Overview of Carbapenem-Resistant Organisms

Sam Cincotta, PharmD, MSc
Antimicrobial Resistance Team
Division of Healthcare Quality and Promotion
Centers for Disease Control and Prevention

Battling multidrug-resistant organisms (MDROs) Spread in Three Steps

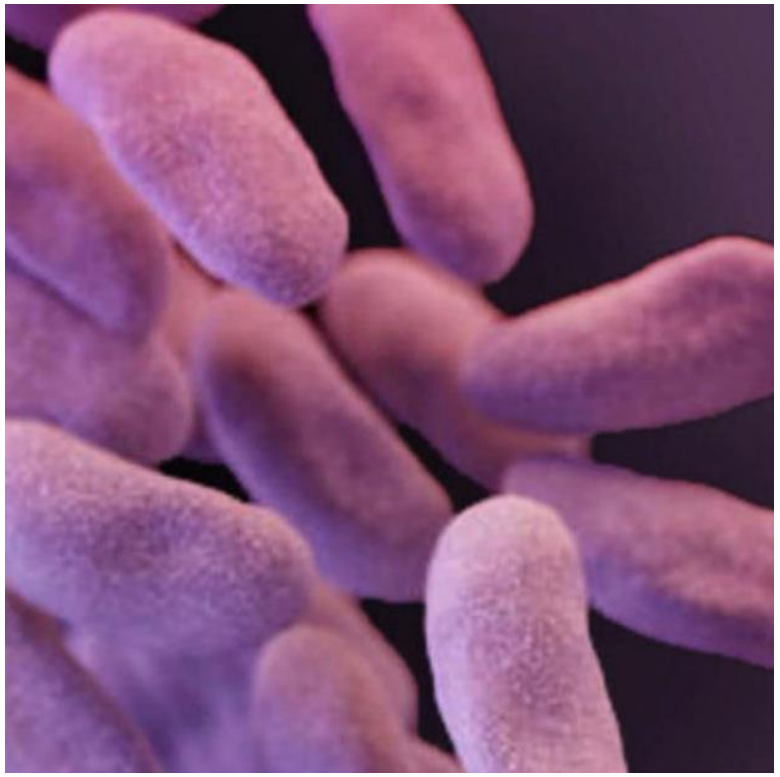
From Previous Webinars

1. Identify as many people as possible who are infected or colonized with MDROs in a region

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

3. Communicate to other facilities about people with known MDROs at transfer

Emerging Carbapenem-Resistant Organisms



Carbapenem-Resistant Enterobacterales

Multidrug-Resistant *Pseudomonas aeruginosa*

Carbapenem-Resistant *Acinetobacter*

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

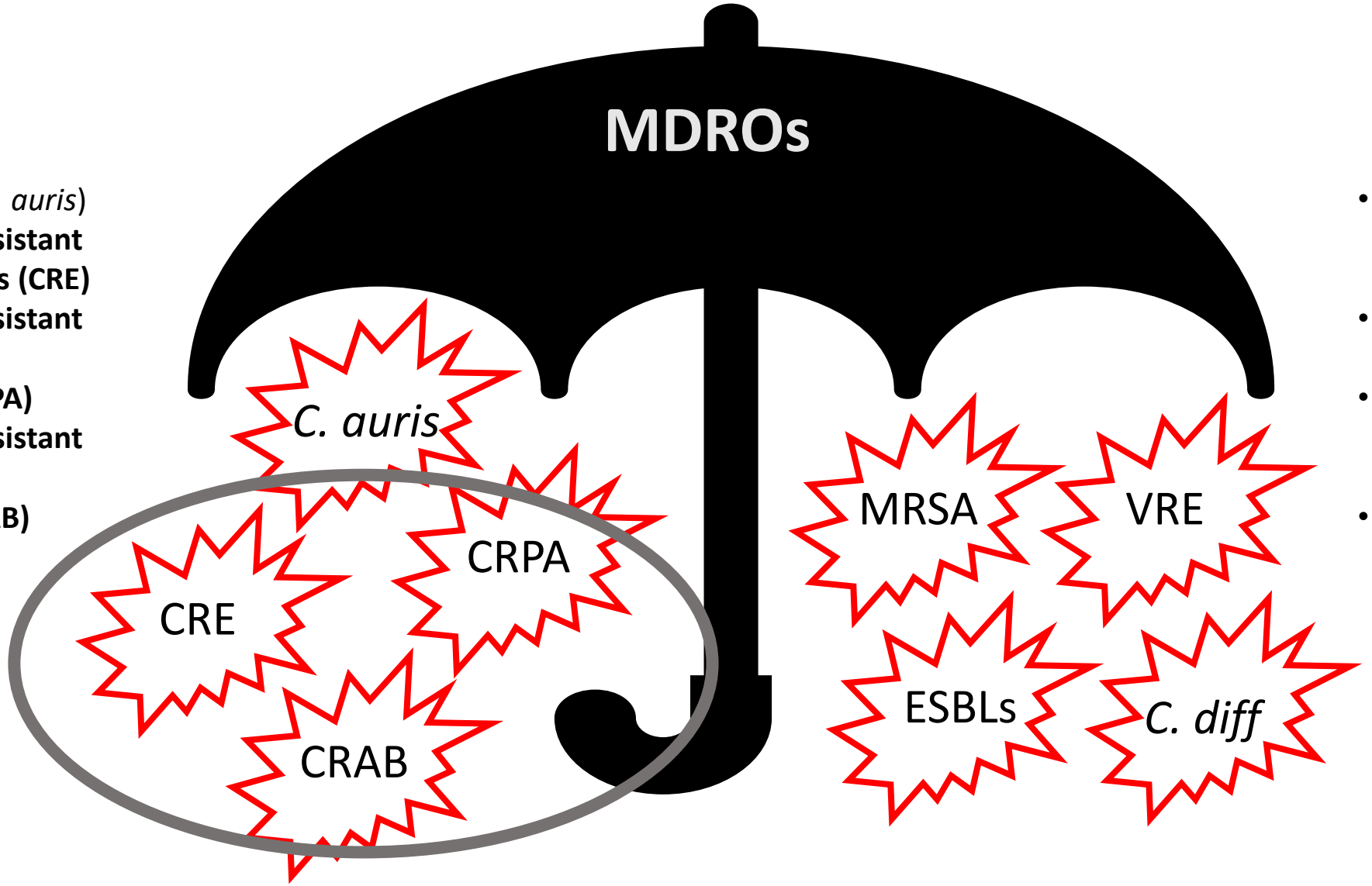
Objectives of Today's Webinar

- Define common abbreviations
- Describe carbapenem antibiotics
- Describe types of pathogens and resistance mechanisms
- Describe laboratory testing of carbapenem-resistant organisms

Attack of the abbreviations!

Multidrug-resistant organisms

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

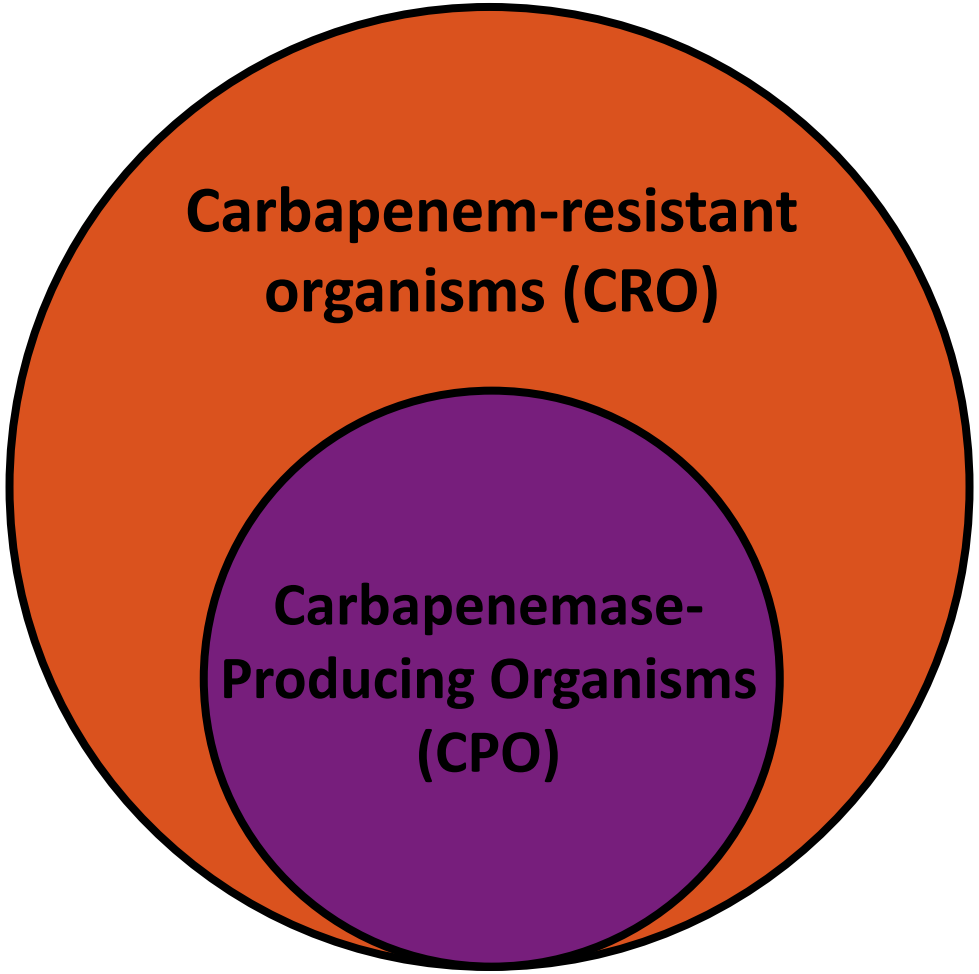


- Methicillin-resistant Staphylococcus aureus (MRSA)
- Vancomycin-resistant Enterococci (VRE)
- extended-spectrum beta-lactamases (ESBLs)
- Clostridioides difficile (*C. Diff*)

CRO versus CPO

- **CRO: Carbapenem-Resistant Organism**
  - Any organism resistant to carbapenem antibiotics regardless of having a carbapenemase or not

- **CPO: Carbapenemase-Producing Organism**
  - Any organism that produces a carbapenemase making them resistant to carbapenem antibiotics
  - A special subset of Carbapenem-Resistant Organisms



CRO versus CPO

- **Carbapenem-Resistant Organisms (CRO)**
  - CRAB: Carbapenem-resistant *Acinetobacter baumannii*
  - CRPA: Carbapenem-resistant *Pseudomonas aeruginosa*
  - CRE: Carbapenem-resistant Enterobacterales
    - Examples: *Escherichia coli* (E. coli) and *Klebsiella pneumoniae*

