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-Pseudomonas and Acinetobacter Extremely Rare in U.S.

- Between January 1 and October 31, 2017, 1117
 CRPA were submitted to Antimicrobial Resistance Laboratory Network
 - 17 CRPA (1.5%) carbapenemase-producers
 - 16 (92%) of carbapenemases were non-KPC (e.g., NDM, VIM, IMP)
 - VIM most common
 - CP-CRPA often extremely resistant
 - Resistant to newer drugs: ceftolozanetazobactam, ceftazidime-avibactam
 - Susceptible only to colistin
- Few CP-Acinetobacter, all NDM



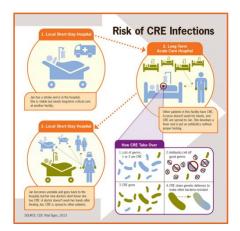
Data are preliminary and subject to change

CP-Pseudomonas Outbreaks

- Several large outbreaks of CP-Pseudomonas
 - VIM and IMP
 - Long term acute care hospitals and ventilator units of skilled nursing facilities
 - Longer length of stay units of short stay acute care hospitals

How Do CP-Organisms Spread in a Healthcare Facility?

- On the hands and clothes of healthcare workers
 - Long length of stay
 - High acuity of care
 - LTACHs and high acuity LTCF units highest risk



How Do CP-Organisms Spread in a Healthcare Facility?

- On the hands and clothes of healthcare workers
- Through inadequately reprocessed devices



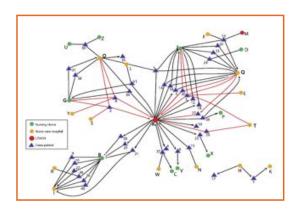
How Do CP-Organisms Spread in a Healthcare Facility?

- On the hands and clothes of healthcare workers
- Through inadequately reprocessed devices
- Through hospital sink drains and hoppers that become colonized with CP-CRE and contaminate patient supplies or environment



How Do CP-Organisms Spread in a Region?

- When transmission occurs undetected
- When patient's MDRO status is not communicated during interfacility transfer



KPC outbreak in Chicago, 2008 Won et al. Clin Infect Dis 2011; 53:532-540

Emerging MDROs – colistin resistance and *mcr-1*

Polymyxin Antibiotics

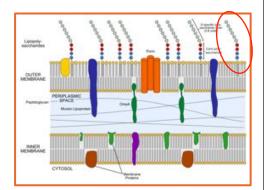
- Colistin (polymyxin E) and polymyxin B
- Used to treat serious, highly resistant infections
 - Broad activity against gram negative bacteria
 - Available in U.S. in topical and IV formulations
 - IV use associated with toxicities
- Used outside of the U.S.
 - Orally for selective digestive decontamination
 - Widely in veterinary medicine, especially animal agriculture



www.alibaba.com

Colistin Resistance

- Chromosomal resistance well-documented
 - Colistin binds lipopolysaccharide
 - Resistance through Lipid A modification
 - ~11% of ESBLs tested at CDC have colistin MIC ≥4 μg/ml
- Plasmid-mediated resistance first reported in November 2015 in China*
 - mcr-1: mobile colistin resistance
 - E. coli (primarily) and K. pneumoniae
 - Meat, animal isolates, clinical isolates



www.bio101.info

*Liu, Lancet Infet Dis 2016; 16: 16-68

Colistin Susceptibility Testing

- Multiple methodological issues and technical challenges
 - No FDA-cleared automated testing methods
 - E-test underestimates MIC by 1-2 doubling dilutions
 - Disk diffusion does not work due to poor diffusion
- ASM 2016: Laboratories that choose to test for collistin susceptibilities for clinical decisions should use broth microdilution
 - Only 1% of hospital labs in U.S. have this capacity
 - Might need to have reference labs perform this testing

Emergence of mcr-1

- Since initial report, found globally
 - >20 countries and 6 continents
 - Food animals, meat, vegetables, surface water
 - Ill patients, asymptomatically colonized patients
- Multiple species: E. coli, K. pneumoniae, Salmonella enterica, Shigella sonnei
- Earliest isolates identified from 1980s (chickens, E. coli, China)
- Earliest human isolate from 2008 (Shigella sonnei, Vietnam)

