Emerging Infectious Disease in the U.S.

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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
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 – Carbpanemesease 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
**Carbapenems**

- Broad spectrum “antibiotics of last resort” for highly resistant infections
- Increasingly important due to emergence and spread of extended-spectrum β-lactamases (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
    - 20%-50% carbapenem resistant in 2006


The US Experience: KPC

- 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 carbapenem\(^1\)
  - In 2014, 7.8% of SSACH and 24% of LTACHs doing surveillance for CAUTI or CLABSI had at least one CRE infection\(^2\)
  - Facilities reported 0-13 LabID CRE Events per month in 2015\(^3\)
    - High incidence states: mean 1.5 events/month
    - Low incidence states: mean 0.08 events/month

\(^1\)Weiner, L. et al., Infect Control Hosp Epidemiol 2016;1–14
\(^2\)Walters, M. et al., SHEA, 2016
\(^3\)Vasquez, 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 sites

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

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 carbapenemase-producers
  - 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

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

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
- IMP: 30 cases from 12 states
- VIM: 41 cases from 9 states
- OXA: 101 cases from 25 states

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

*CDC EIP unpublished data, preliminary and subject to change

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]
**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: ceftolozane-tazobactam, 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
Emerging MDROs – colistin resistance and \textit{mcr-1}

\textbf{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

* Liu, Lancet Infect 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 colistin 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, asymptotically 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)

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

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Emergence of *mcr* in the U.S., n=30

![Graph showing the emergence of *mcr* in the U.S. from 2008 to 2017, with a notable increase in 2016 and 2017.]
**mcr Cases by Location, as of November 1, 2017, n=30**

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

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**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
### mcr-1 Isolate Susceptibilities, Among Isolates Characterized Prior to December 31, 2017, N=9

<table>
<thead>
<tr>
<th>Pathogen</th>
<th>ESBL</th>
<th>Carbapenemase</th>
<th>Colistin MIC</th>
<th>Ceftriaxone</th>
<th>Cefepime</th>
<th>Imipenem</th>
<th>Doripenem</th>
<th>Meropenem</th>
<th>Ticarcillin</th>
<th>Ceftazidime</th>
<th>Piperacillin</th>
<th>Tmp-Smx</th>
<th>Ciprofloxacin</th>
<th>Levofloxacin</th>
<th>Tobramycin</th>
<th>Amikacin</th>
<th>Aztreonam</th>
<th>Piperacillin</th>
<th>Ampicillin</th>
<th>Tigecycline</th>
<th>Amp-sulbactam</th>
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<tr>
<td><em>E. coli</em></td>
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<tr>
<td><em>Salmonella Enteriditis</em></td>
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<tr>
<td><em>Salmonella Typhirium</em></td>
<td>NT</td>
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* E-test for Colistin; MicroScan for all others
* AmpC
* Polymyxin B MIC = 4

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**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. 2008–2016\(^1\)
  - >30,000 *Candida* isolates collected from 4 continents, 1996-2015\(^2\)
    - 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

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**Global *C. auris* situation, September 30, 2017**

https://www.cdc.gov/fungal/diseases/candidiasis/tracking-c-auris.html
C. auris cases reported by state — United States, 2013–July 2017, n=137

C. auris clinical cases reported by state, United States, September 30, 2017, n=137

An additional 184 asymptotically colonized patients have been identified in four states with clinical cases.
**C. auris** is highly resistant

<table>
<thead>
<tr>
<th>Class</th>
<th>C. glabrata</th>
<th>C. auris</th>
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<td>Polyenes</td>
<td>&lt;1% resistant to amphotericin B</td>
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A few isolates resistant to all three classes

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</tbody>
</table>
**C. auris** contaminates the hospital environment

Infection control: List K agents recommended for cleaning and disinfection

![Graph](image)

(Cadnum et al. 2017)
**Candida auris** is difficult to identify

<table>
<thead>
<tr>
<th>Identification Method</th>
<th>Organism C. auris can be misidentified as</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vitek 2 YST</td>
<td>Candida haemulonii, Candida dubosshaemulonii</td>
</tr>
<tr>
<td>API 20C</td>
<td>Rhodotorula glutinis (characteristic red color not present), Candida sake</td>
</tr>
<tr>
<td>BD Phoenix yeast identification system</td>
<td>Candida haemulonii, Candida catenulata</td>
</tr>
<tr>
<td>Microscan</td>
<td>Candida famata, Candida guillermondii (no hyphae/pseudohyphae present on cornmeal agar), Candida lusitaniae (no hyphae/pseudohyphae present on cornmeal agar), Candida parapsilosis (no hyphae/pseudohyphae present on cornmeal agar)</td>
</tr>
</tbody>
</table>

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

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 carbapenemase-producing 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

[Image: CDC website link]

Containment Response Matrix

<table>
<thead>
<tr>
<th>Tier 1</th>
<th>Tier 2</th>
<th>Tier 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Novel resistance mechanisms, PanR</td>
<td>Mechanisms and organisms not regularly found in a region</td>
<td>Mechanisms and organisms regularly found in a region but not endemic</td>
</tr>
</tbody>
</table>

Infection control assessment  
Prospective surveillance  
Lab Lookback  
Screening of healthcare roommates  
Broader screening of healthcare contacts  
Household contact screening  
Environmental sampling  
Healthcare personnel screening

[Table: Response matrix with decision matrix]
Approach to screening healthcare contacts

Source Patient with target MDRO

On Contact Precautions for entire stay

Screen Roommates

Tier 1 Organism: Novel pathogen

Broad Contact Screening is Recommended

Tier 1 Other Organism or Tier 2 Organism

Screening contacts is generally not recommended, but could be considered in specific instances

Tier 3 Organism

Not on Contact Precautions for entire stay

Screen Roommates

Tier 1 or 2 Organism

Broader Contact Screening is Recommended

Tier 3 Organism

Simulating containment interventions

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

Courtesy of Prabasaj Paul and Rachel Slayton
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
Antimicrobial Resistance Laboratory Network (ARLN)

ARLN Support for Containment - Detection

Hospitals/Clinical Laboratories

Public Health Laboratories
50 States
5 Local Health Departments

- CRE/CRPA isolates
- Species identification
- Confirmatory AST
- Phenotypic screening for carbapenemase production
- Carbapenemase mechanism testing
- mcr-1 testing (some labs)
ARLN Support for Containment – Contact Screening

- Swabs from CP-CRE+ patient contacts
- Swabs positioned regionally for rapid deployment to facilities where screening taking place
- Rapid PCR-based detection from swab (Cepheid)

ARLN Support for Containment – Contact Screening

- Swabs from CP-CRE+ patient contacts
- Report within 1 working day of results
- ≤1 day turnaround
- Provide or request assistance; Initiate investigation

Report within 1 working day of results
ARLN Support for Containment – Detection and Screening for patients with known risk factors

Following increased reports of non-KPC CRE, CDC now also recommends the following for patients with a history of an overnight stay in a healthcare facility (within the last 6 months) outside the United States:

- When a CRE is identified, test to determine the carbapenem resistance mechanism.
- Consider each of the following:
  - Perform rectal screening cultures to detect CRE colonization.
  - Place patients on Contact Precautions while awaiting the results of these screening cultures.

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!

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

The findings and conclusions in this report are those of the authors and do not necessarily represent the official position of the Centers for Disease Control and Prevention.

Summary: Novel MDROs - Resources

- 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

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