- **Carbapenemase Producing Organisms (CPO)**
  - CP-CRAB: Carbapenemase-Producing Carbapenem-resistant *Acinetobacter baumannii*
  - CP-CRPA: Carbapenemase-Producing Carbapenem-resistant *Pseudomonas aeruginosa*
  - CP-CRE: Carbapenemase-Producing Carbapenem-resistant Enterobacterales

Common Carbapenemases

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

Highly drug-resistant

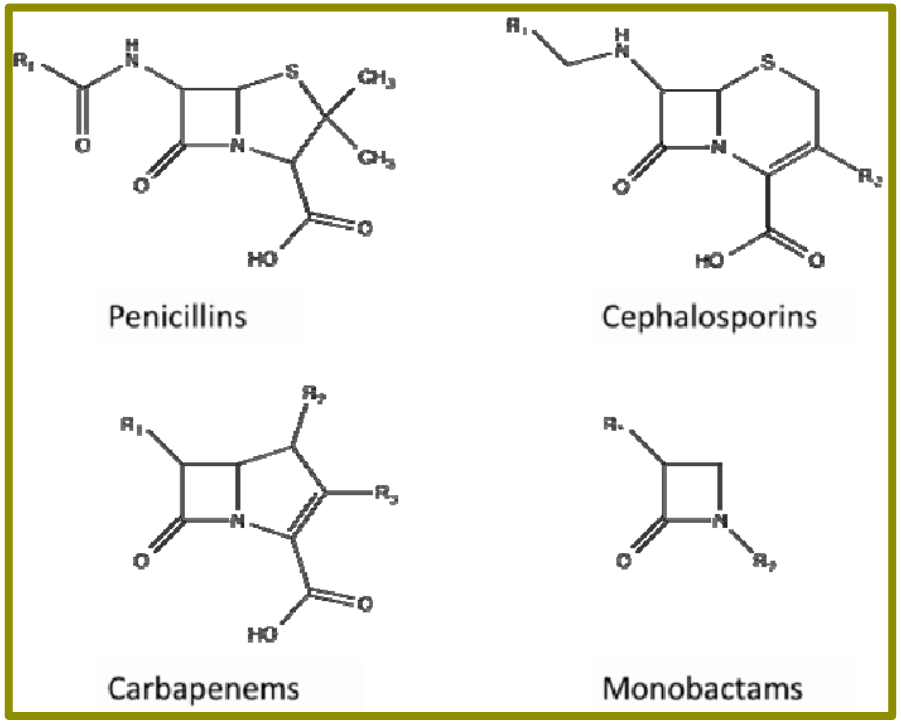
Carbapenem Antibiotics

Antibiotics

- Drugs that treat infections by killing or slowing the growth of bacteria
- Target specific parts or processes of susceptible germs
- Common targets
  - Cell wall or membrane
  - Protein synthesis
  - DNA replication

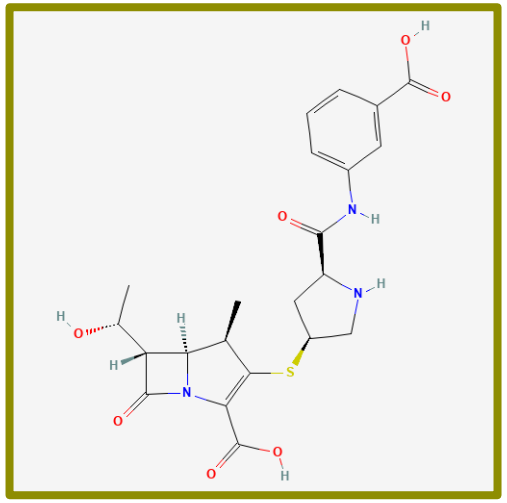
β-lactam Antibiotics

- Commonly prescribed antibiotics
- Examples
  - Penicillins
  - Cephalosporins
  - Carbapenems
- Used to treat a wide range of bacterial infections
- Target cell wall synthesis

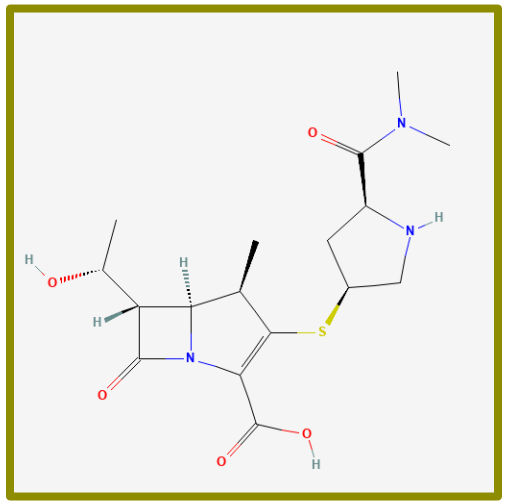


β-lactam Antibiotics

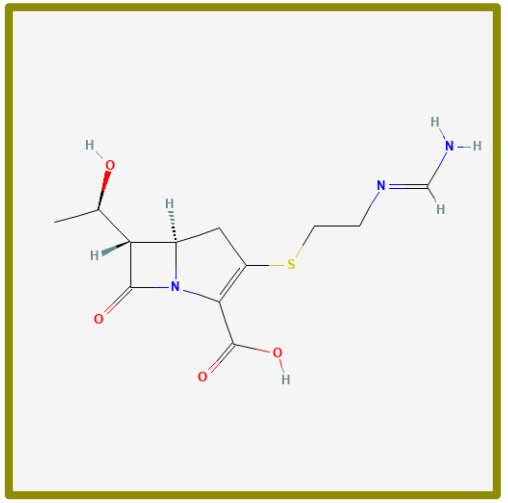
Carbapenem Antibiotics



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.)

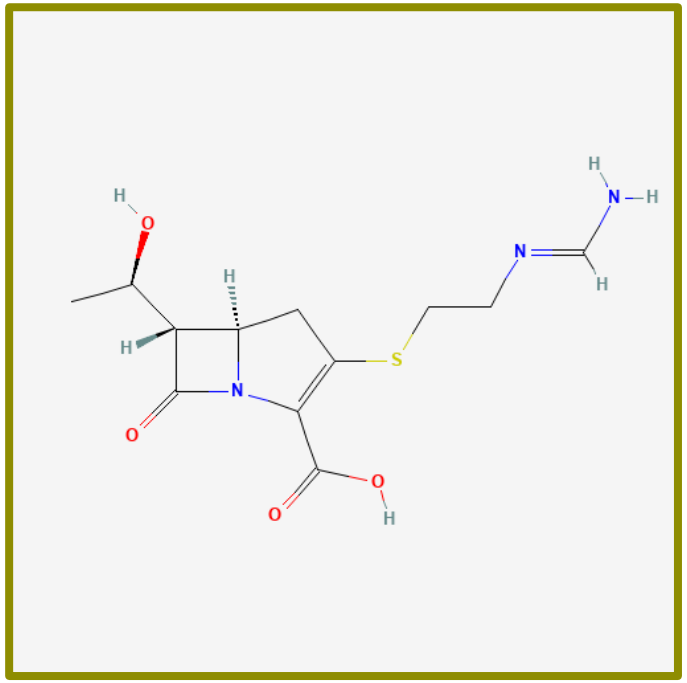
250 mg/ 250 mg* per vial

***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

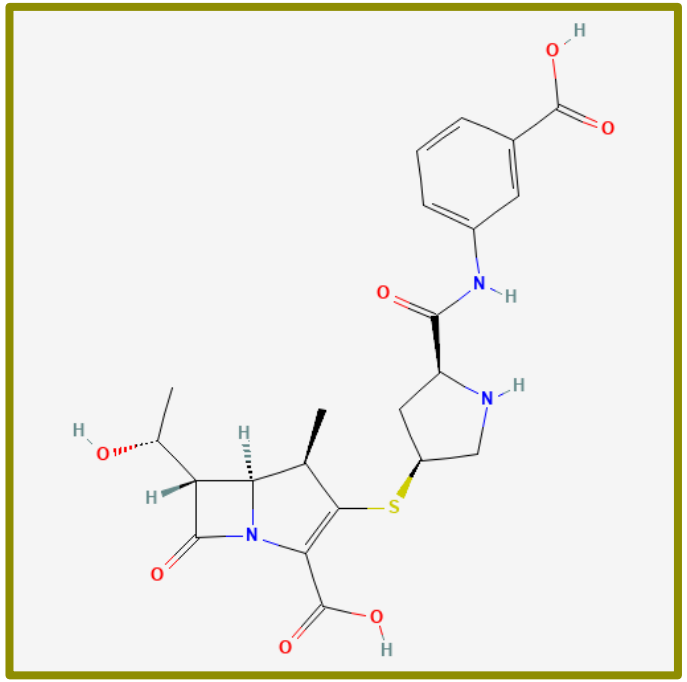
- Antibacterial agents with a broad range of antimicrobial activity and a critical place in therapy
- Active against many organisms that are resistant to other β-lactam antibiotics
- Increasingly important due to increase in resistance to other antibiotics
- Relied on to treat sickest patients and most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



The carbapenem antibiotic imipenem

Carbapenem use

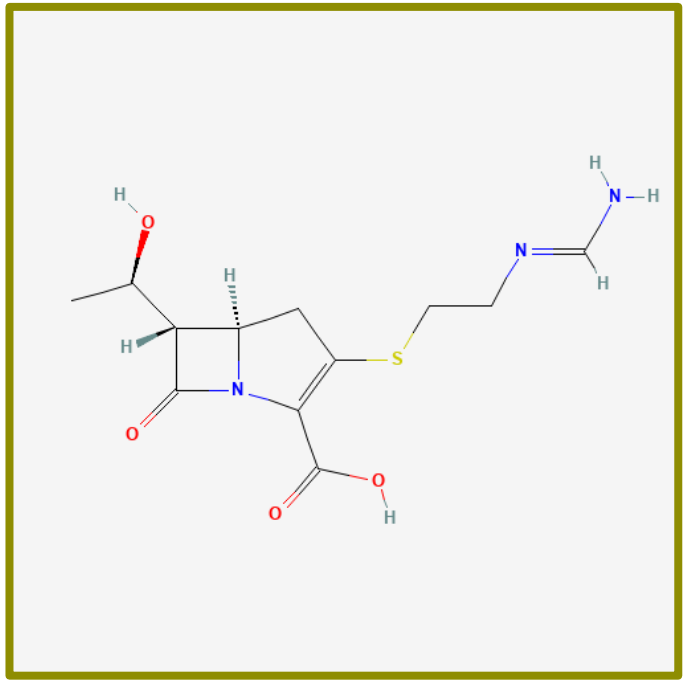
- Utilized for different infections
  - Pneumonia
  - Intra-abdominal infections
  - Urinary tract infections
  - Meningitis
- Off-label use
  - Most other sites of infection