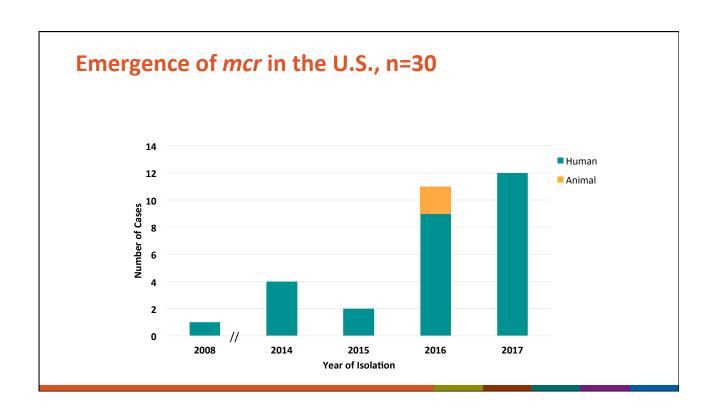
Liu, Lancet Infet Dis 2016; 16: 16-68 Skov, Euro Surveill 2016; 21(9):pii=30155

Molecular features of mcr-1

- Highly transmissible
 - In laboratory experiments among E. coli, K. pneumoniae and P. aeruginosa
 - Stably maintained in absence of polymyxin drug pressure
 - Potential for movement and rapid spread through epidemic clones
- Increased colistin MICs 8 to 16-fold
 - Typical MICs 4 to 8 μg/ml
- Other mobile colistin resistance mechanisms identified
 - 5 closely related variants mcr-1.2 to mcr-1.7
 - 4 homologs mcr-2 to mcr-5

Surveillance for *mcr-1* in the U.S.

- Retrospective surveillance
 - U.S. Government: National Antimicrobial Resistance Monitoring System (NARMS; retail meat, animal, clinical); DHQP reference and surveillance isolates; National Center for Biotechnology Information
 - Academia and private labs: SENTRY, Rutgers
- Prospective surveillance
 - CDC HAN, June 2016: Send Enterobacteriaceae with colistin MIC ≥4 μg/ml to CDC for mechanism testing
 - Sequencing all Salmonella spp.
 - Walter Reed Army Institute of Research MDRO Surveillance Network
 - Special surveillance project at 7 regional laboratories

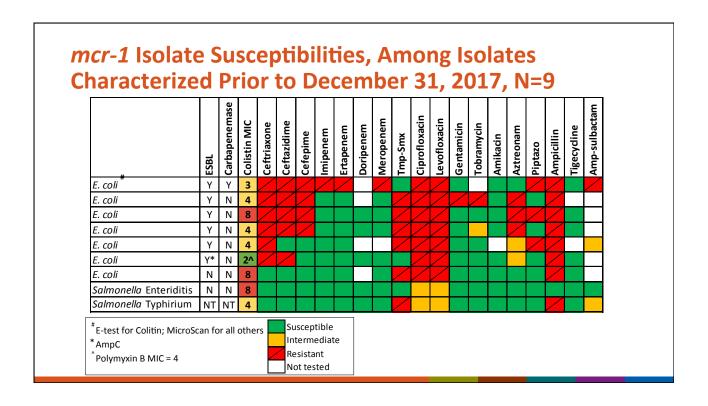




https://www.cdc.gov/drugresistance/tracking-mcr1.html

U.S. mcr-1 Cases

- 26 cases identified as of August 31, 2017 24 mcr-1, 2 mcr-3
- 14 E. coli (1 STEC), 10 Salmonella, 2 Klebsiella pneumoniae
- 22/26 had international travel in year prior
 - Dominican Republic (n=6), Vietnam (n=3), Cambodia (n=2), China (n=2),
 Mexico (n=2), Bahrain, Columbia, Jamaica, St. Vincent, Bahamas, Lebanon,
 Portugal, Thailand
 - Many had traveler's diarrhea
 - 2 were hospitalized outside the U.S.
- 9 had hospitalization in the U.S. in year prior to positive
 - 1 potential transmission in healthcare



