Carbapenemase-producing Organisms: Prevention and Response in Healthcare Settings

Cal Ham, MD, MPH
Deputy Lead, Antimicrobial Resistance Team
Prevention and Response Branch
Division of Healthcare Quality Promotion

February 15, 2024

Today's Content

- Background and Epidemiology
- Spread in Healthcare Facilities
- Public Health Solutions
- Collaboration Between Public Health and Healthcare Facilities

Polling Question #1

What type of healthcare setting do you work in?

A. Short-term acute care hospital

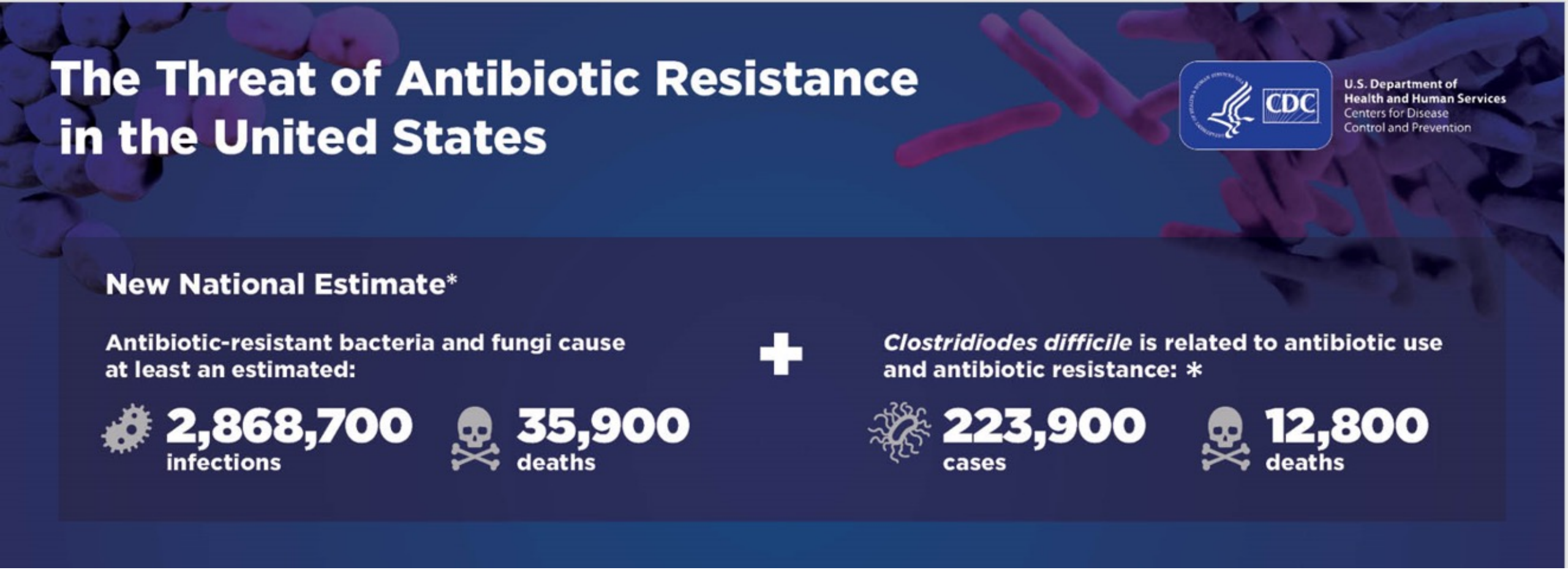
B. Long-term acute care hospital

C. Nursing home

D. Outpatient clinic

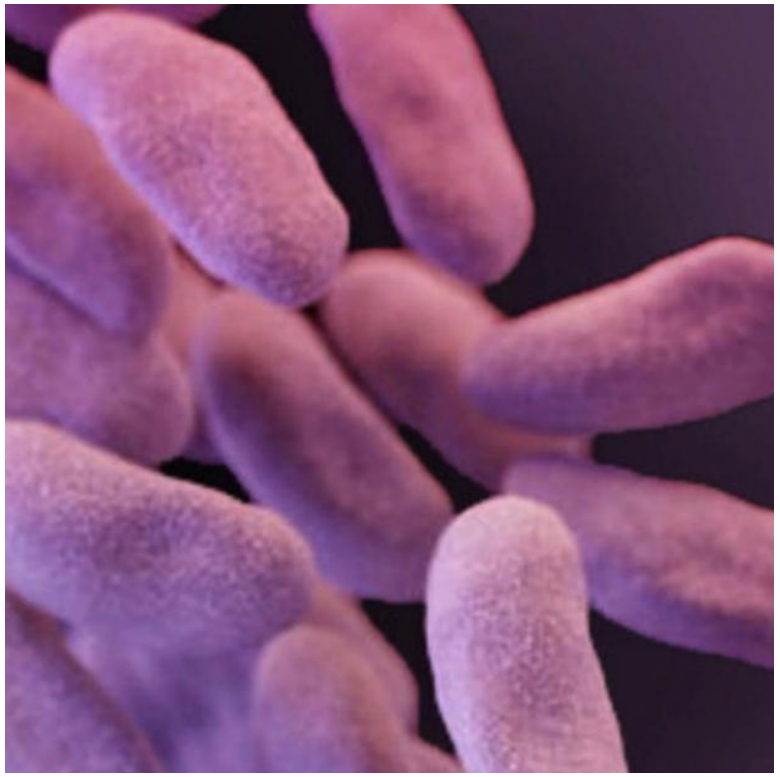
E. Other

Antimicrobial Resistance (AR) is One of the Biggest Challenges of Our Time

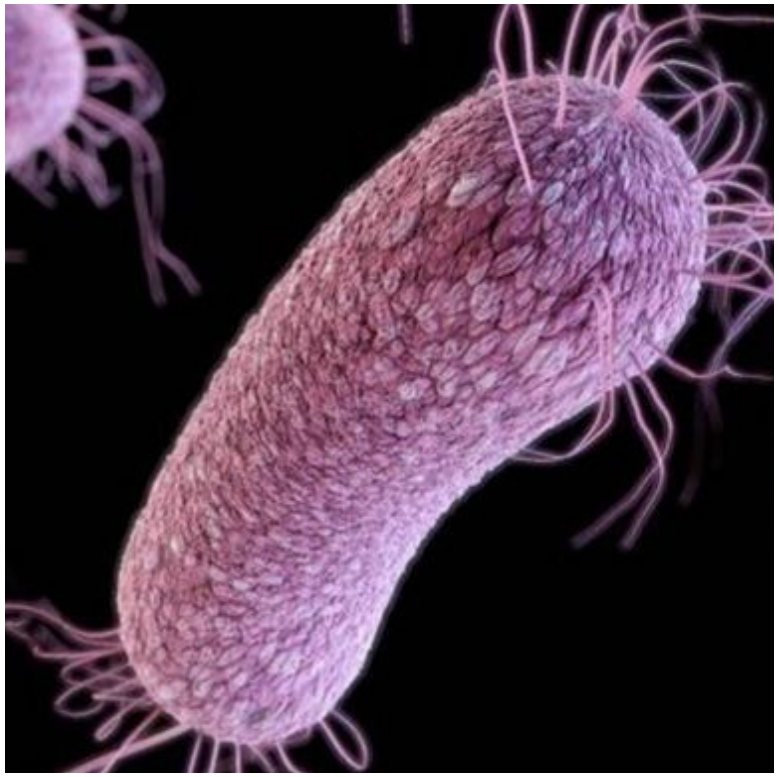


https://www.cdc.gov/drugresistance/pdf/threats-report/2019-ar-threats-report-508.pdf

Emerging Carbapenem-resistant Organisms



Carbapenem-Resistant Enterobacterales (Urgent Threat)



Multidrug-Resistant *Pseudomonas aeruginosa* (Serious Threat)

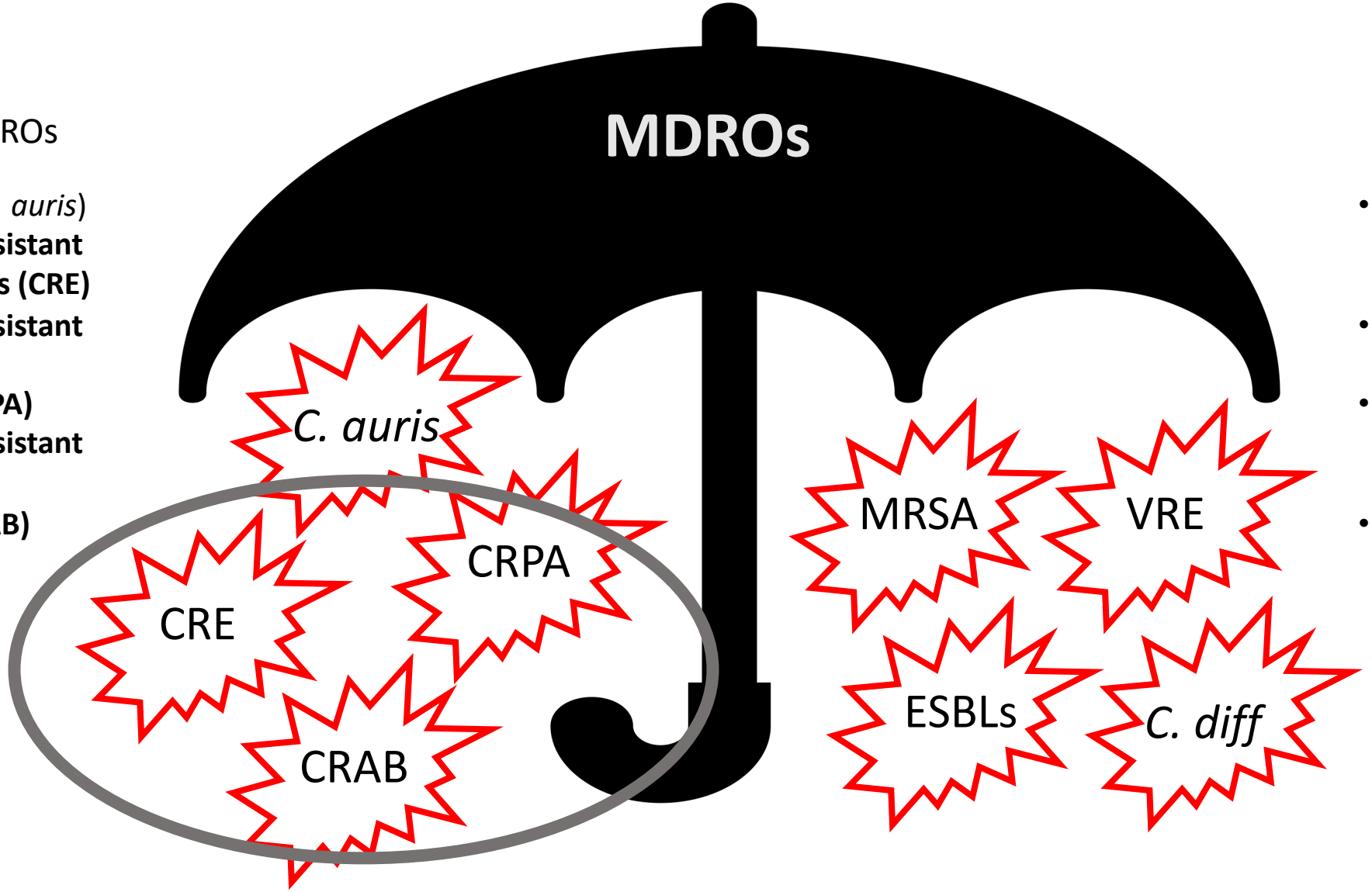
Carbapenem-Resistant *Acinetobacter* (Urgent Threat)

https://www.cdc.gov/drugresistance/pdf/threats-report/2019-ar-threats-report-508.pdf