The carbapenem antibiotic ertapenem

Carbapenem antibiotics summary

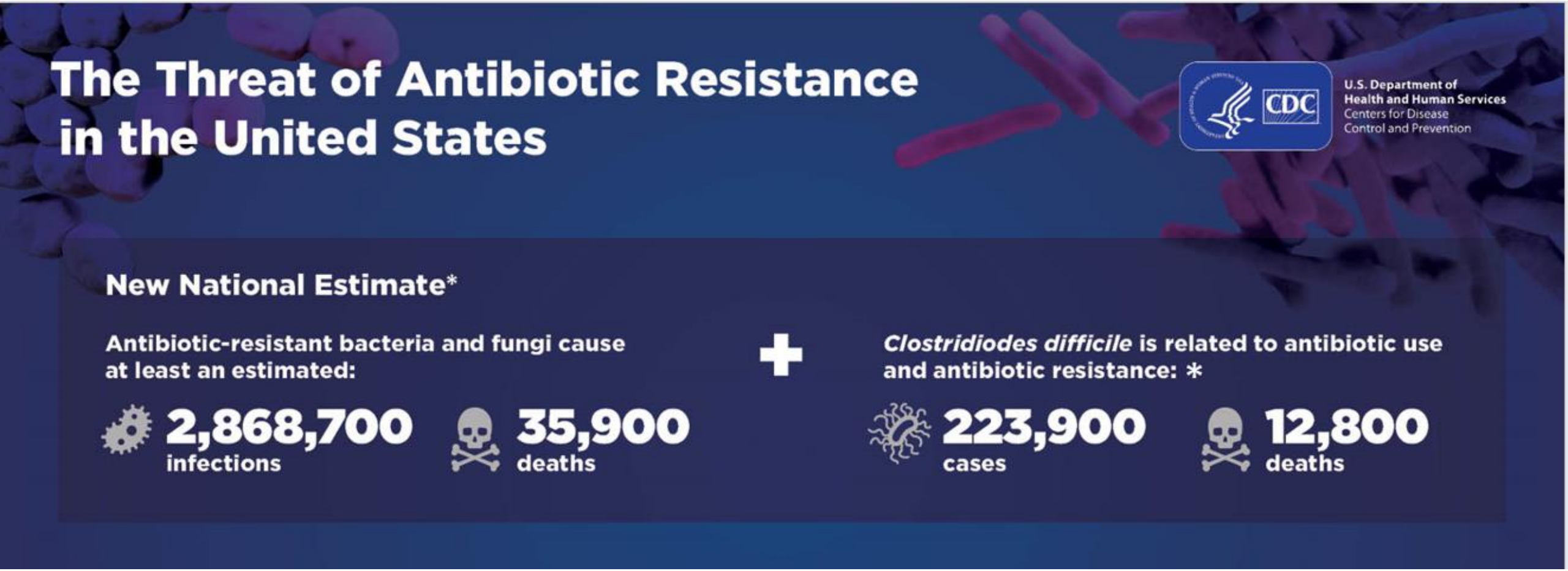
- Important subset of the beta-lactam antibiotics
- Versatile group of antibiotics with activity against many gram-positive and gram-negative organisms
- Reserved for serious, resistant infections
- Increasingly important due to increase in resistance to other antibiotics



The carbapenem antibiotic meropenem

Pathogens and Resistance

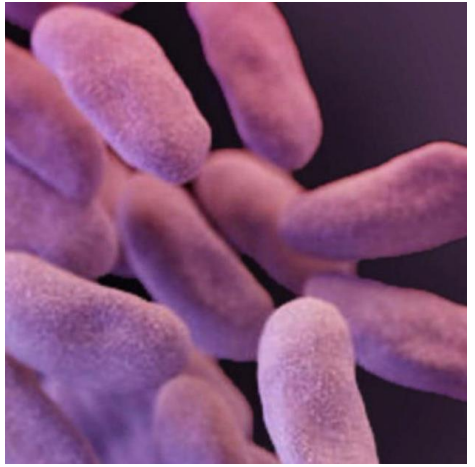
Antimicrobial Resistance is One of the Biggest Challenges of Our Time



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

Carbapenem resistance

- Carbapenem resistant organisms include organisms among the most urgent threats of antibiotic resistant organisms
- Prior to 2001, carbapenem resistance in clinical isolates was due to combination of acquired genes and mutations
- Resistance used to be rare (~1%) and increased rapidly due to the spread of carbapenemases

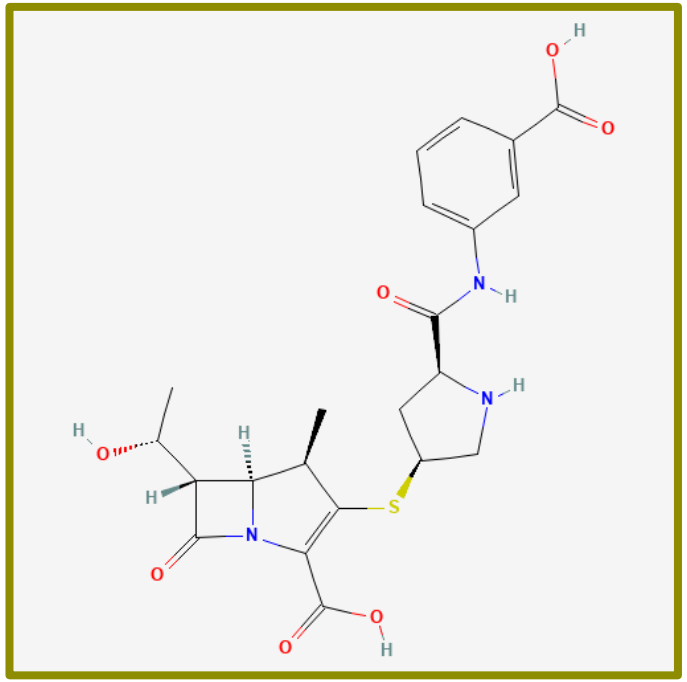


Carbapenem resistance mechanisms

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
   - Most common carbapenemase genes:
     - **KPC**, **NDM**, **VIM**, **IMP,** and **OXA**
   - Pan-resistant strains have been identified