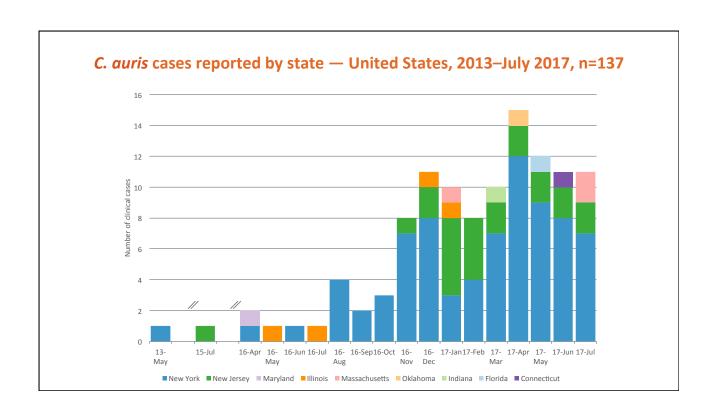
Emerging MDROs – Candida auris

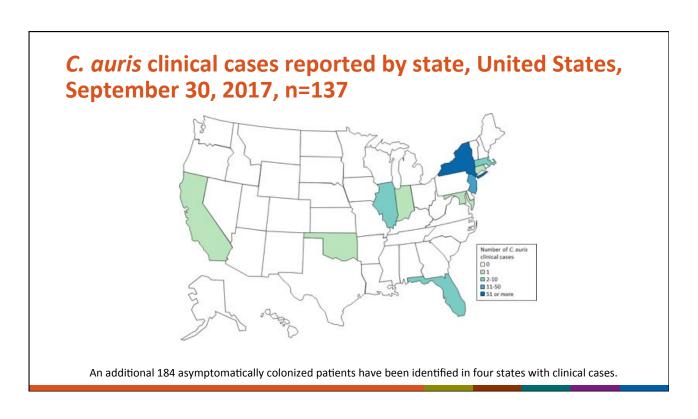
Candida auris

- Fungus that causes invasive infections with high mortality (60%)
- Explosive global spread since discovery in Japan in 2009
 - − No C. auris in >7000 Candida isolates collected in U.S. 2008 −2016¹
 - ->30,000 Candida isolates collected from 4 continents, 1996-2015²
 - No C. auris before 2009
- Unlike most other Candida species
 - Colonizes skin
 - Transmitted person-to-person in healthcare
 - High level resistance
 - Difficult to identify in laboratory

¹CDC EIP Candidemia surveillance ²SENTRY and ARTEMIS programs

Global C. auris situation, September 30, 2017 Single C. auris case reported Transmission or multiple cases of C. auris reported To be filtered tays in these countries https://www.cdc.gov/fungal/diseases/candidiasis/tracking-c-auris.html





C. auris is highly resistant

Polyenes

AMPHOTERICII For injection Size vial contains: Application 5 or gr Value Son 1A 10047 or Son Lucion

C. glabrata

<1% resistant to amphotericin B

C. auris

35% resistant to amphotericin B

Azoles



11% resistant to fluconazole

93% resistant to fluconazole 54% resistant to voriconazole

Echinocandins



Up to 12% resistant to echinocandins

7% resistant to echinocandins

A few isolates resistant to all three classes



C. glabrata

<1% resistant to amphotericin [

C. auris

35% resistant to amphotericin B



11% resistant

93% resistant to fluconazole 54% resistant to voriconazole

Echinocandins

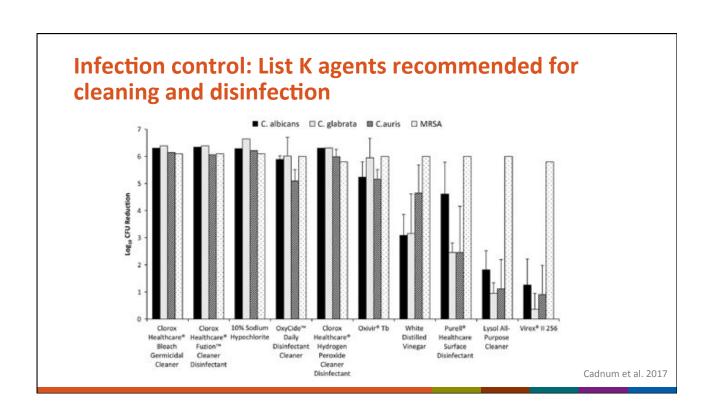


up to 12% resistant to echinocandins

7% resistant to echinocandins

C. auris contaminates the hospital environment





Candida auris is difficult to identify

Identification Method	Organism C. auris can be misidentified as
Vitek 2 YST	Candida haemulonii Candida duobushaemulonii
API 20C	Rhodotorula glutinis (characteristic red color not present) Candida sake
BD Phoenix yeast identification system	Candida haemulonii Candida catenulata
Microscan	Candida famata Candida guilliermondii (no hyphae/pseudohyphae present on commeal agar) Candida Justianiae (no hyphae/pseudohyphae present on commeal agar) Candida parapsilosis (no hyphae/pseudohyphae present on commeal agar)

Please note that this list is based on current knowledge about C. suris misidentification. It may change from time to time as we learn more about misidentification of C. suris.