Multidrug-resistant organisms (MDROs)

Emerging MDROs

- Candida auris (*C. auris*)
- **Carbapenem-resistant Enterobacterales (CRE)**
- **Carbapenem-resistant *Pseudomonas aeruginosa* (CRPA)**
- **Carbapenem-resistant *Acinetobacter baumannii* (CRAB)**



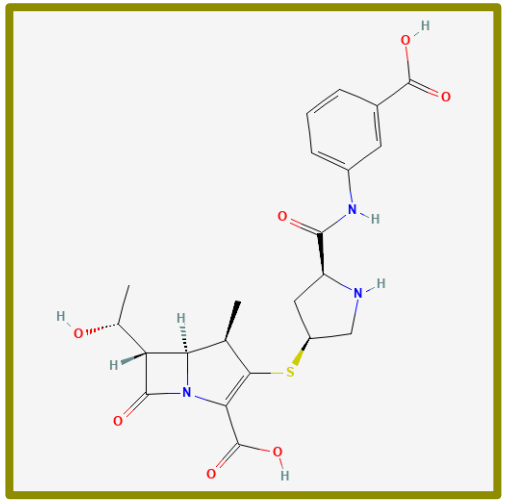
Endemic MDROs

- Methicillin-resistant *Staphylococcus aureus* (MRSA)
- Vancomycin-resistant Enterococci (VRE)
- extended-spectrum beta-lactamases (ESBLs)
- *Clostridioides difficile* (*C. diff*)

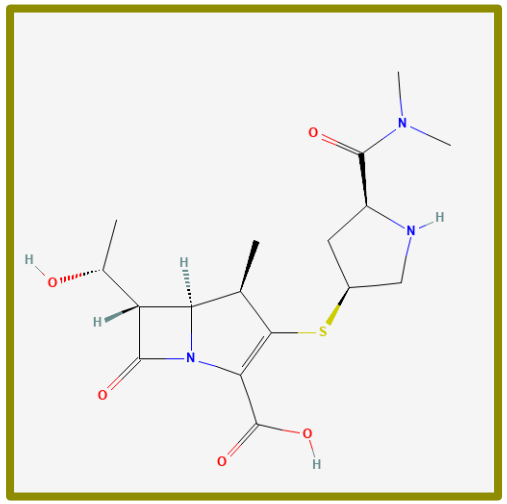
Polling question #2

- What are the names of carbapenem antibiotics?

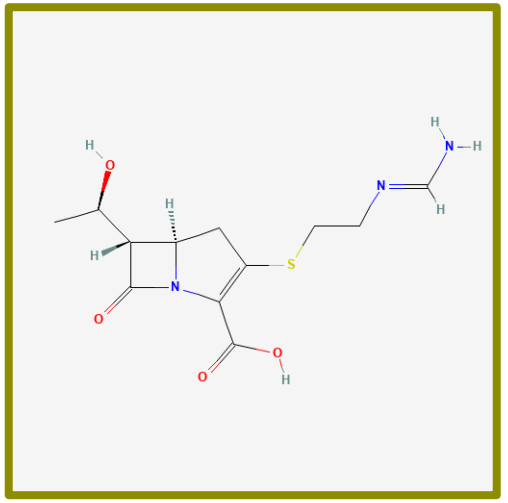
Carbapenem antibiotics



Ertapenem



Meropenem



Imipenem

Ertapenem for Injection

1 gram/vial

For Intravenous or Intramuscular Use
Each vial contains: 1.046 grams ertapenem sodium, equiv. to 1 gram ertapenem.
Prior to Constitution: Store lyophilized powder below 25°C (77°F).

Meropenem for Injection, USP

500 mg per vial

Meropenem Equivalent

For Intravenous Use Only Rx Only

Imipenem and Cilastatin
for Injection, USP (I.V.)

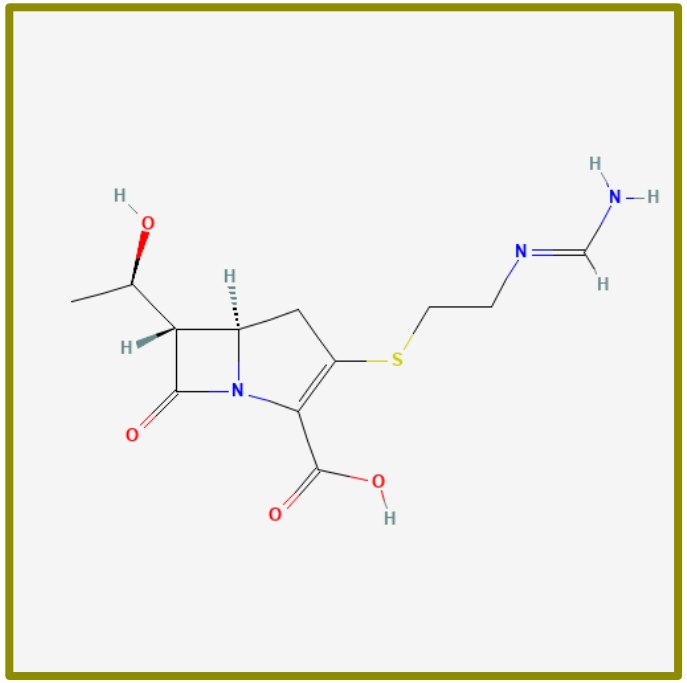
250 mg/ 250 mg* per vial

***Each vial contains:** Imipenem 250 mg (Anhydrous Equivalent) and Cilastatin Sodium equivalent to 250 mg of Cilastatin

CAUTION: SINGLE-DOSE VIAL
NOT FOR DIRECT INFUSION
FOR I.V. USE ONLY **Rx only**

Carbapenem Place in Therapy

- Antibacterial agents with a broad range of antimicrobial activity and a critical place in therapy
- Active against many organisms that are resistant to other β-lactam antibiotics
- Increasingly important due to increase in resistance to other antibiotics
- Relied on to treat sickest patients and most resistant bacteria for over 20 years

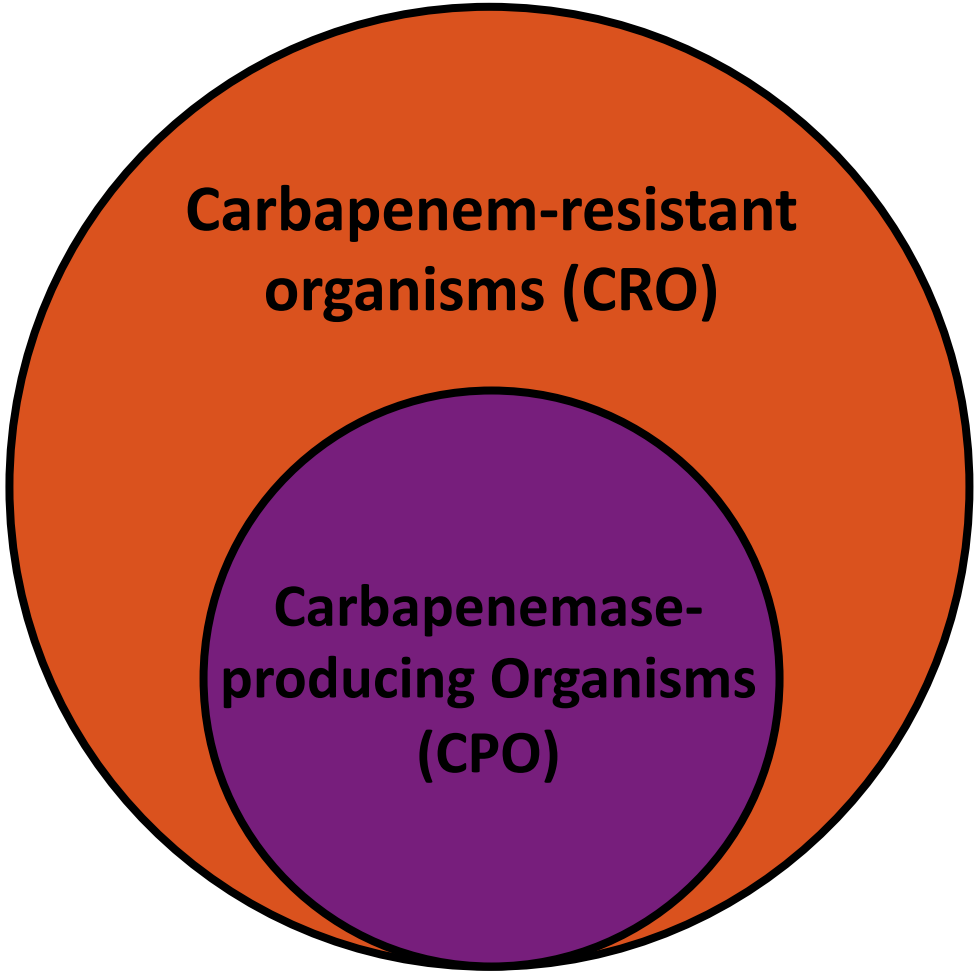


The carbapenem antibiotic imipenem

CRO versus CPO

- **CRO: Carbapenem-resistant Organism**
  - Any organism resistant to carbapenem antibiotics
  - Not dependent on a carbapenemase

- **CPO: Carbapenemase-producing Organism**
  - Any organism that produces a carbapenemase
  - A special subset of Carbapenem-Resistant Organisms



Disclaimer: Figure is intended for illustration purposes only and not proportional to the percent of CROs that are CPOs

Common Carbapenemases

- **KPC** – *Klebsiella pneumoniae* carbapenemase

Common Carbapenemases

- **KPC** – *Klebsiella pneumoniae* carbapenemase
- **NDM** - New Delhi Metallo-β-lactamase