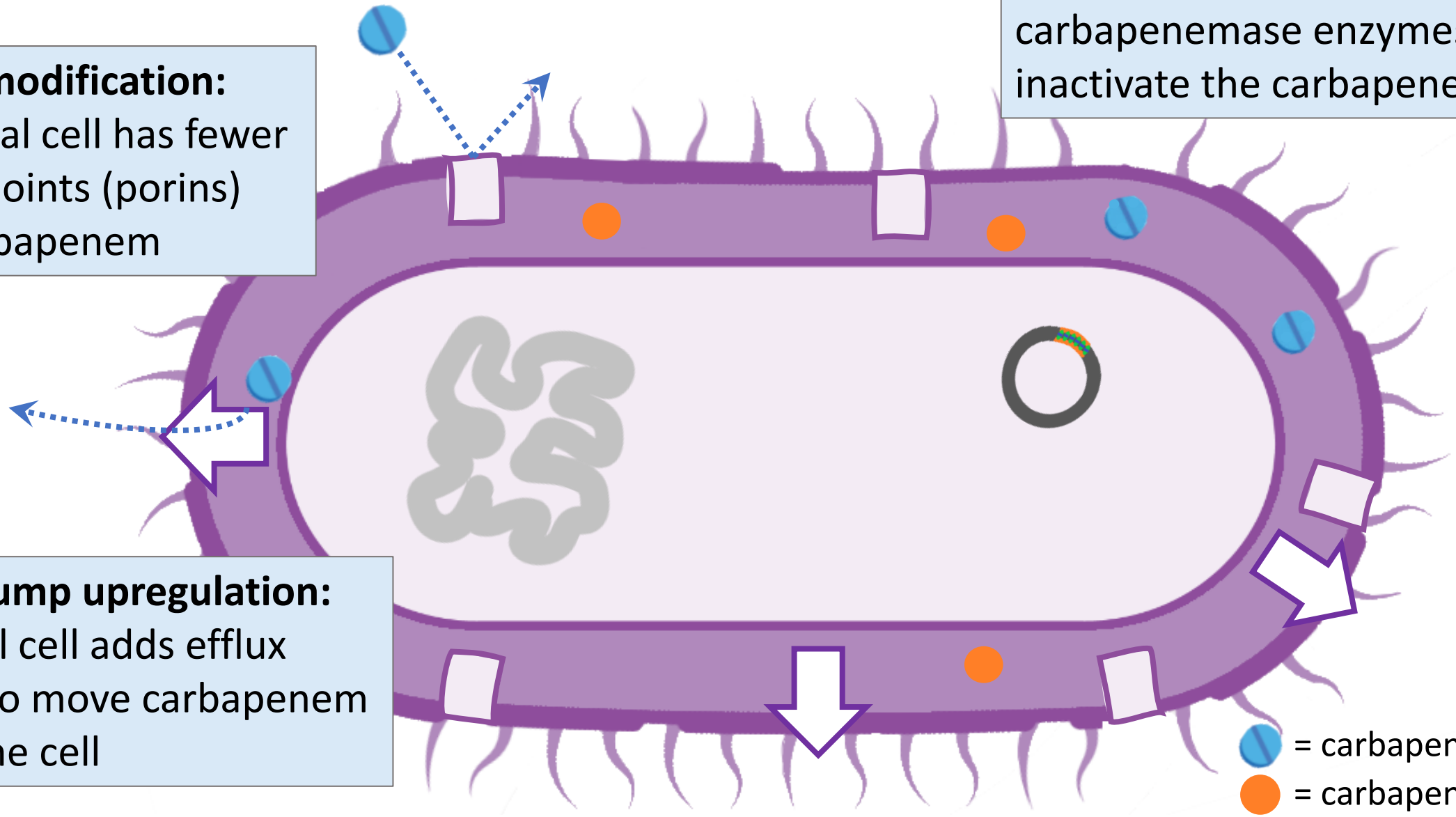


The carbapenem antibiotic ertapenem

Mechanisms of Carbapenem Resistance

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

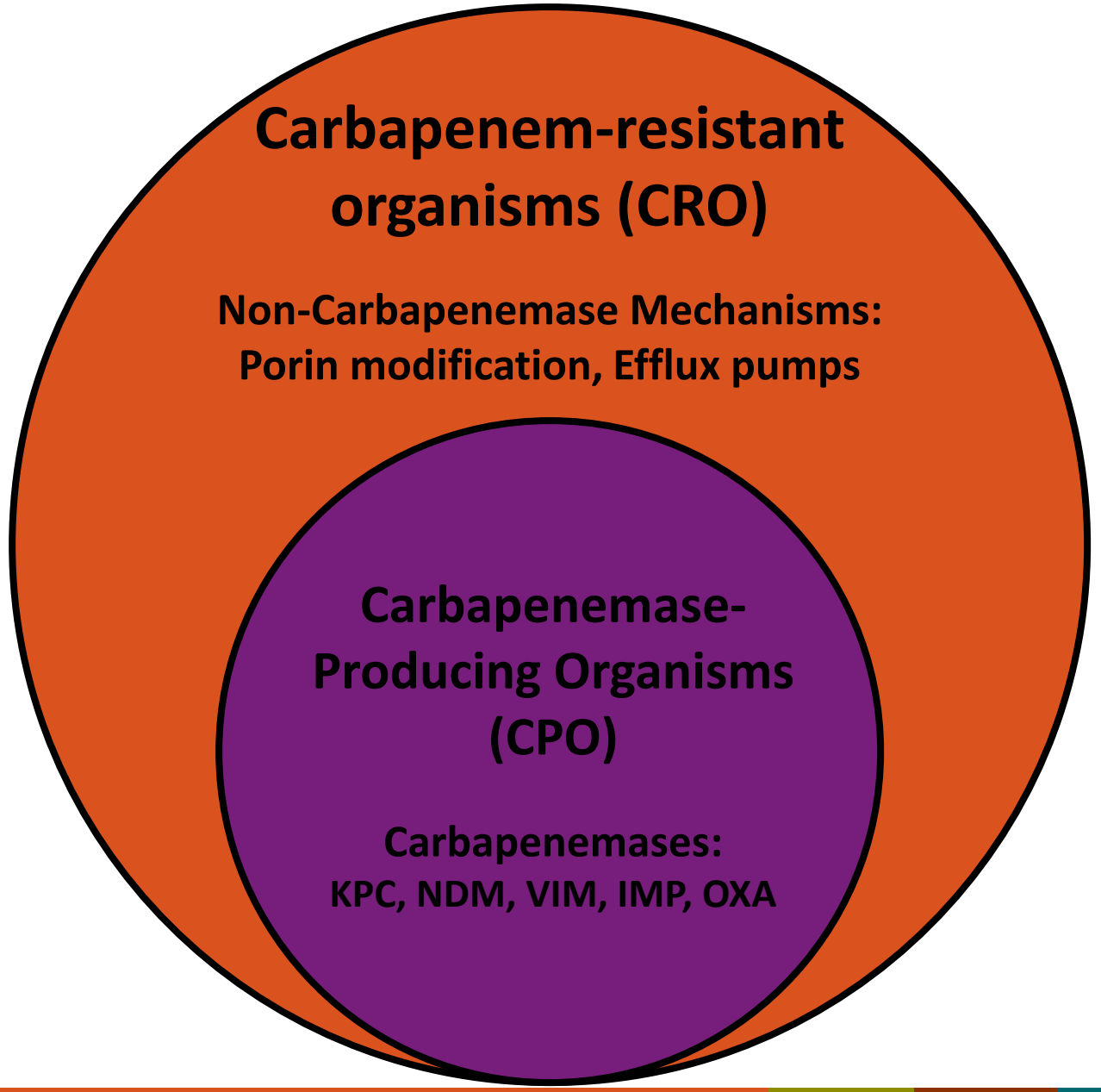
Porin modification:
Bacterial cell has fewer entry points (porins) for carbapenem



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

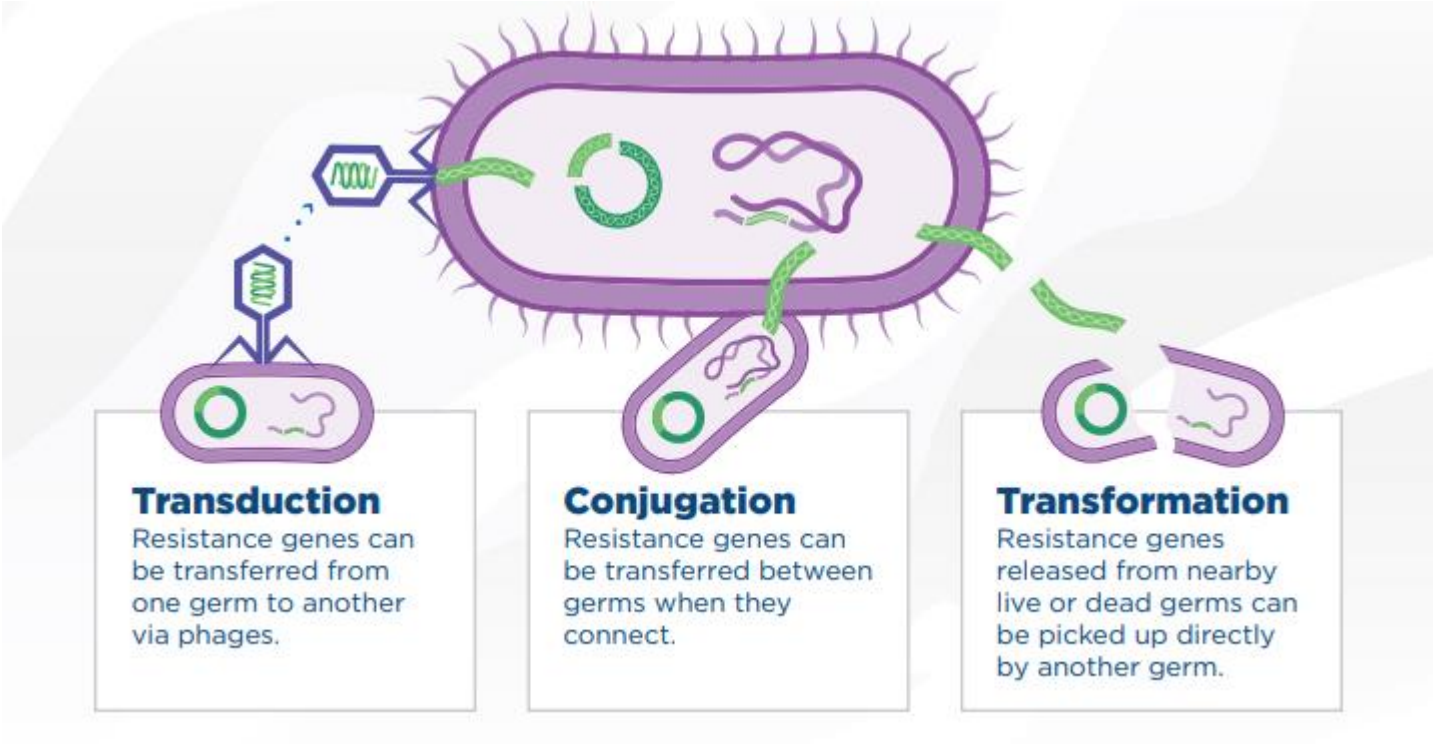
= carbapenem
= carbapenemase

Carbapenem resistance mechanisms

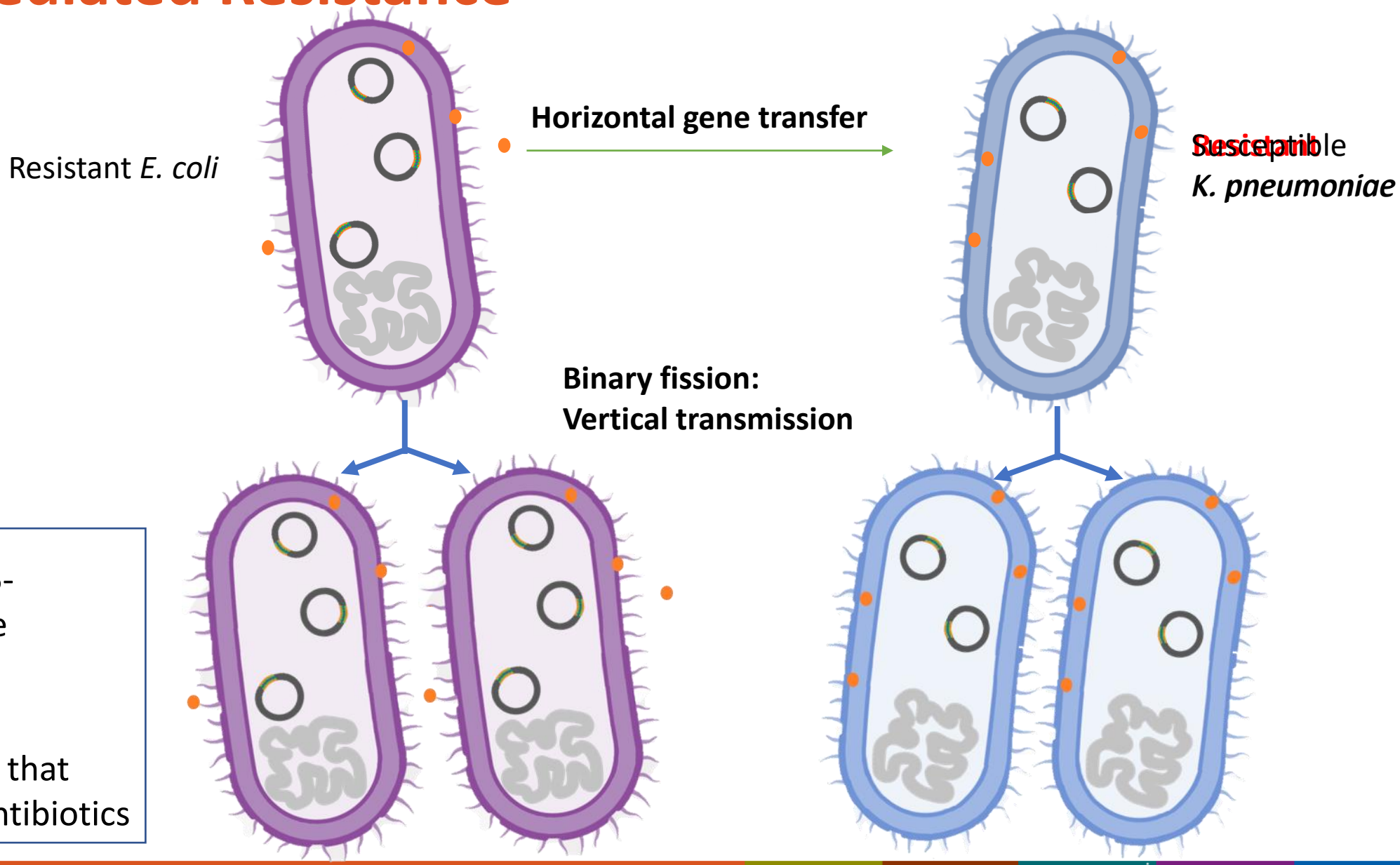


Bacterial Resistance Mechanisms

- **Genetic code for some resistance mechanisms can be shared**
  - On mobile genetic elements such as plasmids
  - Across different strains, species, and taxonomic families
  - With strains that have not been exposed to antibiotics
  - Often with other antibiotic resistance genes
  - Potential for rapid spread