Detailed algorithms for identification are available on CDC C. auris page

https://www.cdc.gov/fungal/diseases/candidiasis/recommendations.html

Summary: Novel MDROs

- Highly transmissible resistance mechanisms or organisms
 - Plasmid mediated (CRE, mcr-1)
 - Skin colonization, persistent environmental contamination (C. auris)
- *C. auris* and non-KPC carbapenemases initially associated with recent hospitalization outside the U.S. and importation
 - · Now transmission in the US
 - Possible spread to community (carbapenemase-producing organisms)
- mcr-1: primarily international travel without healthcare
 - Concern for spread in healthcare settings with more resistant bacteria and greater drug pressure
- Long length of stay, high acuity facilities and units can serve as amplifiers

Key Infection Control Actions for Novel MDROs

- Timely, accurate detection
- Notify patients of their results
- Educate healthcare personnel and visitors
- Meticulous adherence to hand hygiene and transmission-based precautions
- Environmental cleaning
 - Using List K agent for C. auris
- Interfacility notifications when transferring patients
 - · If present at admission notify transferring facility
- Flag patient record to ensure appropriate precautions if readmitted
- Public health investigations to identify and stop transmission

New Tools and Approaches: Containment Strategy

Why are new strategies needed?

- MDROS have previously spread unchecked due to
 - Limited capacity to detect target organisms/mechanisms
 - Expense and lack of availability of screening
 - No guidance for response
- Improved detection, infection control, and identification of asymptomatic carriage can slow the spread of carbapenemaseproducing organisms
- Slowing spread of resistance buys time for development of new drugs, novel therapies

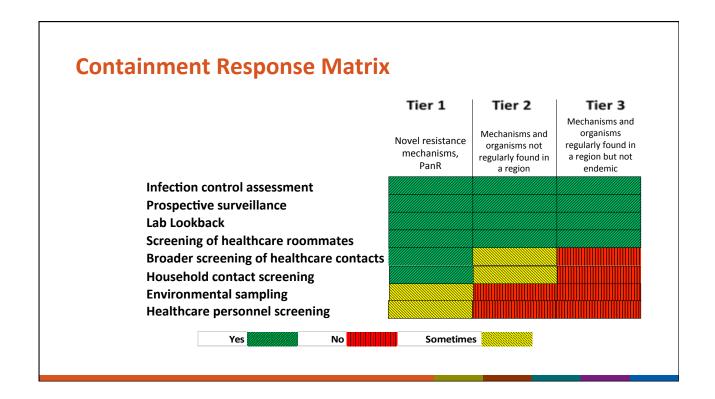
Containment Strategy

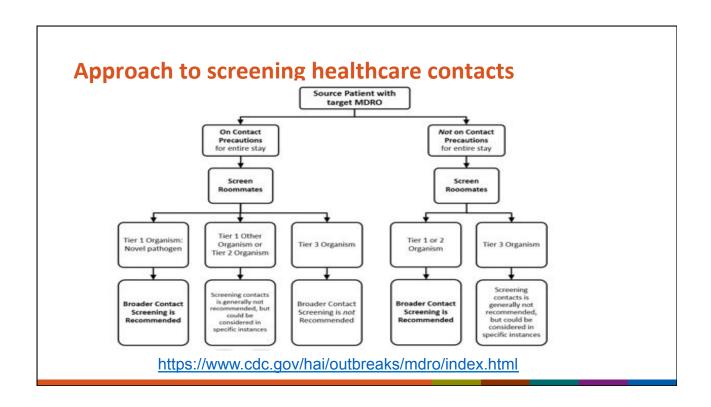
- Systematic approach to slow spread of novel or rare multidrug-resistant organisms or mechanisms through aggressive response to ≥1 case of targeted organisms
 - Carbapenemase-producing organisms, mcr-1
 - · Pan-resistant organisms
 - Candida auris
- Emphasis on settings that historically are linked to amplification
 - Long term care facilities (e.g., skilled nursing)
 - Long term acute care facilities and high acuity skilled nursing (e.g., vSNF)