Common Carbapenemases

- **KPC** – *Klebsiella pneumoniae* carbapenemase
- **NDM** - New Delhi Metallo-β-lactamase
- **VIM** - Verona Integron-Encoded Metallo-β-lactamase

Common Carbapenemases

- **KPC** – *Klebsiella pneumoniae* carbapenemase
- **NDM** - New Delhi Metallo-β-lactamase
- **VIM** - Verona Integron-Encoded Metallo-β-lactamase
- **IMP** - active-on-imipenem Metallo-β-lactamase

Common Carbapenemases

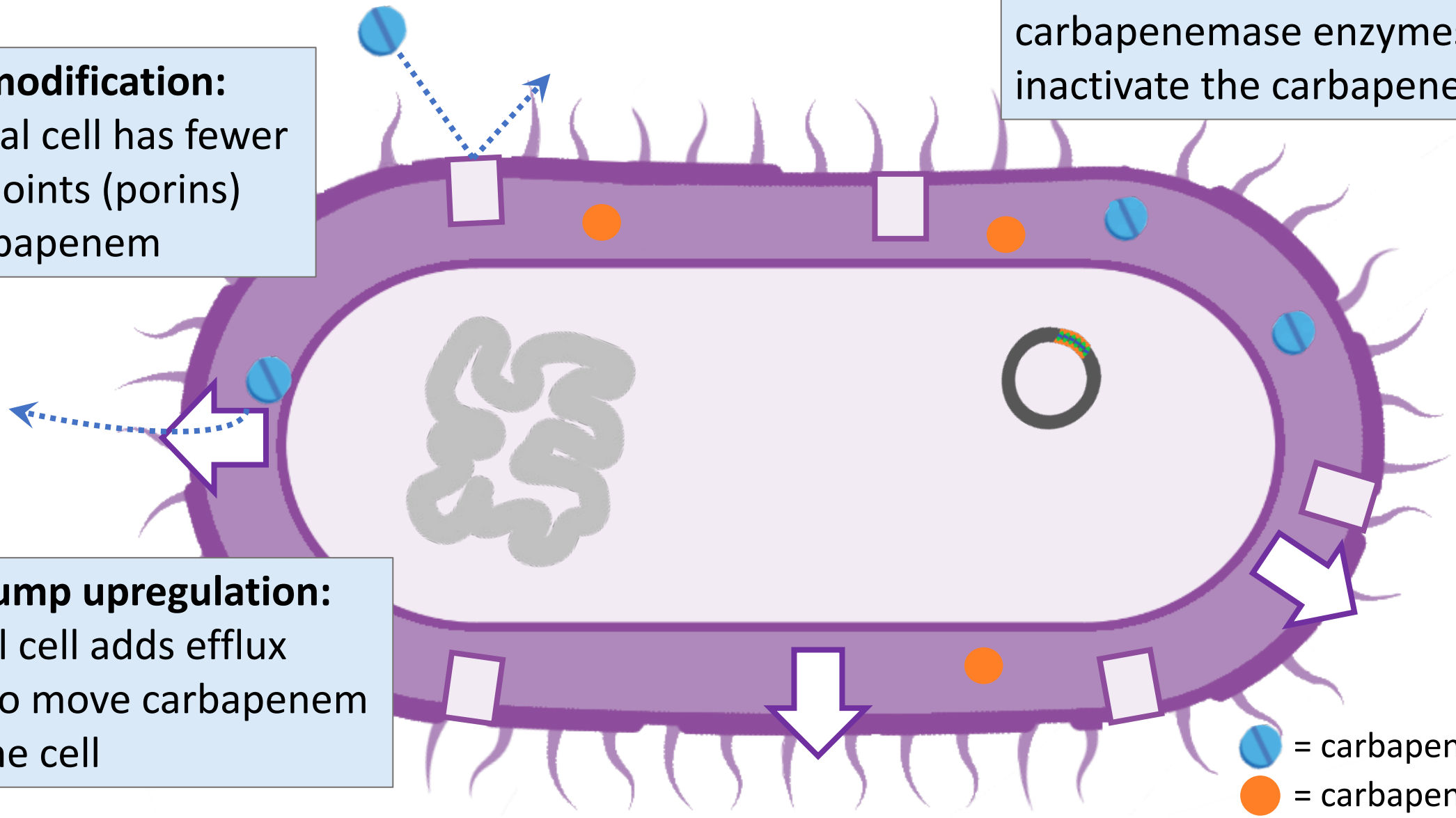
- **KPC** – *Klebsiella pneumoniae* carbapenemase
- **NDM** - New Delhi Metallo-β-lactamase
- **VIM** - Verona Integron-Encoded Metallo-β-lactamase
- **IMP** - active-on-imipenem Metallo-β-lactamase
- **OXA** - Oxacillinase

Pathogens and Resistance

Mechanisms of Carbapenem Resistance

Carbapenemase-producing:
Bacteria makes carbapenemase enzymes to inactivate the carbapenem

Porin modification:
Bacterial cell has fewer entry points (porins) for carbapenem



Efflux pump upregulation:
Bacterial cell adds efflux pumps to move carbapenem out of the cell

= carbapenem
= carbapenemase

Carbapenem resistance mechanisms

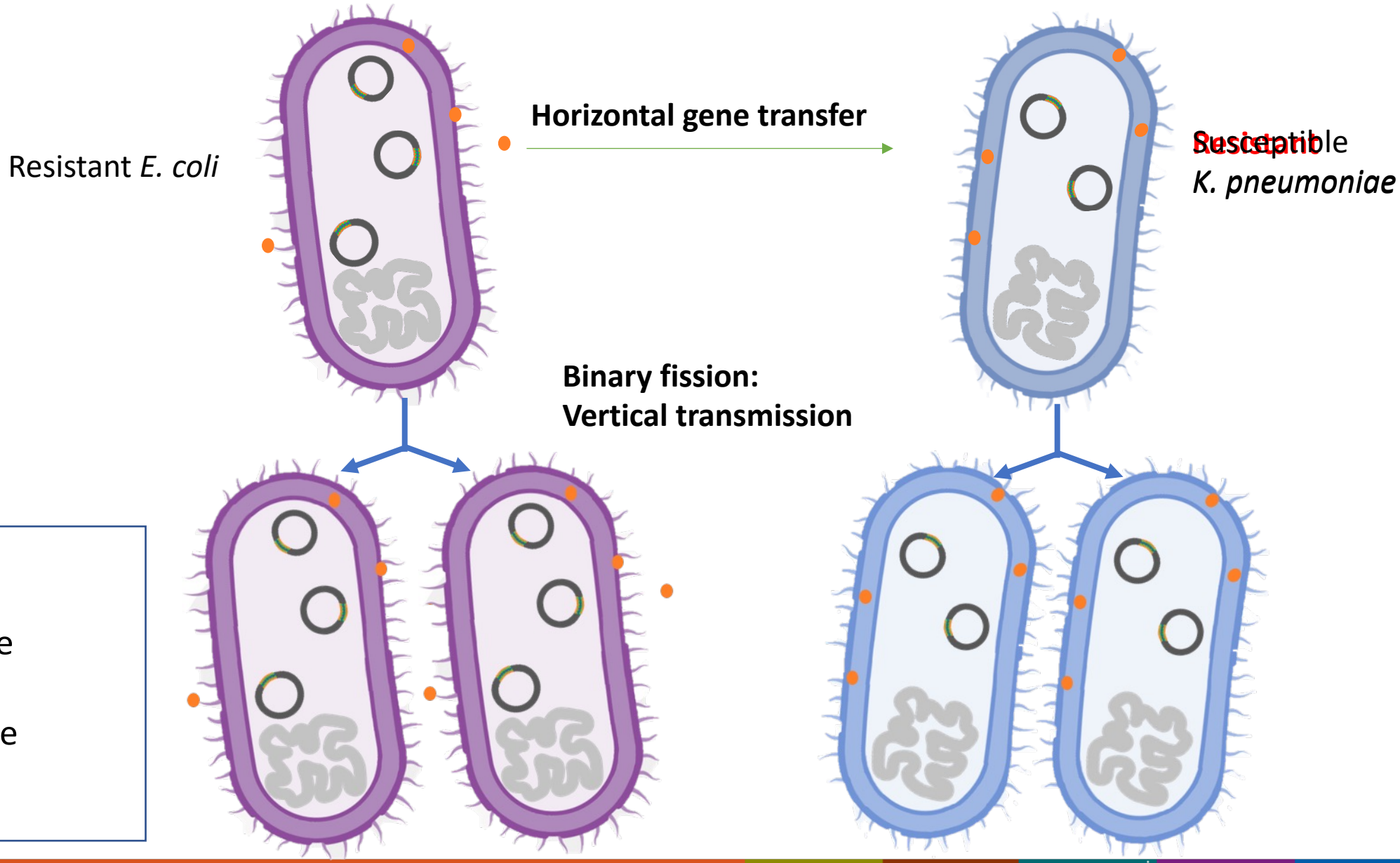
1. Acquired genes and mutations that change the cell to reduce how much carbapenem antibiotic gets in or stays in the bacterial cell

Carbapenem resistance mechanisms

1. Acquired genes and mutations that change the cell to reduce how much carbapenem antibiotic gets in or stays in the bacterial cell