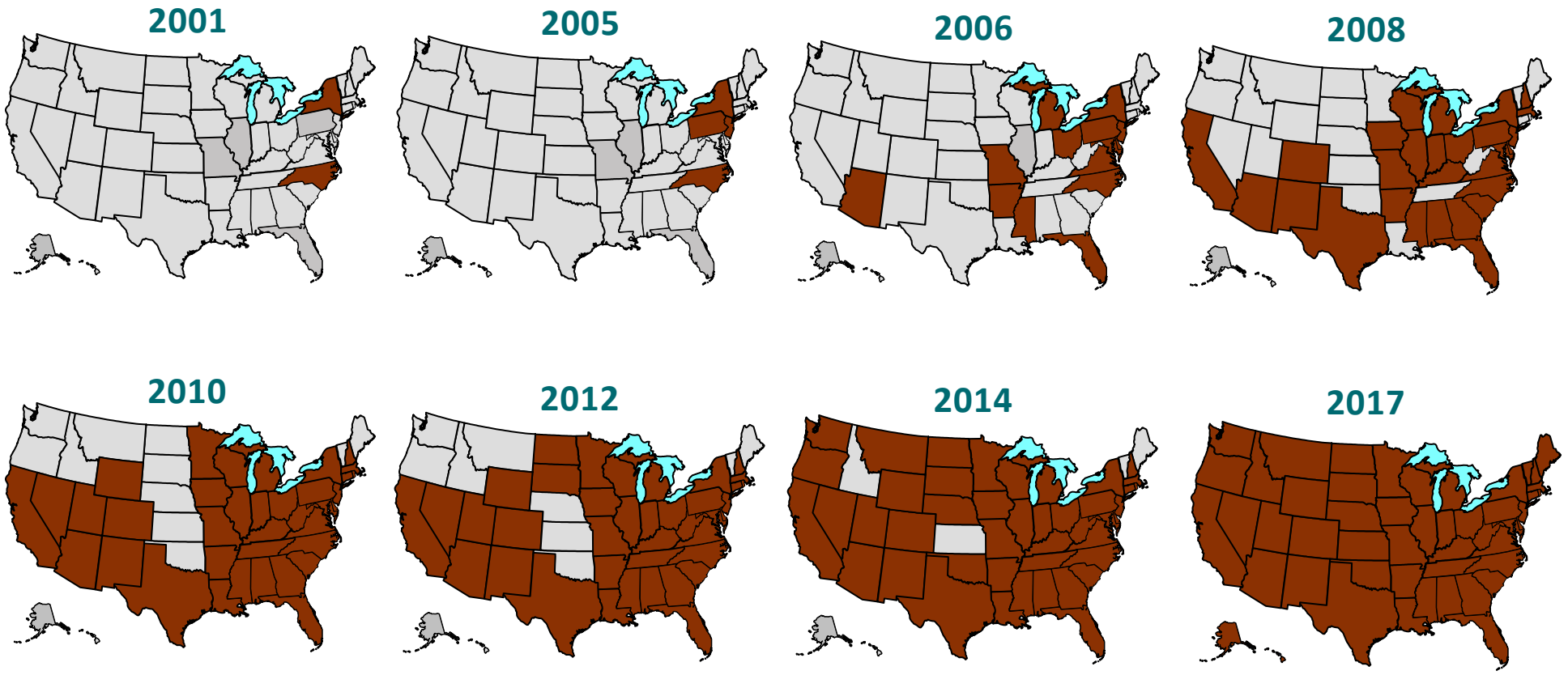


Plasmid-Mediated Resistance



Carbapenemases can Spread Rapidly

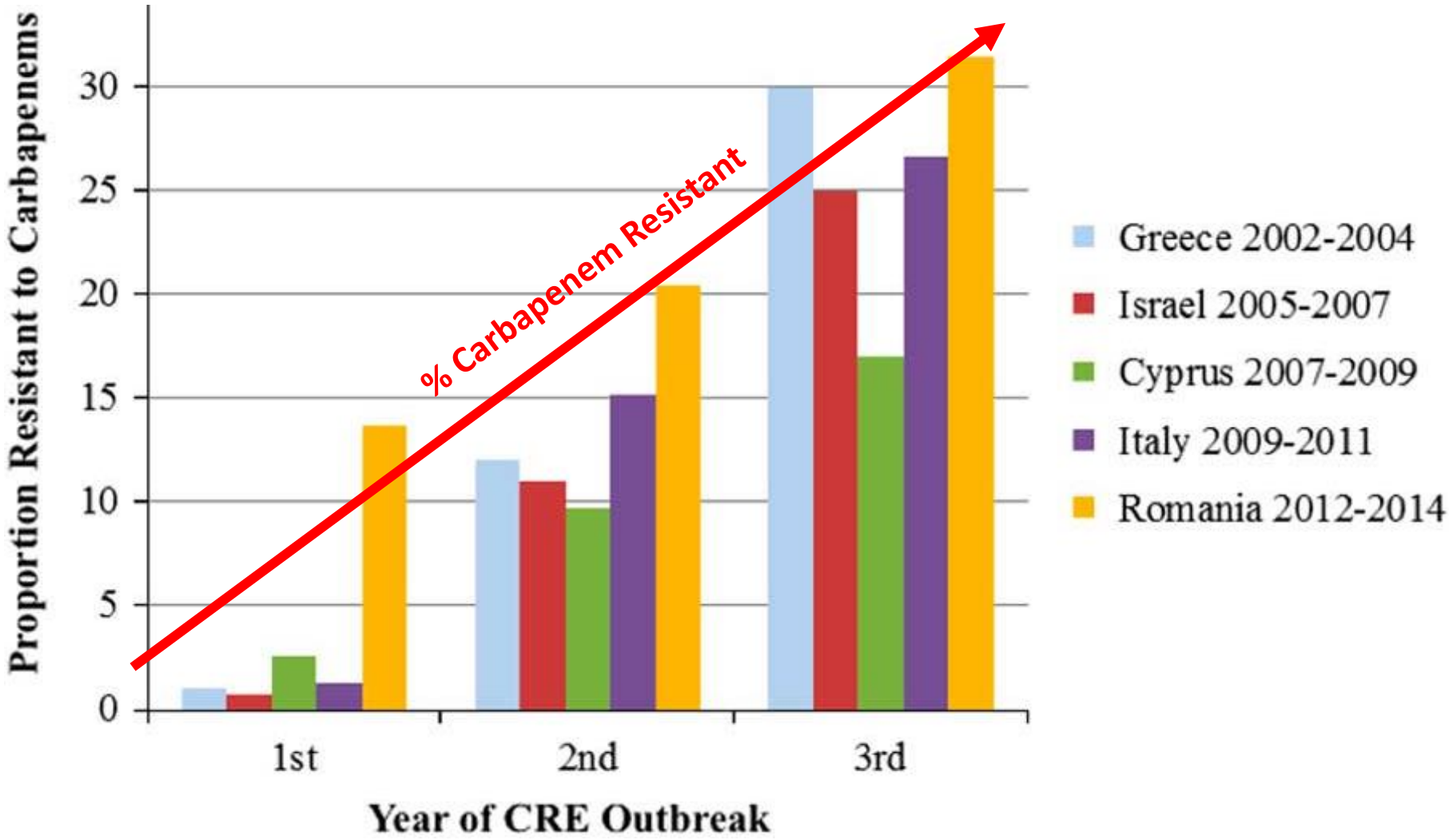
KPC-CRE found in the US spread from 2 states in 2001 to 50 states, DC, and PR by 2017



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

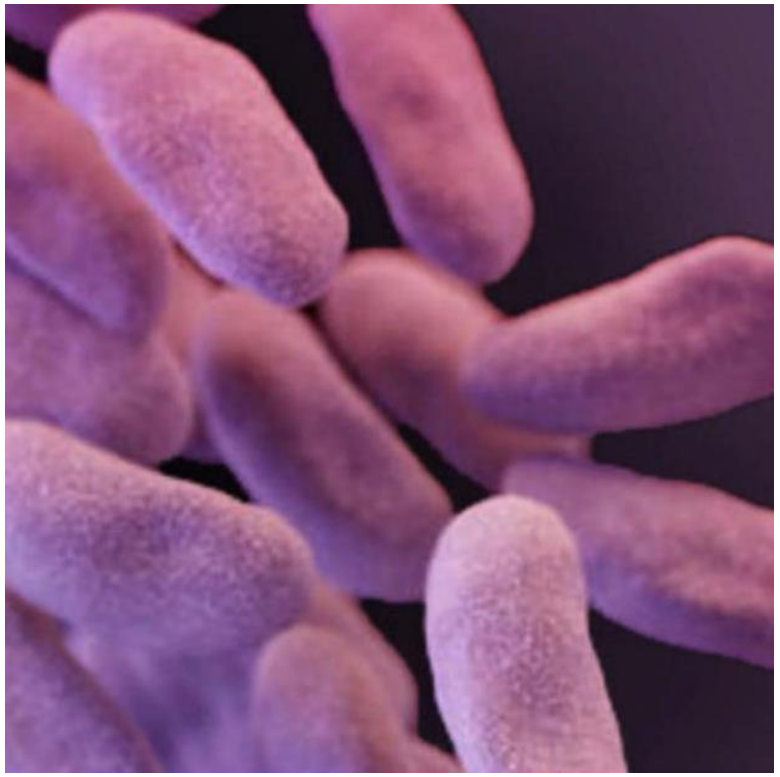
https://www.cdc.gov/hai/organisms/cre/trackingcre.html