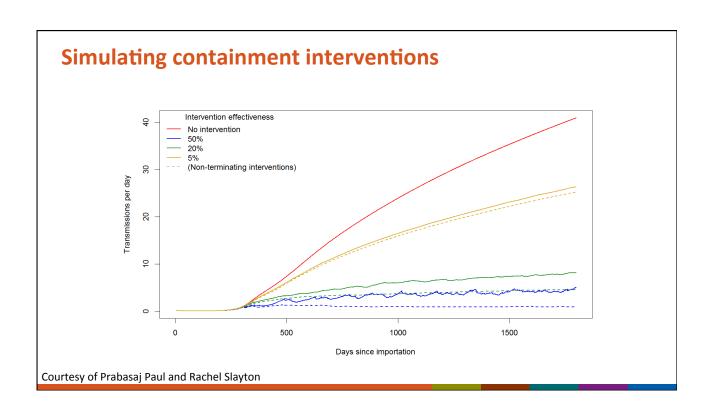
Containment Approach

- Main components
 - Detection
 - Infection control assessments
 - Screening for asymptomatic colonization
- Response tiers based on pathogen/ resistance mechanism
- Guidance document available on CDC website
- Complements existing guidance
 - CRE Toolkit
 - VRSA Investigation Guide







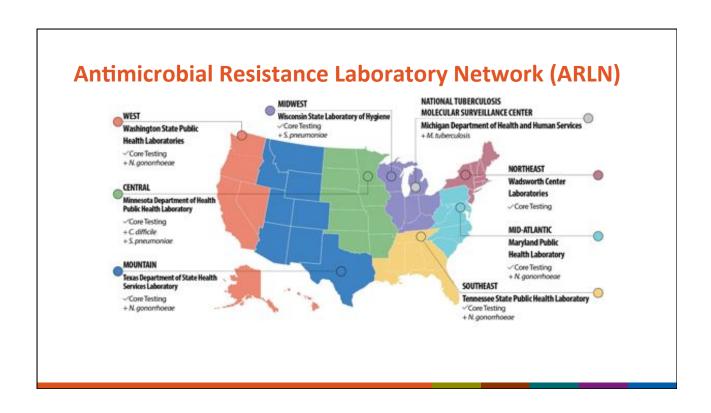


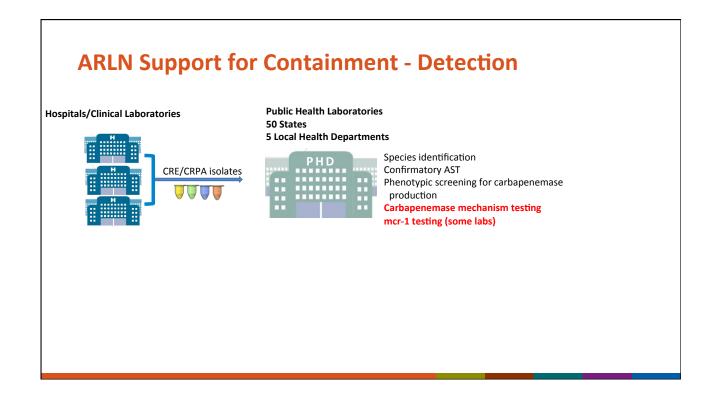
New Tools and Approaches: Improved Detection & Access to Screening

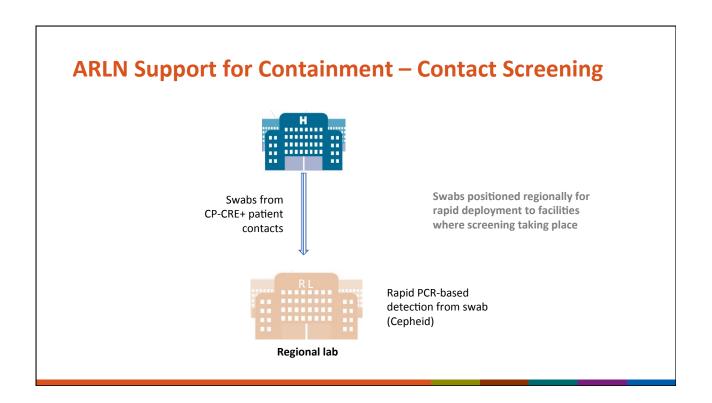
Implementation of Containment: HAI/AR programs in every state