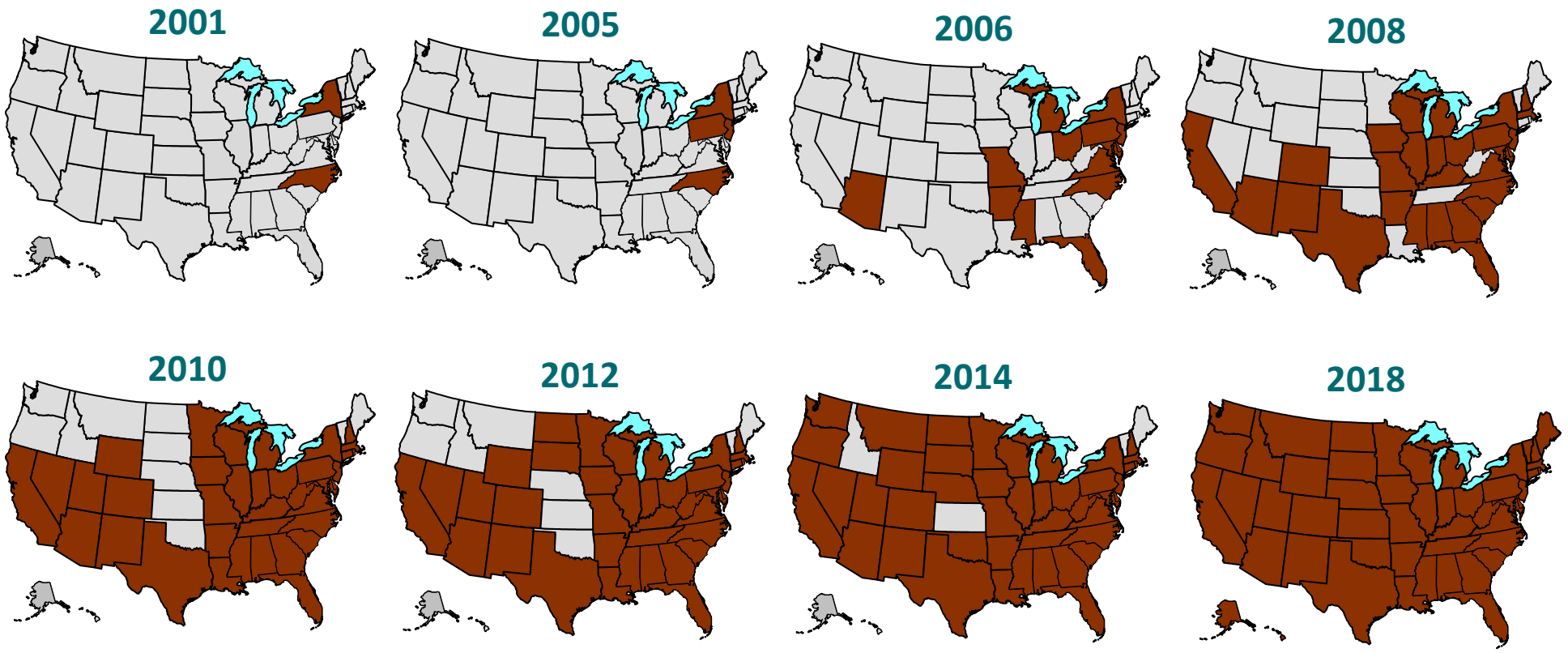
2. Enzymes called carbapenemases:
   - Inactivate carbapenems and other β-lactam antibiotics, including penicillins and cephalosporins
   - Pan-resistant strains have been identified
   - Often encoded on mobile genetic elements (e.g., plasmids)

Plasmid-mediated Resistance



Plasmid-mediated Carbapenem Resistance in U.S.

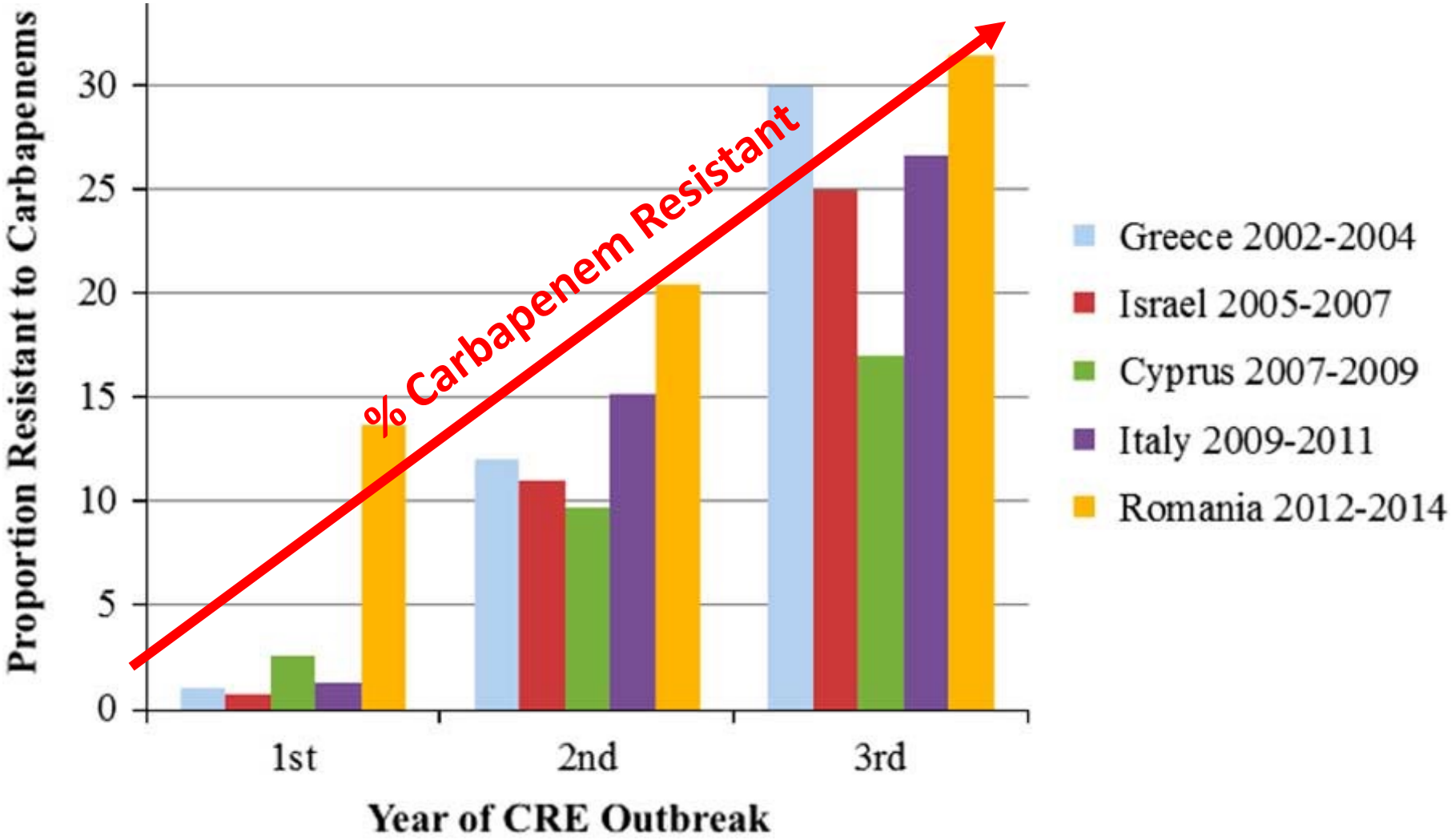
KPC-Carbapenem-Resistant Enterobacterales spread from 2 states in 2001 to 50 states, DC, and PR by 2018