Important Antibiotics Can Quickly Lose Efficacy



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

Emerging Carbapenem-Resistant Organisms



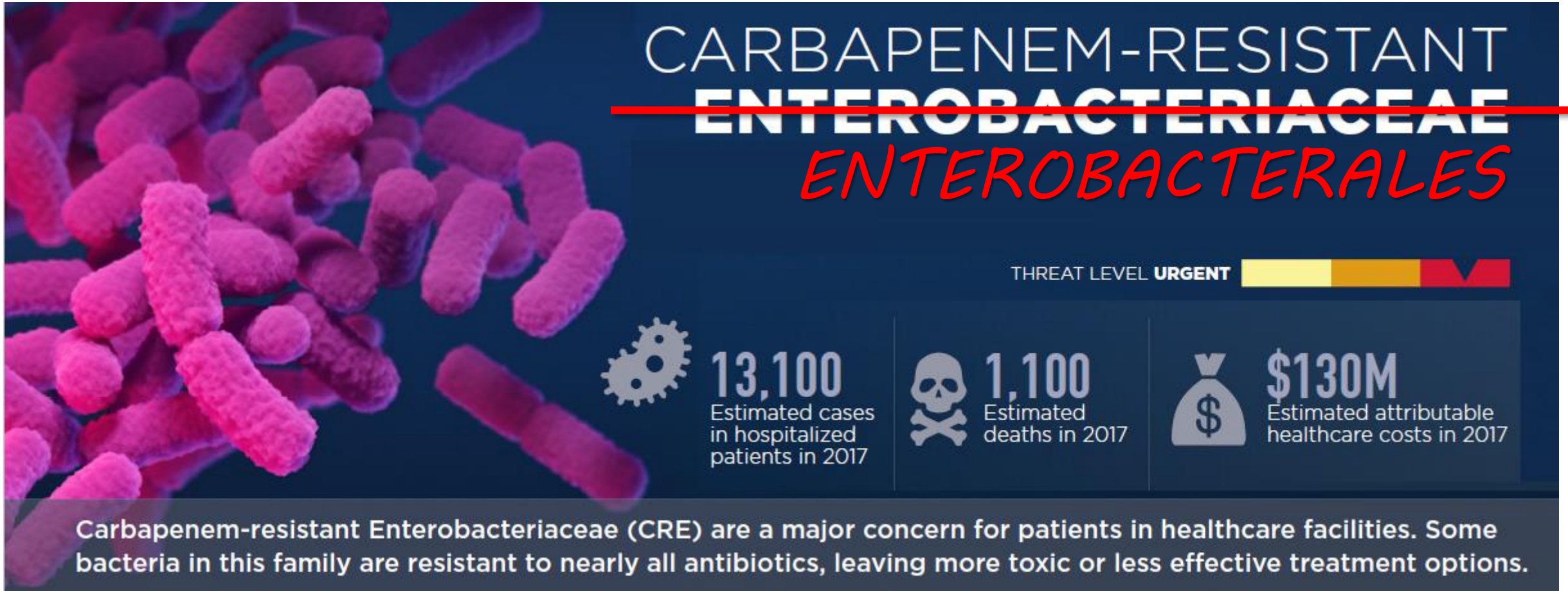
Carbapenem-Resistant Enterobacterales

Multidrug-Resistant *Pseudomonas aeruginosa*

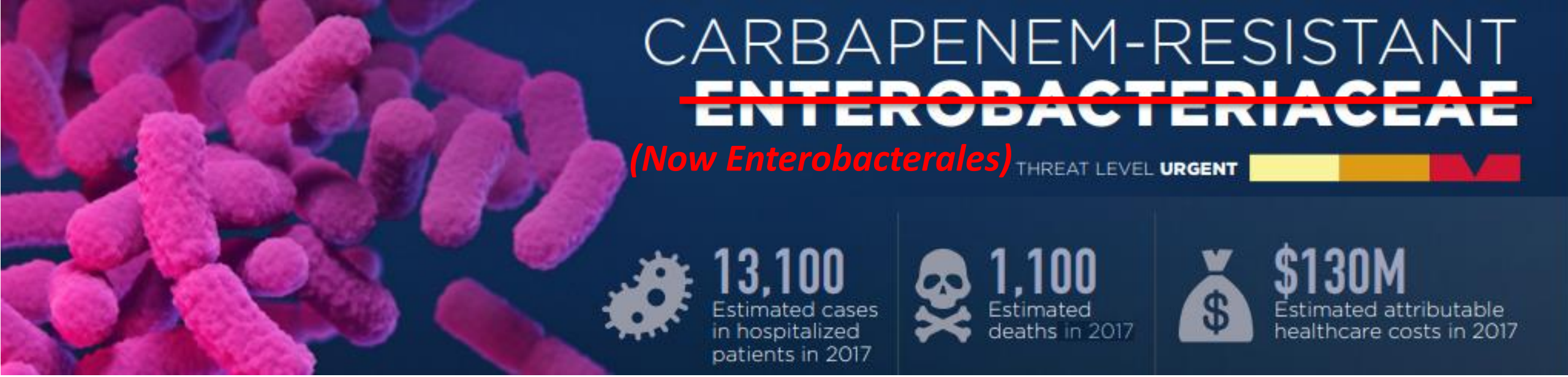
Carbapenem-Resistant *Acinetobacter*

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

Carbapenem-Resistant Enterobacterales (CRE)



If mechanism of carbapenem-resistance is carbapenemase-production: CP-CRE



- In the U.S., approximately 35% of CRE carry a gene for carbapenemases, which inactivate carbapenem and other β-lactam antibiotics and can spread rapidly among different strains
- Currently most U.S. CRE identified in persons with recent hospitalization, surgery, or long-term care
- Carried in the digestive tract of patients and healthcare facilities

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

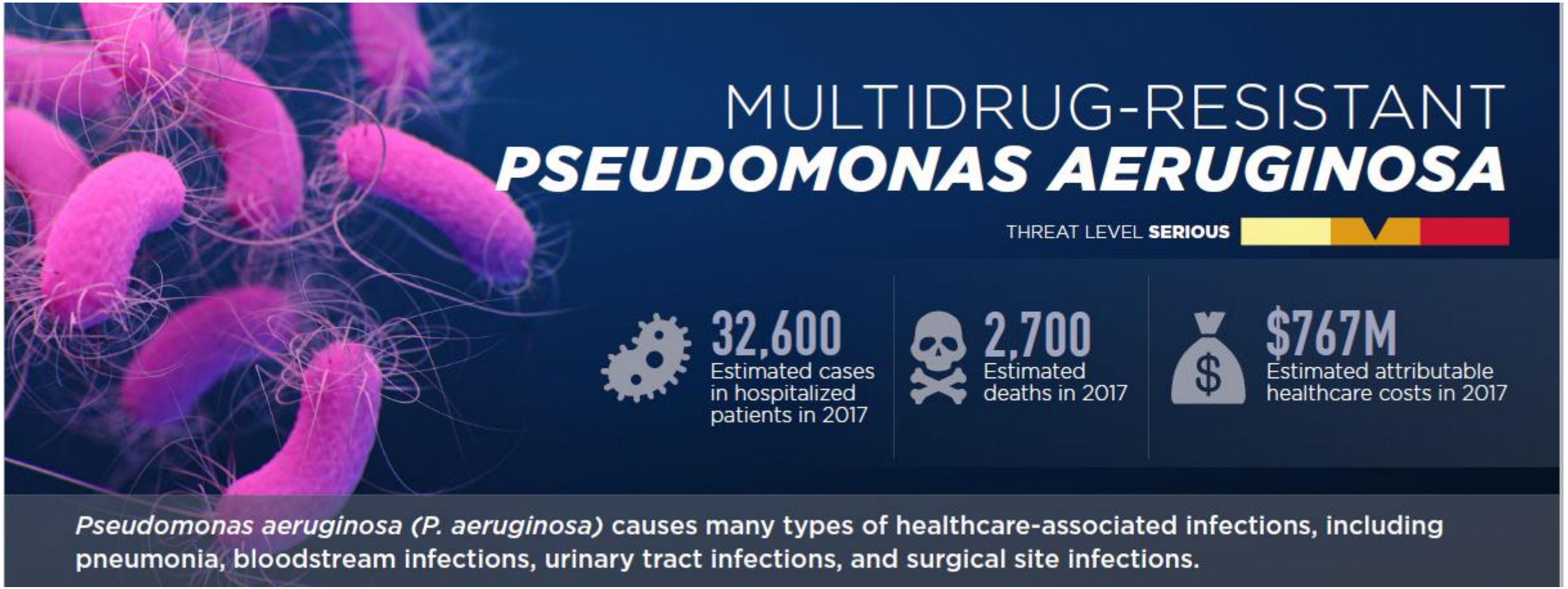
Carbapenem-resistant Enterobacterales

- Who is at risk?
  - Patients who:
    - are on breathing machines (ventilators)
    - have devices such as catheters
    - take long courses of certain antibiotics
    - have weakened immune systems

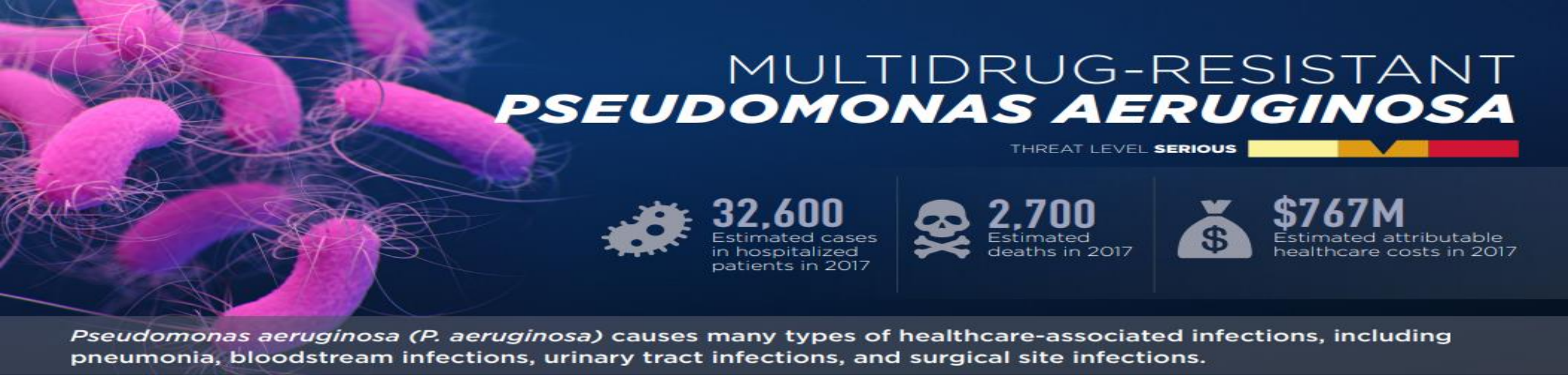
Carbapenem-resistant Enterobacterales

- How is it spread?
  - person to person contact with infected or colonized people, particularly contact with wounds or stool
  - contact can occur via the hands of healthcare workers, or through medical equipment and devices that have not been correctly cleaned

Carbapenem-Resistant *Pseudomonas aeruginosa* (CRPA)



If mechanism of carbapenem-resistance is carbapenemase-production: CP-CRPA



- Infections usually occur in hospitalized patients or with weakened immune systems
- Some types of multidrug-resistant (MDR) P. aeruginosa are resistant to nearly all antibiotics, including carbapenems
- Few treatment options

https://www.cdc.gov/drugresistance/pdf/threats-report/pseudomonas-aeruginosa-508.pdf