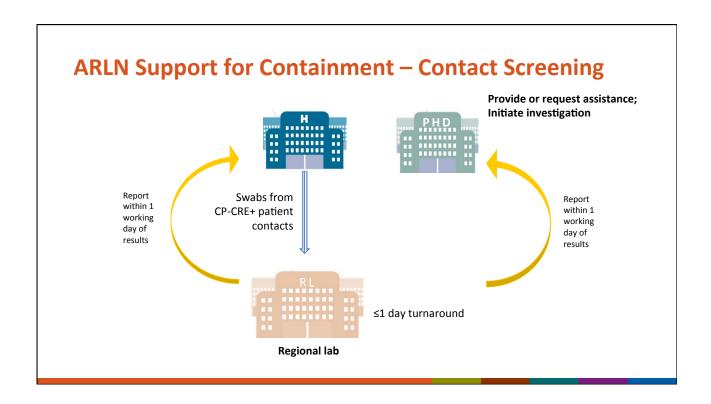
- In 50 states, 6 cities and Puerto Rico
 - Local AR/HAI expertise and support for systematic infection control assessments
 - Lab capacity to improve identification and response to emerging AR threats
 - Carbapenemase testing for Enterobacteriaceae and *Pseudomonas spp.*
- Expanded capacities at 7 regional labs
 - Carbapenemase-producing organism screening
 - mcr-1 testing (targeted surveillance)
 - C. auris confirmatory testing

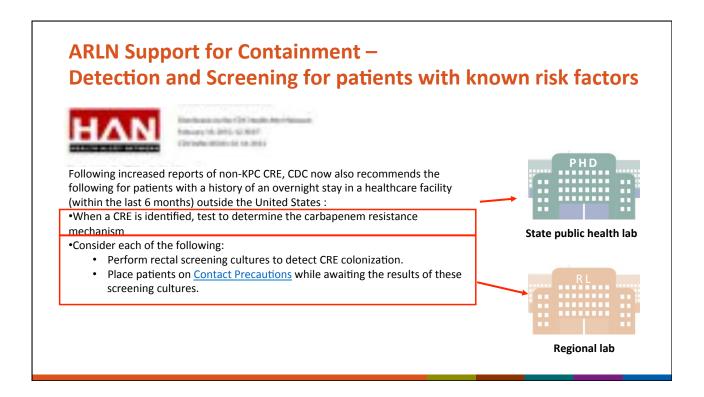
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Summary – New Approach and Resources

- "Containment" approach represents a more aggressive response to novel MDROs
 - Facilitated by Public Health
 - Tiers have flexibility to reflect regional epidemiology (e.g., KPC may be Tier 2 in some states and Tier 3 in others)
 - Goal is to slow spread through identification and isolation, infection control interventions, and identification of transmission
- New resources available for facilities: Guidance, infection control support, AST/ Resistance mechanism testing, colonization screening
- Successful containment requires collaboration among many players
 - CDC, State and local health departments, facilities across the continuum of care, clinical and public health laboratories

Thank you!

Contact: MSWalters@cdc.gov

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

Slide Acknowledgements

- CDC Division of Healthcare Quality Promotion
 - · Prevention and Response Branch
 - Alex Kallen
 - AR team
 - Epidemiology Research and Innovations Branch
 - · Rachel Slayton and Prabasaj Paul
 - Antimicrobial Resistance Laboratory Network
 - · Allison Brown
- · CDC Mycotic Diseases Branch
 - · Snigdha Vallabhaneni

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.



Summary: Novel MDROs - Resources

- CDC CRE Toolkit: https://www.cdc.gov/hai/organisms/cre/cre-toolkit/index.html
- CDC HAN for mcr-1: https://emergency.cdc.gov/han/han00390.asp
- Candida auris Interim Recommendations for Healthcare Facilities and Laboratories
 - https://www.cdc.gov/fungal/diseases/candidiasis/recommendations.html
- C. auris Reporting: candidaauris@cdc.gov