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

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

Important Antibiotics Can Quickly Lose Efficacy

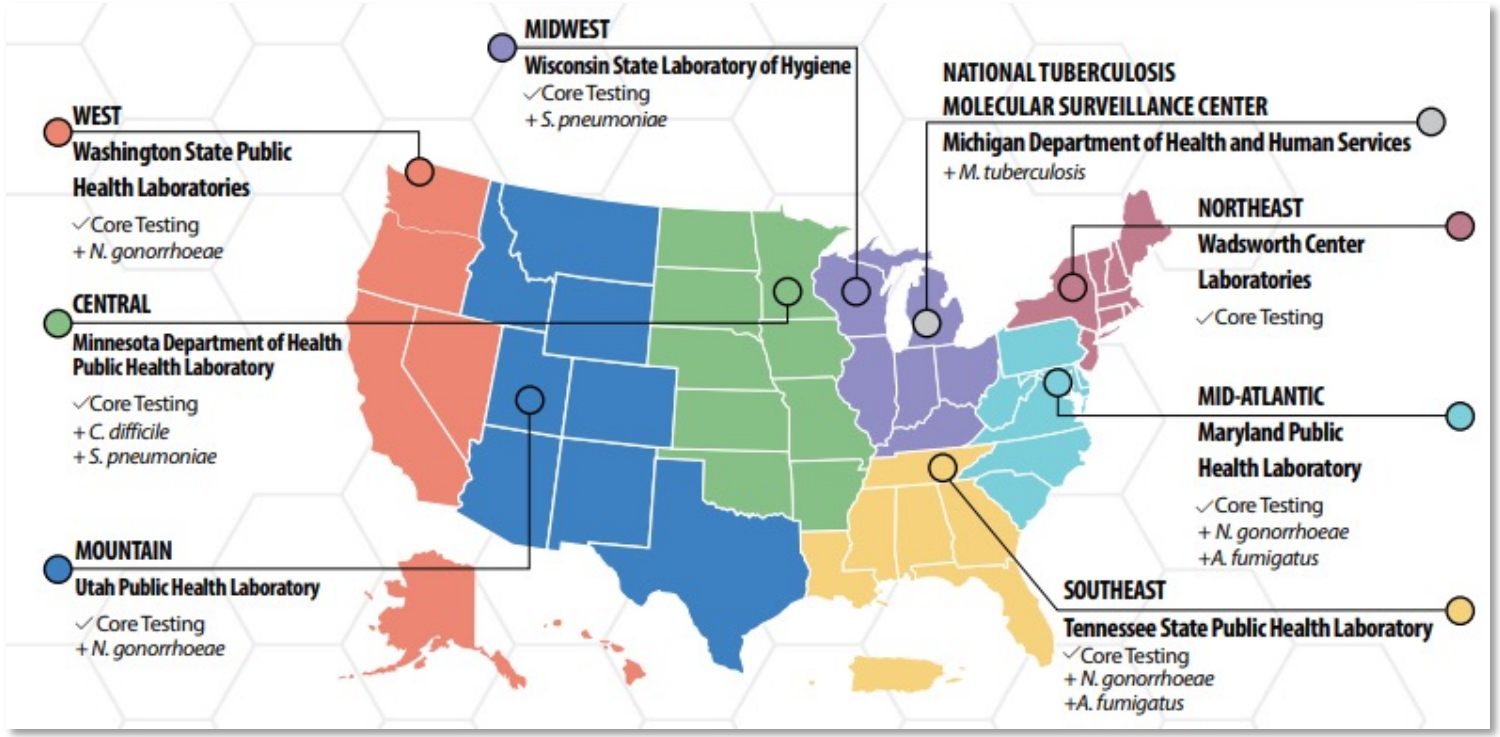


Friedman N, *et. al.* (2017). doi:10.1017/ice.2017.42

Epidemiology of Carbapenemase-producing Organisms in the United States

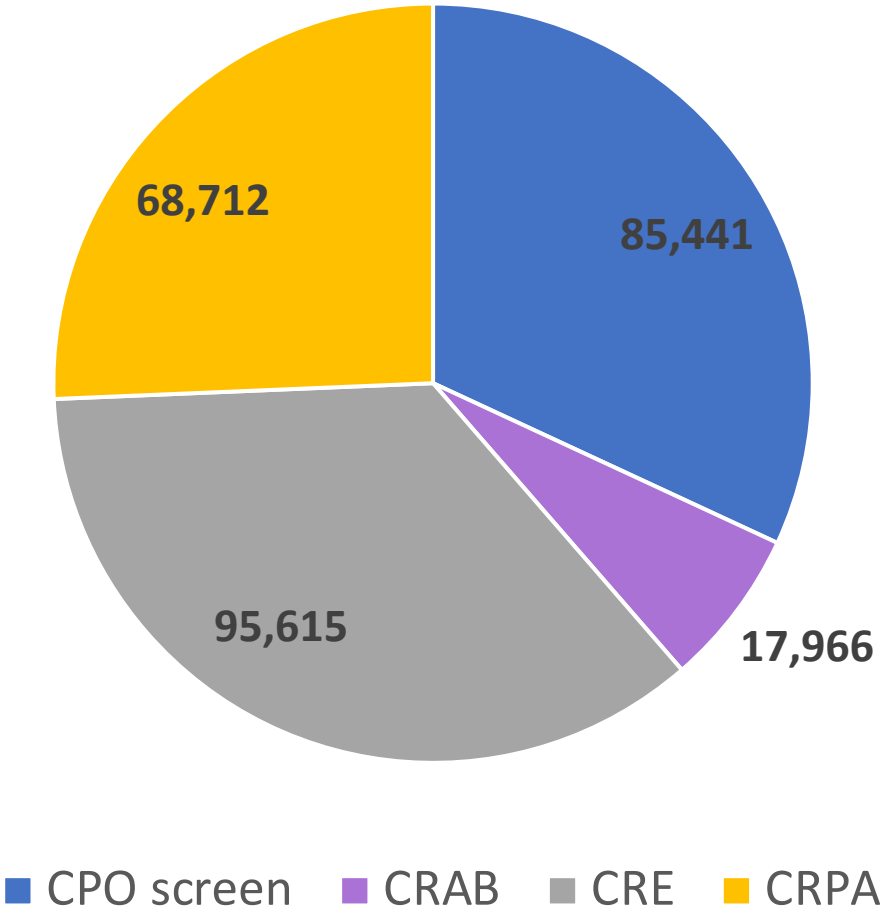
CDC's Antimicrobial Resistance Laboratory Network

- **56 Public Health Labs**
  - CRE, CRPA, CRAB isolate testing
- **45 Public Health Labs**
  - Whole Genome Sequencing
- **7 Regional Labs**
  - CPO colonization screening



https://www.cdc.gov/drugresistance/laboratories.html

Total Specimens Tested—AR Lab Network, 2017–2022



Carbapenemases Vary By Organism

- **Carbapenem-Resistant Enterobacterales (CRE)**
  - ~30% harbor a carbapenemase
  - KPC most common followed by NDM
- **Carbapenem-resistant *Pseudomonas aeruginosa* (CRPA)**
  - ~2% harbor a carbapenemase
  - VIM most common
- **Carbapenem-resistant *Acinetobacter baumannii* (CRAB)**
  - Most harbor a carbapenemase
  - OXA (e.g., OXA-23) most common

Antibiotic Resistance & Patient Safety Portal (AR PSP)

Antibiotic Resistance

Antimicrobial Resistance Laboratory Network

In 2016, CDC established the Antimicrobial Resistance Laboratory Network (AR Lab Network) in every state and in many large cities and U.S. territories. The AR Lab Network provides local experts access to gold-standard public health lab testing—for organisms found in healthcare, food, and the community—to help combat the spread of antibiotic resistance.

In healthcare settings, AR Lab Network testing helps identify and protect patients from some of the most dangerous antibiotic-resistant germs. This includes germs that carry some types of resistance genes. When bacteria carry carbapenemase genes—genetic elements that make enzymes that break down carbapenems (strong antibiotics)—they can cause serious infections with limited treatment options. Knowing when these germs and genes are in their facilities can help healthcare providers take action to keep the threat contained. The AR Lab Network gives experts the data they need to launch into action and stop these dangerous infections at just one case.

Note: The AR Lab Network was not designed to be a traditional surveillance system. Isolates tested are a convenience sample and include clinical, surveillance, and outbreak specimens. Within each state, isolate submissions and testing are determined by state priorities and reporting regulations.

COMPARING CARBAPENEMASE GENE DETECTION ACROSS HIGH-PRIORITY ORGANISMS

The AR Lab Network performs carbapenemase gene testing on three priority healthcare pathogens, plus colonization screening for five targeted carbapenemase genes. The data below capture how frequently a carbapenemase gene was detected in these pathogens and screens. To learn more about each of the four priority areas dedicated to healthcare-associated infections in the AR Lab Network, visit the AR Lab Network data profile associated with each priority area visualization below.

FEATURED ITEMS

September 2023
THE ANTIMICROBIAL RESISTANCE LABORATORY NETWORK: Improving detection of emerging AR threats in healthcare

September 2023
Expanded Antimicrobial Susceptibility Testing for Hard-to-Treat Infections (ExAST): Guiding clinical healthcare decision-making through the AR Lab Network

September 2022
Carbapenem-resistant Enterobacterales (CRE) and *Pseudomonas aeruginosa* (CRPA) carrying multiple targeted carbapenemase genes

Detection of Carbapenemase Genes Among All Isolates Tested by Priority Area

Carbapenem-Resistant Enterobacterales (CRE)

34.74% of CRE submitted to the AR Lab Network from 2017 through 2022 had a targeted carbapenemase gene detected.

Carbapenem-Resistant *Pseudomonas aeruginosa* (CRPA)

2.23% of CRPA submitted to the AR Lab Network from 2017 through 2022 had a targeted carbapenemase gene detected.

Targeted Carbapenemase Genes Detected by Priority Area

Carbapenem-Resistant *Acinetobacter baumannii* (CRAB)

2.45% of CRAB submitted to the AR Lab Network from 2017 through 2022 had a targeted carbapenemase gene detected.

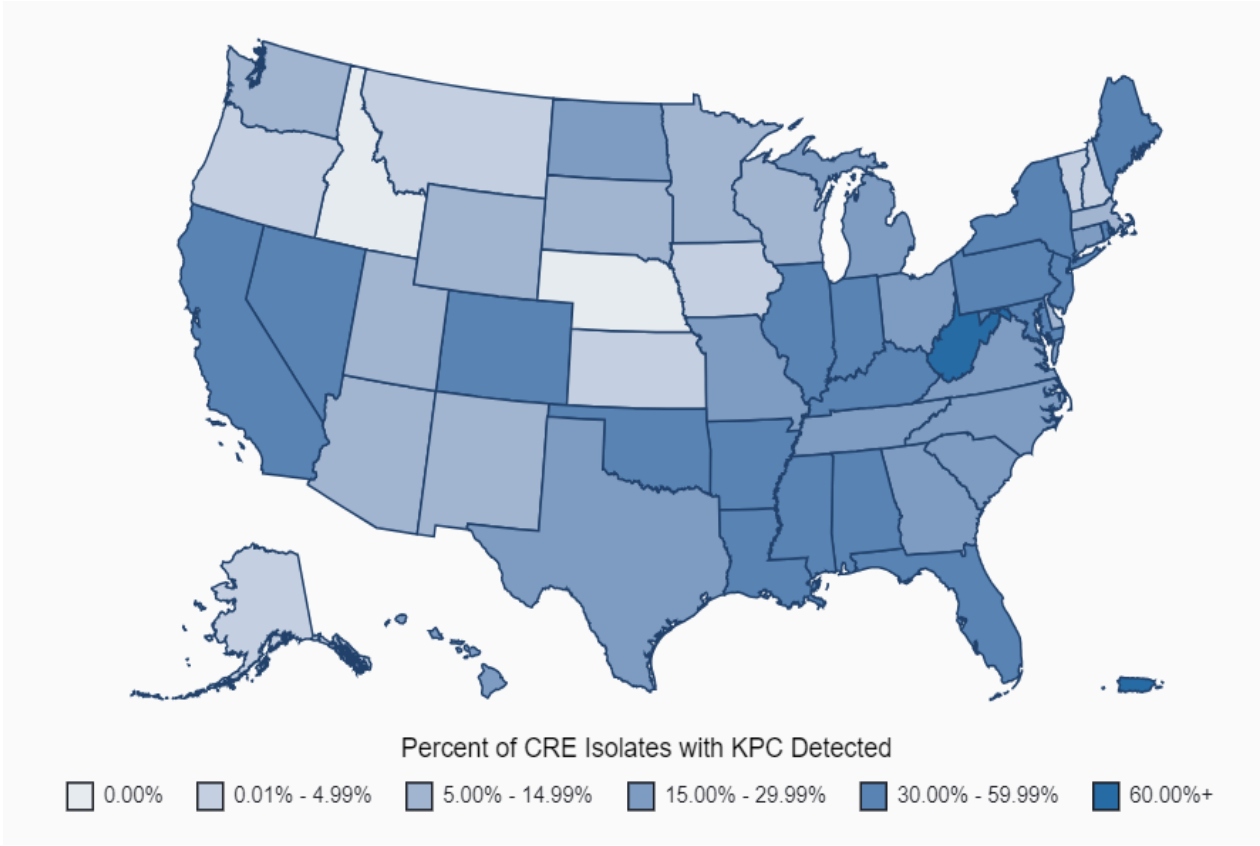
Carbapenemase Gene Screens

5.45% of Colonization Screens submitted to the AR Lab Network from 2017 through 2022 had a targeted carbapenemase gene detected.