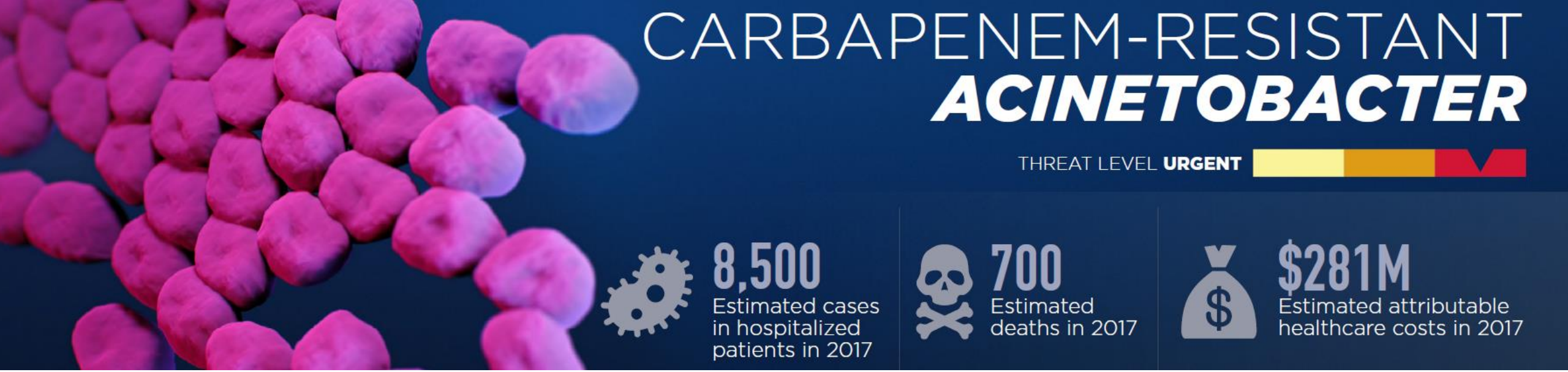
Pseudomonas aeruginosa

- Who is at risk?
  - Patients who:
    - are on breathing machines (ventilators)
    - have devices such as catheters
    - have open wounds from surgery or burns

Pseudomonas aeruginosa

- How is it spread?
  - It lives in the environment and can be spread to people in healthcare settings when they are exposed to water or soil that is contaminated with these germs
  - Resistant strains of the germ can also spread in healthcare settings from one person to another through contaminated hands, equipment, or surfaces

Carbapenem-Resistant *Acinetobacter*

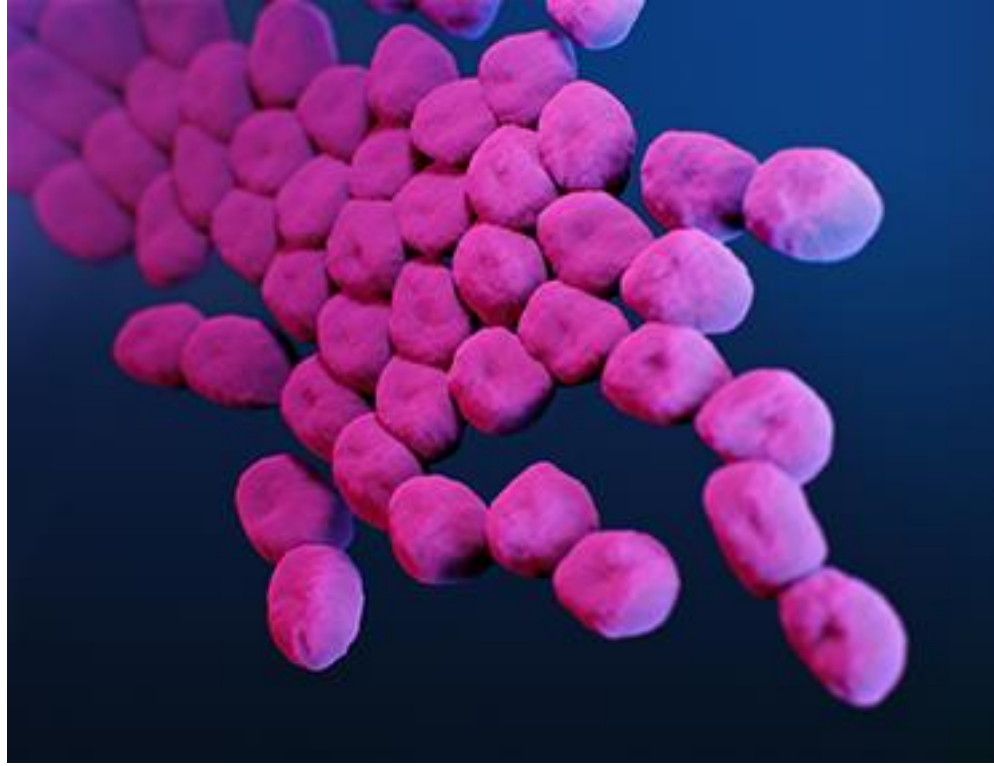


- Infections occur almost exclusively in patients with recent hospitalizations, surgeries, or residence in long term care facilities
- Causes a variety of infections: bloodstream, respiratory, and wound
- Survives for extended period on surfaces and shared medical equipment
- Associated with large regional outbreaks
  - Especially strains that have carbapenemases
- Few treatment options

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

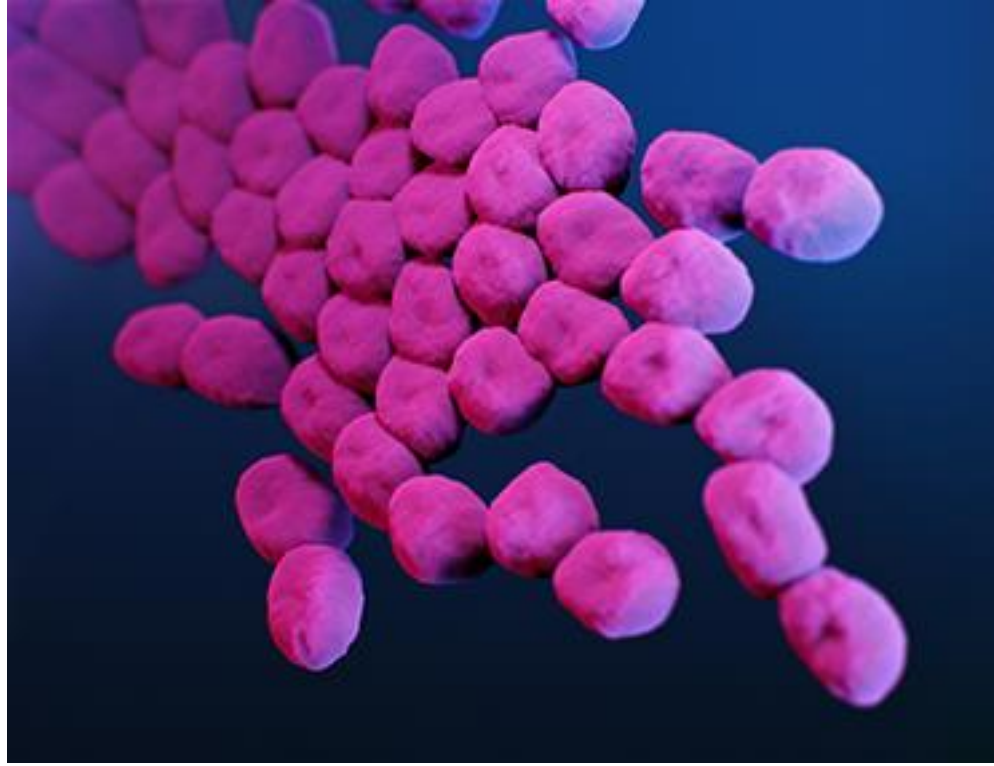
Acinetobacter baumannii

- Who is at risk?
  - Patients who:
    - are on breathing machines (ventilators)
    - have devices such as catheters
    - have open wounds from surgery
    - are in intensive care units
    - have prolonged hospital stays



Acinetobacter baumannii

- How is it spread?
  - It can live for long periods on environmental surfaces and shared equipment if they are not properly cleaned
  - The germs can spread from one person to another through contact with these contaminated surfaces or equipment or though person to person spread, often via contaminated hands



Pathogens and Resistance Summary

- There are multiple mechanisms of carbapenem-resistance; most concerning is carbapenemase-production
  - Carbapenemase genes are carried on mobile genetic elements (i.e., plasmids)
  - Plasmids can be copied and shared with other bacteria causing rapid spread of carbapenem-resistance in clinical isolates in a region
- Emerging MDROs include:
  - Carbapenemase-producing organisms:
    - Enterobacterales
    - Pseudomonas spp.
    - Acinetobacter spp.

How Carbapenem-Resistant Organisms are Identified

Clinical Laboratory

- Validated microbiological tests used for patient care
- Commonly in-house:
  - Organism Identification
  - Antibiotic Susceptibility Testing
- Commonly external:
  - Phenotypic Carbapenemase Testing
  - Genotypic Carbapenemase Testing

Organism Identification

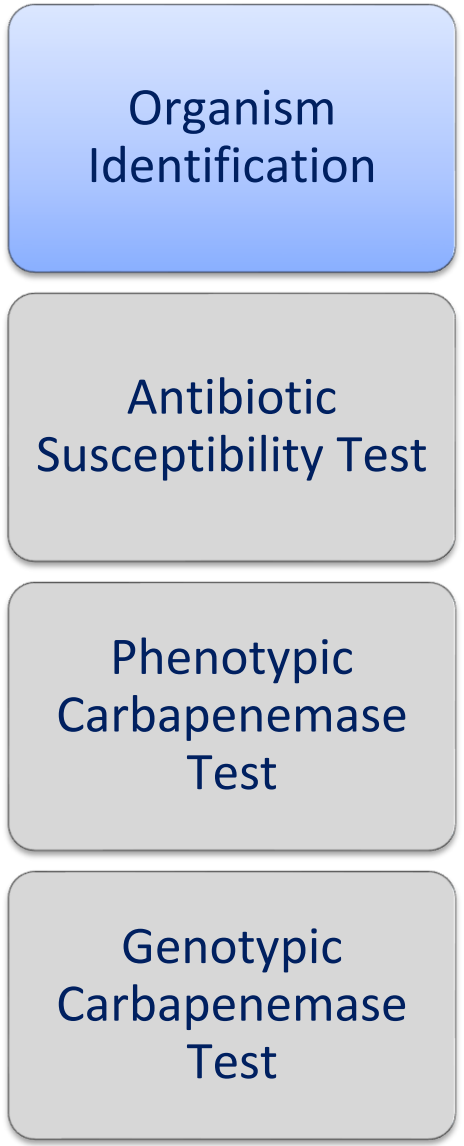
Antibiotic Susceptibility Test

Phenotypic Carbapenemase Test

Genotypic Carbapenemase Test

Organism Identification

- Laboratory test to distinguish certain organisms from others
  - Identifying organisms to the species level
- Newer technology is rapid and reliable
- Helps in clinical decision making

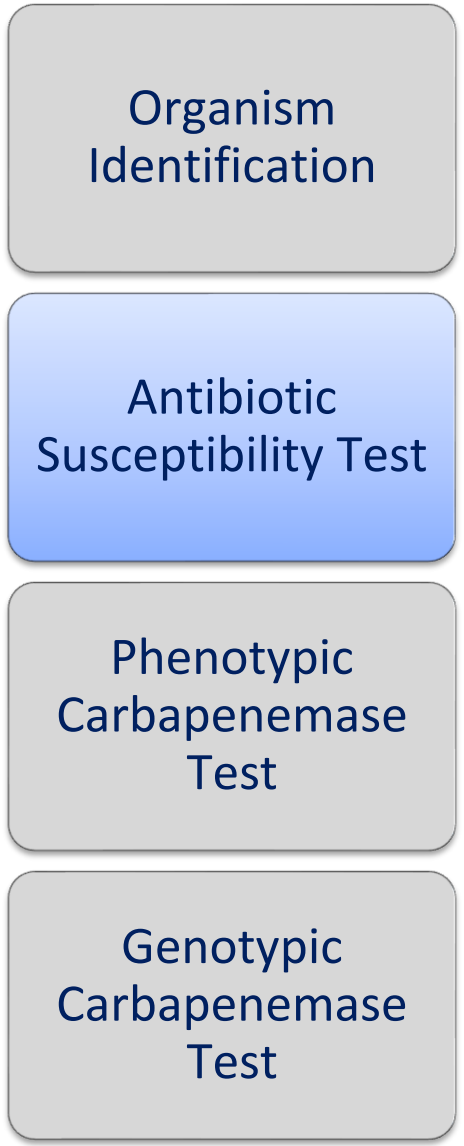


Antimicrobial Susceptibility Testing

- Laboratory test to check if a germ is susceptible/sensitive (or resistant to) an antibiotic at varying amounts.