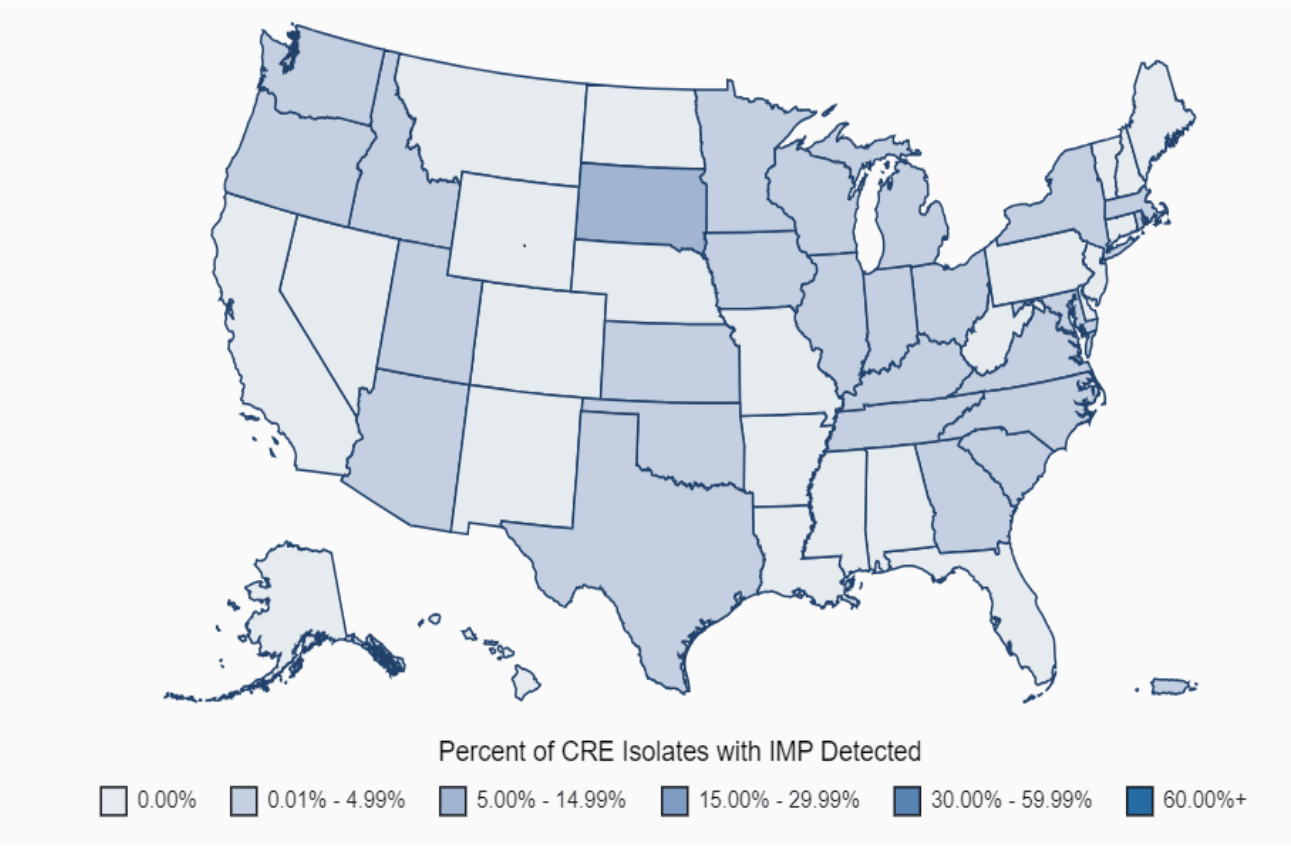
https://arpsp.cdc.gov/profile/antibiotic-resistance?tab=ar-lab-network

Antibiotic Resistance & Patient Safety Portal (AR PSP)

Percent of CRE Tested With KPC Detected, 2022



Percent of CRE Tested With IMP Detected, 2022



https://arpsp.cdc.gov/profile/antibiotic-resistance?tab=ar-lab-network

What Causes Antimicrobial Resistance to Spread In Healthcare Settings?

Common Themes Among Emerging Antimicrobial Resistance Threats

- **Affect the sickest of the sick**
  - Multiple/prolonged healthcare stays
  - Invasive medical devices
  - Ventilator-dependent
  - Recent antibiotic treatment
- **Exploit gaps in infection control**
- **Spreads silently**

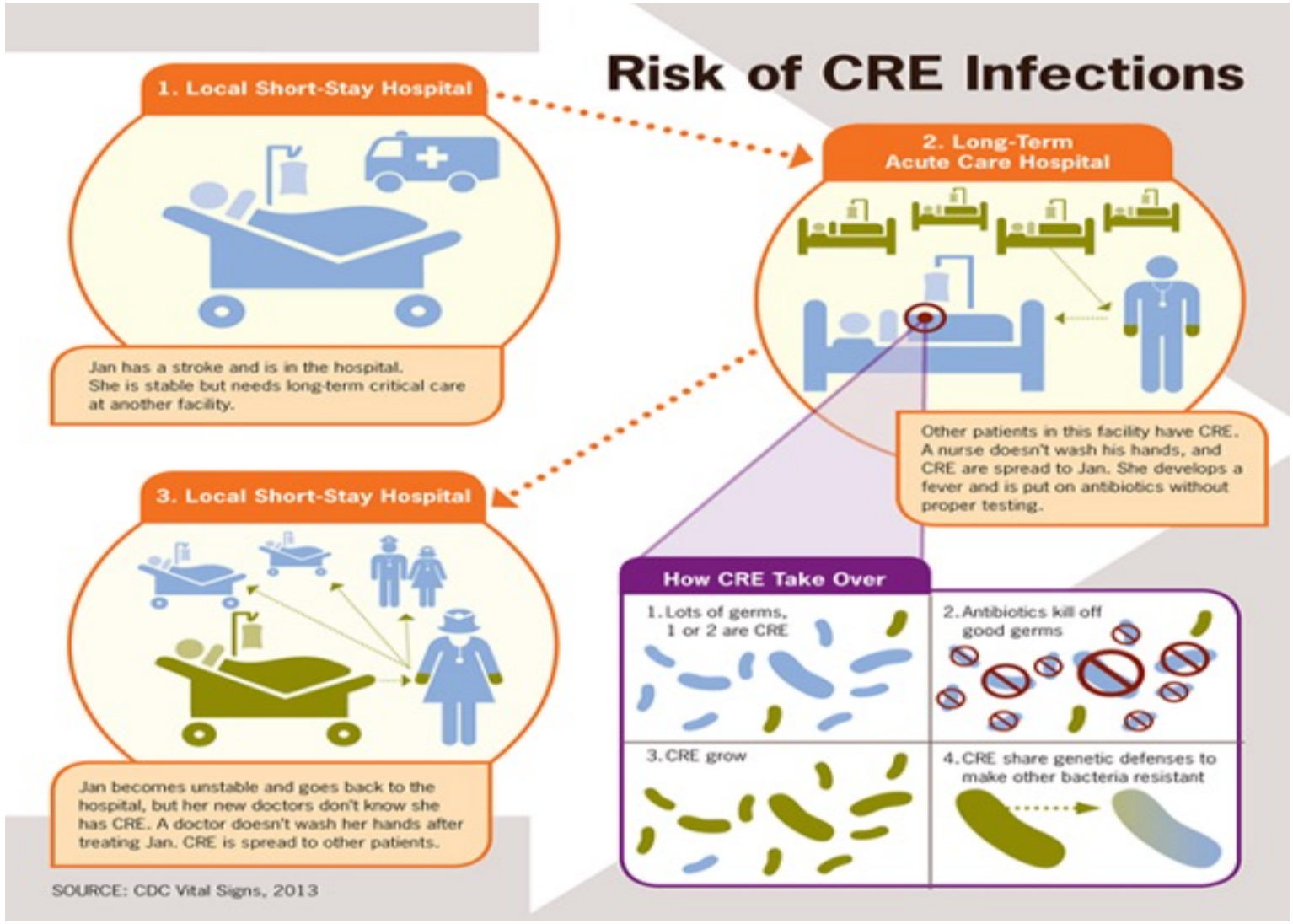
Poll question #3

- **What types of healthcare facilities have carbapenemase-producing organism outbreaks been identified in?**
  A. Acute care hospitals
  B. Long-term acute care hospitals
  C. Skilled nursing facilities, including ventilator-capable skilled nursing facilities
  D. All of the above

Poll question #3

- **What types of healthcare facilities have carbapenemase-producing organism outbreaks been identified in?**
  A. Acute care hospitals
  B. Long-term acute care hospitals
  C. Skilled nursing facilities, including ventilator-capable skilled nursing facilities
  D. **All of the above**

How Antibiotic Resistant Pathogens Spread



Reservoir of colonized and infected patients

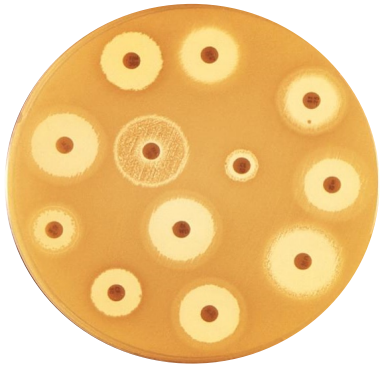
Transmission via HCP hands or contaminated surfaces or equipment

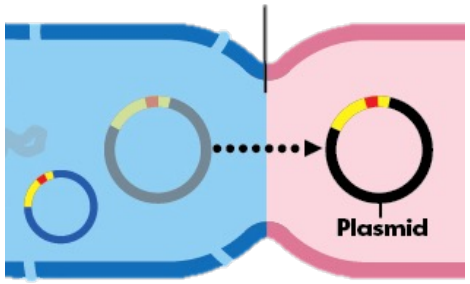
Gaps in communicating status at transfer and in adhering to core infection control practices

Patients at risk of acquiring CRE due to antibiotic exposures and indwelling medical devices

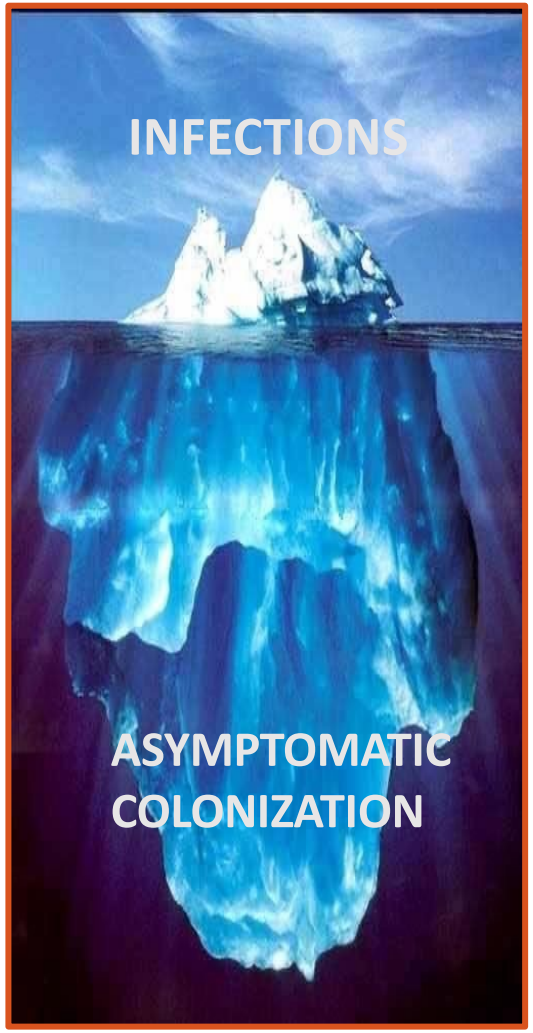
Modifiable Factors that Drive Spread of AR in Healthcare