Key Terms

- **Isolate**: a pure sample of a germ.
- **Susceptible** (S): germ is vulnerable to an antimicrobial
- **Resistant** (R): germ can overcome the antimicrobial
  - **Multidrug-resistant**: Germ is resistant to multiple antibiotics, usually across antibiotic categories.
- **Intermediate** (I): germ is between the S and R categories for an antimicrobial
- **Not susceptible** (NS): either intermediate or resistant



Carbapenemase Testing

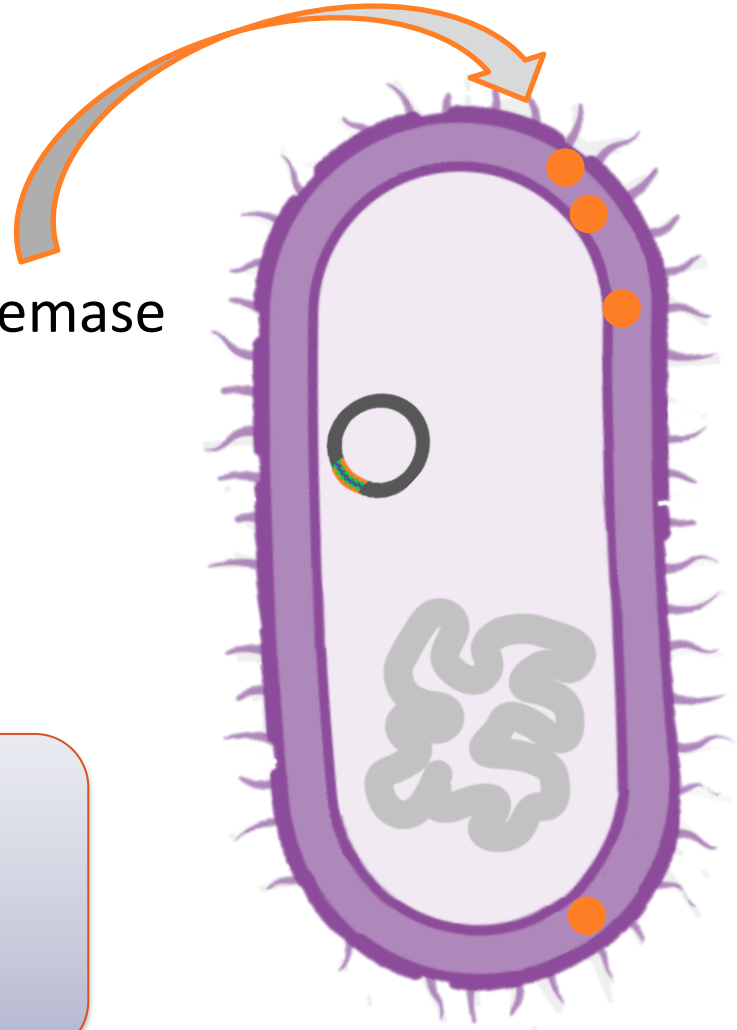
Phenotypic test

- Identifies if a germ produces a carbapenemase

= plasmid with CP gene

= chromosome

= carbapenemase



Example Tests & Methods:
- mCIM
- Carba-NP

Organism Identification

Antibiotic Susceptibility Test

Phenotypic Carbapenemase Test

Genotypic Carbapenemase Test

Carbapenemase Testing

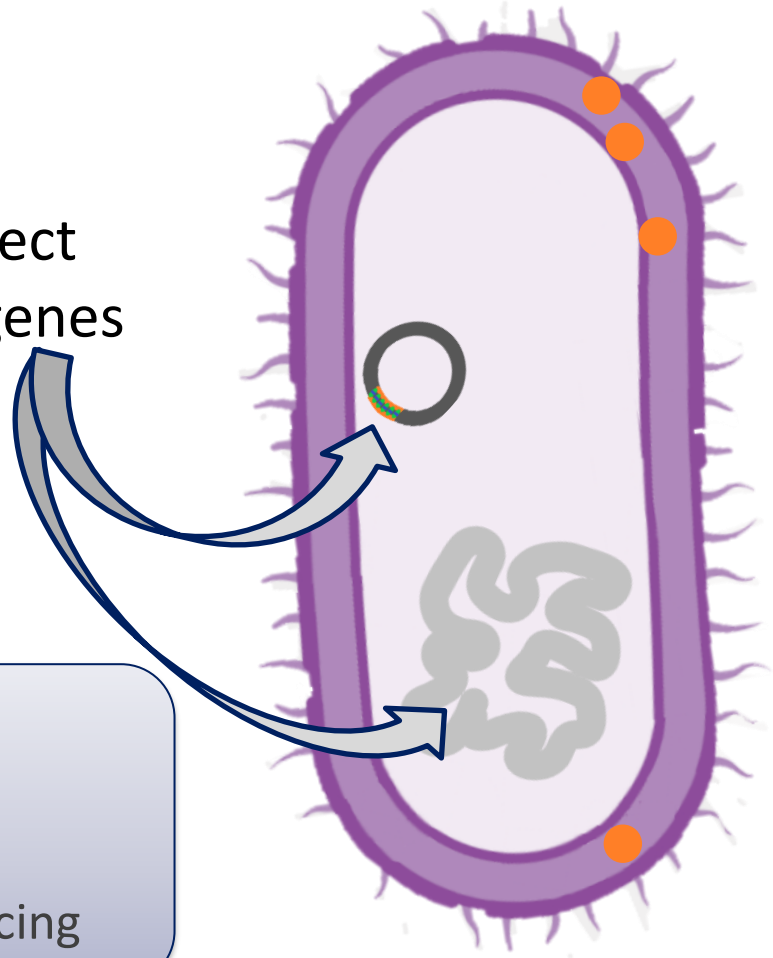
Genotypic test

- Molecular testing techniques that detect specific resistance genes

= plasmid with CP gene

= chromosome

= carbapenemase



Example Tests & Methods:
- In-house RT-PCR
- Other assays available
- Whole genome sequencing

Organism Identification

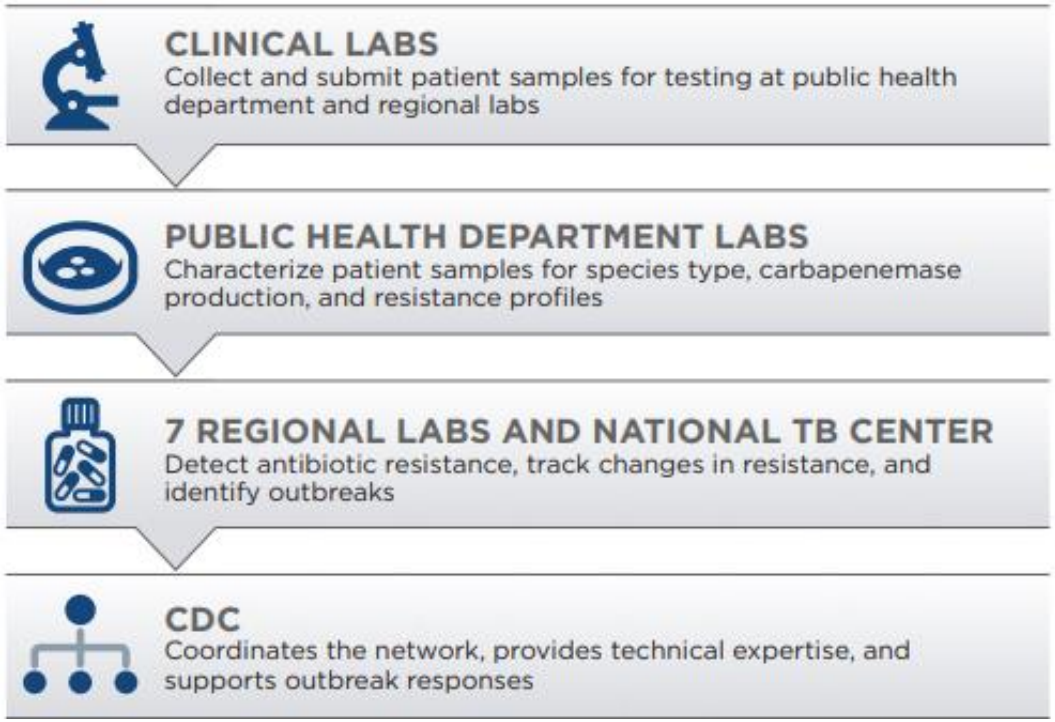
Antibiotic Susceptibility Test

Phenotypic Carbapenemase Test

Genotypic Carbapenemase Test

Antibiotic Resistance Laboratory Network

- Laboratory infrastructure to rapidly detect and respond to unusual threats
- Laboratories nationwide work together to fight antibiotic resistance
- CDC coordinated network



Clinical Laboratory Testing Summary

- A series of validated microbiological tests used for patient care
- Clinical tests can be used to accurately detect carbapenem resistance
- Testing is useful to help slow the spread of antimicrobial resistance
- The Antibiotic Resistance Laboratory Network provides healthcare facilities and state health departments with access to gold-standard public health lab testing

Summary

Summary

- It takes time to become familiar with MDRO abbreviations, jargon
- Emerging MDROs include carbapenemase-producing organisms: Enterobacterales, Pseudomonas spp., Acinetobacter spp.
  - Plasmid-mediated carbapenemases include KPC, NDM, OXA, VIM, and IMP
- Resistance mechanisms can reduce the effectiveness of antibiotics
- Carbapenem resistance is often hard to treat and can spread rapidly
- Clinical tests can be used to accurately detect carbapenem resistance

Thank you!

ARLN@cdc.gov
HAIAR@cdc.gov

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