Identification Challenges

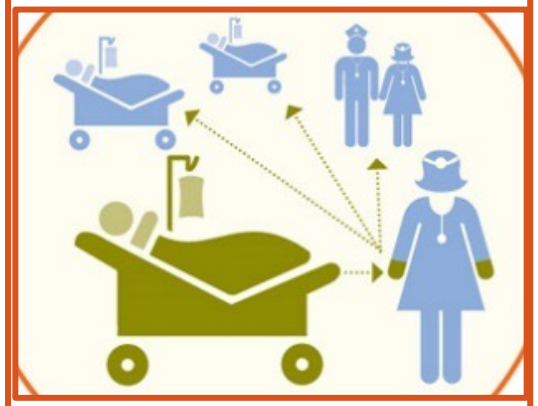




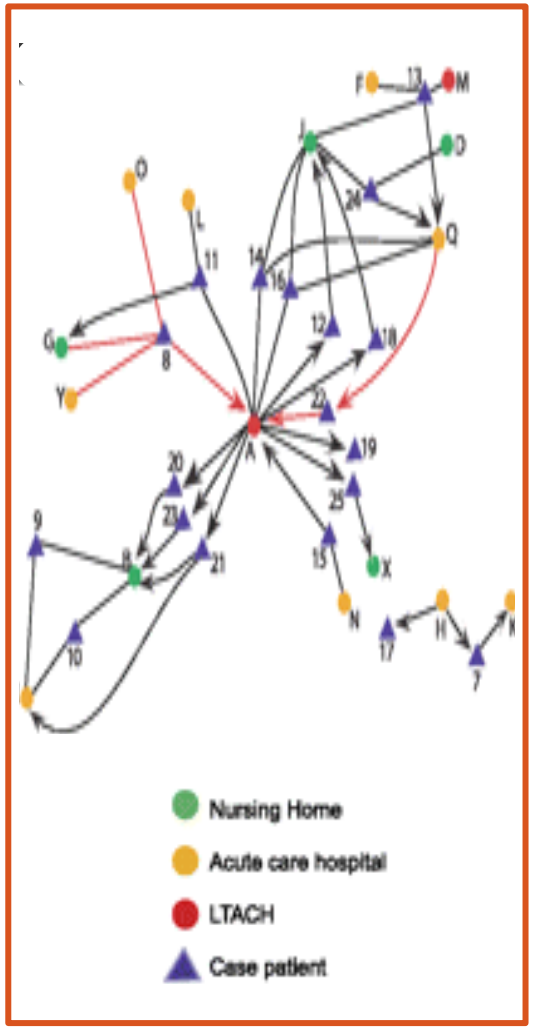
Under Detection



Infection Control Gaps



Interfacility Communication Gaps



Identification Challenges at Clinical Laboratories: Carbapenemase-Producing Organisms

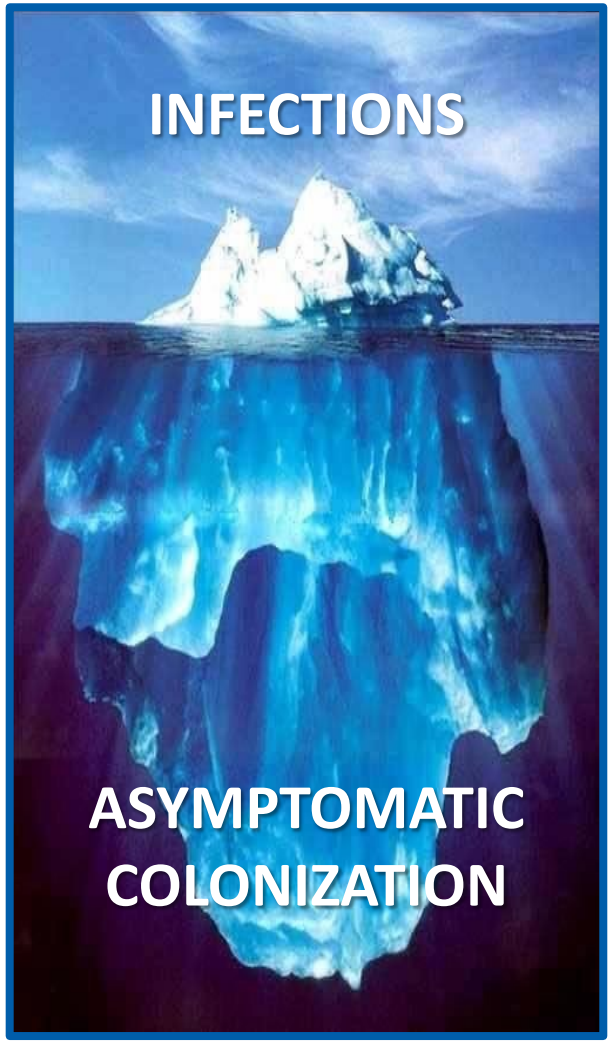
- **Identifying genotype, not just carbapenem resistance phenotype**
- **Clinical laboratories may not have mechanism testing available**
  - Available through CDC's Antimicrobial Resistance Laboratory Network
- **Time needed to develop tests once new resistance detected**

Under Detection of Colonization

Infections are only a fraction of the total burden of AR

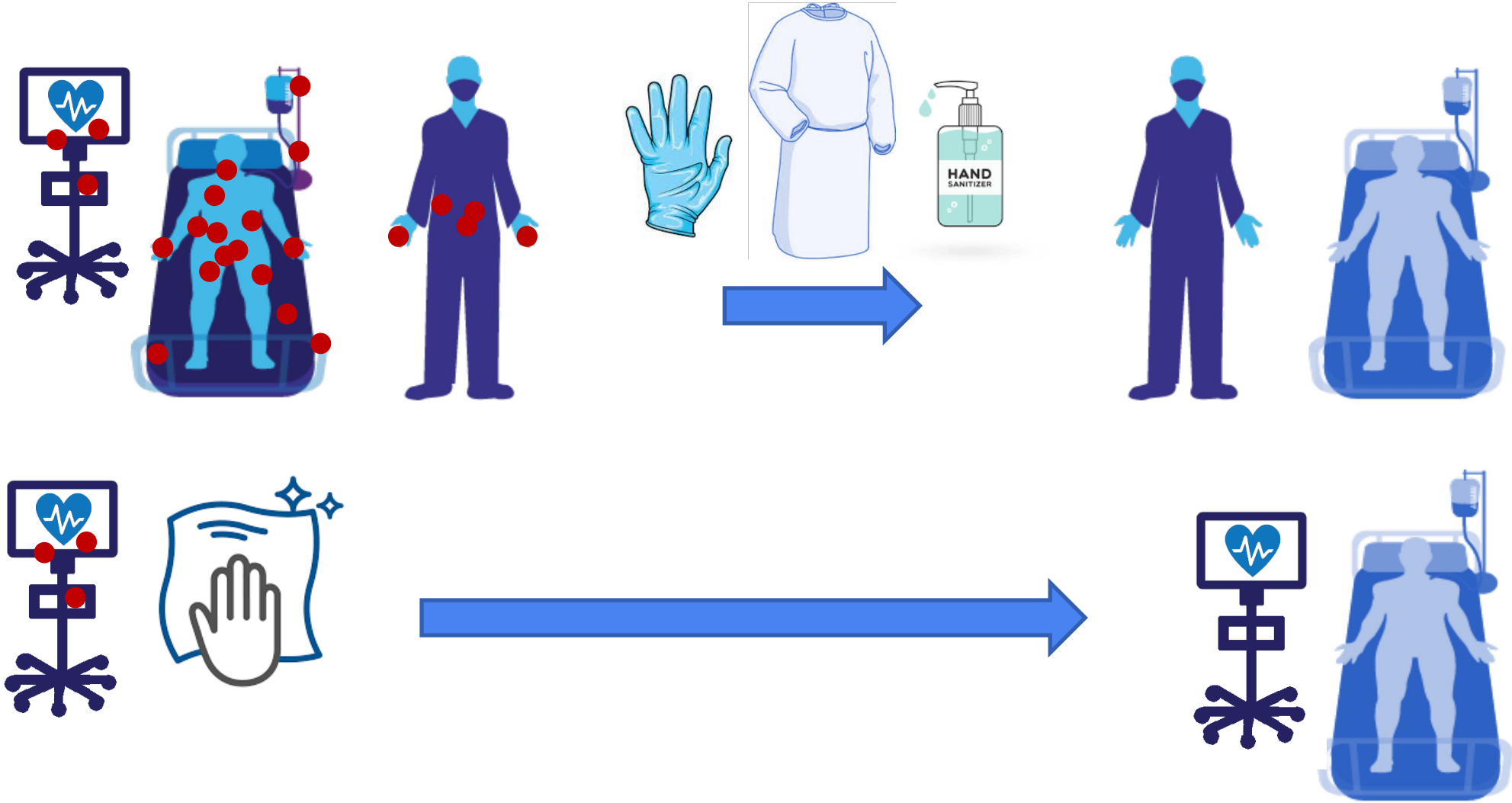
Colonized Patients

- Carry an MDRO on or in their body without showing signs or symptoms of infection
  - Prolonged, no decolonization methods
- Source of transmission and risk for infections
- Can be identified with screening tests
  - Historically, limited availability, expensive



Infection Control Challenges

Strong Infection Prevention and Control (IPC) Practices Can Reduce Transmission

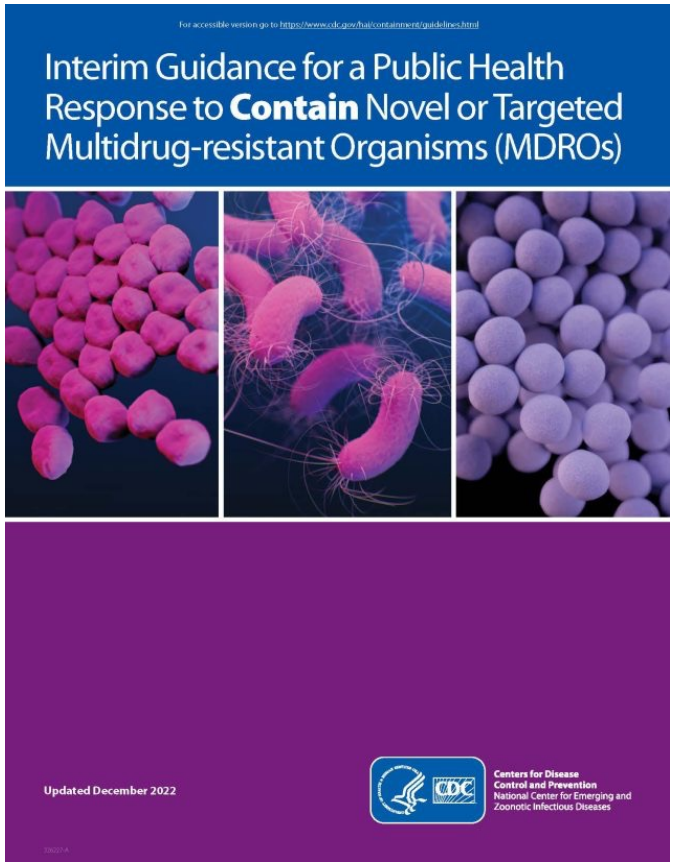


Interfacility Communication

- Intricate patient sharing networks mean that healthcare facilities are interconnected
- What a facility does or does not do can impact other facilities across the region
  - Detection
  - Infection control
  - Communication when transferring patients

Public Health Solutions

CDC's MDRO Containment And Prevention Strategies



https://www.cdc.gov/hai/mdro-guides/index.html

Rapid Response to Rare Resistance: Containment Strategy

Goal: identify new resistance and control transmission

- Aggressive, systematic response to ≥1 case of targeted organisms – responding at first spark to stop transmission 🔥
- Slows but does not stop spread

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

Containment Response Elements

		Tier 1	Tier 2	Tier 3	Tier 4
Healthcare investigation	Review the patient's healthcare exposures prior to and after the positive culture	**30 days**	**30 days**	**Current admission/ sometimes prior admission**	**Prioritize Prevention; Containment principles generally do not apply**
Contact investigation	Screen healthcare roommates				
	Screen additional healthcare contacts				
	Screen household contacts				
	Screen healthcare personnel				
If transmission identified	Repeat point prevalence survey (PPS) at regular intervals if cases identified*				
	Evaluate potential for spread to linked facilities				
Clinical surveillance	Prospective laboratory surveillance				
	Retrospective laboratory				
Environmental cultures	Environmental Sampling				
Ensure adherence to IPC	Infection control assessment w/ observations of practice				

*Periodic (e.g., every two weeks) response-driven PPS should be conducted until transmission is controlled, defined as two consecutive PPS with no new cases identified or, in facilities with high colonization pressure, substantially decreased transmission. If high levels of transmission persist across multiple point prevalence surveys in long term care settings, consider increasing the interval between surveys or temporarily pausing them while reassessing infection control and implementing interventions.

	ALWAYS
	USUALLY
	SOMETIMES
	RARELY

CDC's MDRO Prevention Guidance

- Developed for state, local, territorial, and tribal health departments working in close collaboration with partners
- Support development, implementation, and coordination of activities designed to prevent the spread of novel and targeted MDROs within a jurisdiction
- Intended to guide long-term, multi-year endeavors
- Applies at all stages of spread, from pre-introduction to endemicity

Prevention Guidance

Section I. Preparing to Implement an MDRO Prevention Plan	• Determining the MDRO(s) that will be the focus • Risk stratifying healthcare facilities within the jurisdiction • Prioritizing where to begin implementation • Evaluating jurisdictional laboratory capacity and surveillance • Defining outcome and process measures
Section II. Elements of an MDRO Prevention Plan	• Providing education • Improving general IPC practices • Detecting colonized individuals • Facilitating communication

Collaboration Between Public Health and Healthcare Facilities

Key Principles of Combatting MDRO Spread In Healthcare Settings

1. **Identify as many people as possible who are infected or colonized with MDROs**

2. **Have good baseline IPC practices and use recommended infection control practices for people with MDROs in healthcare facilities**

3. **Communicate at transfer to other facilities which people have MDRO(s)**

Identification of Novel or Targeted MDROs

- **Report and submit MDRO isolates to Public Health**
  - May include CRE, CRAB and CRPA depending on your jurisdiction

Identification of Novel or Targeted MDROs

- **Colonization screening: Using a swab to sample body sites to determine if that person has the MDRO of interest (i.e., colonized but not infected)**
  - Point prevalence survey
  - Admission screening
  - Discharge screening

- **Colonization screening is available free of charge through CDC's AR Lab Network**

IPC Practices

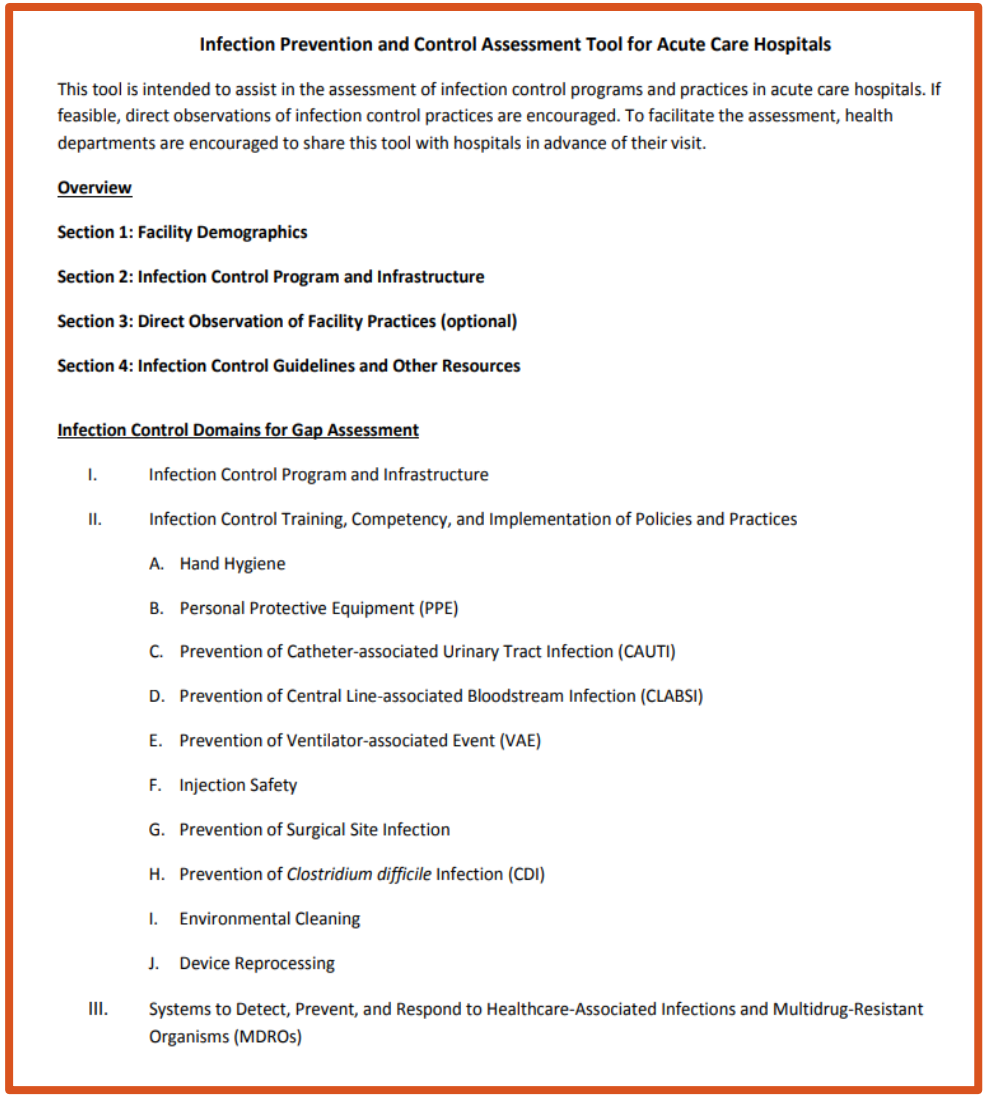
- **Identify where gaps in your IPC practices exist and work on them before you have a problem**

- **Four core IPC practices to limit the spread of MDROs**
  - Hand hygiene
  - Standard Precautions
  - Contact Precautions for CPO carriers
    - Enhanced Barrier Precautions may be used in nursing homes
  - Environmental cleaning and disinfection
    - Sink hygiene: https://www.cdc.gov/hai/prevent/environment/water.html

CDC Infection Control Assessment and Response (ICAR) Tools

- Standardized tools to assess infection prevention programs

- Designed for use by health departments
  - Non-punitive
  - Used for prevention or response



Infection Prevention and Control Assessment Tool for Acute Care Hospitals

This tool is intended to assist in the assessment of infection control programs and practices in acute care hospitals. If feasible, direct observations of infection control practices are encouraged. To facilitate the assessment, health departments are encouraged to share this tool with hospitals in advance of their visit.

Overview

Section 1: Facility Demographics

Section 2: Infection Control Program and Infrastructure

Section 3: Direct Observation of Facility Practices (optional)

Section 4: Infection Control Guidelines and Other Resources

Infection Control Domains for Gap Assessment

I. Infection Control Program and Infrastructure

II. Infection Control Training, Competency, and Implementation of Policies and Practices

- A. Hand Hygiene
- B. Personal Protective Equipment (PPE)
- C. Prevention of Catheter-associated Urinary Tract Infection (CAUTI)
- D. Prevention of Central Line-associated Bloodstream Infection (CLABSI)
- E. Prevention of Ventilator-associated Event (VAE)
- F. Injection Safety
- G. Prevention of Surgical Site Infection
- H. Prevention of *Clostridium difficile* Infection (CDI)
- I. Environmental Cleaning
- J. Device Reprocessing

III. Systems to Detect, Prevent, and Respond to Healthcare-Associated Infections and Multidrug-Resistant Organisms (MDROs)

Infection Control Assessment Tools | HAI | CDC: https://www.cdc.gov/hai/prevent/infection-control-assessment-tools.html

Polling Question #4

Have you participated in an ICAR at your facility?

A. Yes

B. No

Interfacility Communication

- Assess your current communication practices
- What can be done to improve them as individual facilities?
- What can be done to improve them as a region of facilities?
- CDC interfacility transfer form: https://www.cdc.gov/hai/pdfs/toolkits/Interfacility-IC-Transfer-Form-508.pdf

Summary

- Many of the most concerning MDROs are primarily associated with healthcare settings
- A single resistance phenotype can have multiple underlying mechanisms that vary in risk of spread
- Healthcare facilities are connected: what you do in your facility has implications for the entire region
- Improving identification of CPOs, detection of colonized individuals, improved IPC practices, and communication across healthcare facilities can slow spread of emerging resistance

Four Things You Can Do At Your Facility

- Understand your clinical laboratory's ability to identify CRE, CRAB, and CRPA using current CLSI breakpoints
- Understand the availability of carbapenemase mechanism testing at your clinical laboratory or State Public Health Laboratory
- Connect with your State Public Health Department to understand the local epidemiology of CPOs
- Ensure that when CRE, CRAB, or CRPA are identified that appropriate IPC measures are implemented

Resources

https://www.cdc.gov/hai/mdro-guides/index.html

https://www.cdc.gov/hai/organisms/cre/cre-clinicians.html

https://www.cdc.gov/hai/organisms/cre/cre-facilities.html

https://www.cdc.gov/hai/containment/guidelines.html

https://www.cdc.gov/hai/mdro-guides/prevention-strategy.html

https://www.cdc.gov/hai/prevent/environment/water.html

Resources

https://www.cdc.gov/infectioncontrol/guidelines/core-practices/index.html

https://www.cdc.gov/hai/containment/PPE-Nursing-Homes.html

https://www.cdc.gov/infectioncontrol/basics/transmission-based-precautions.html

https://www.cdc.gov/handhygiene/index.html

https://www.who.int/teams/integrated-health-services/infection-prevention-control/hand-hygiene/tools-and-resources

https://www.cdc.gov/infectioncontrol/projectfirstline/index.html

Thank you!

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

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