Carbapenem Resistant Enterobacterales

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April 11, 2024

Project ECHO
Serious Communicable Diseases Program
EMORY

Disclosures

- Nothing to disclose

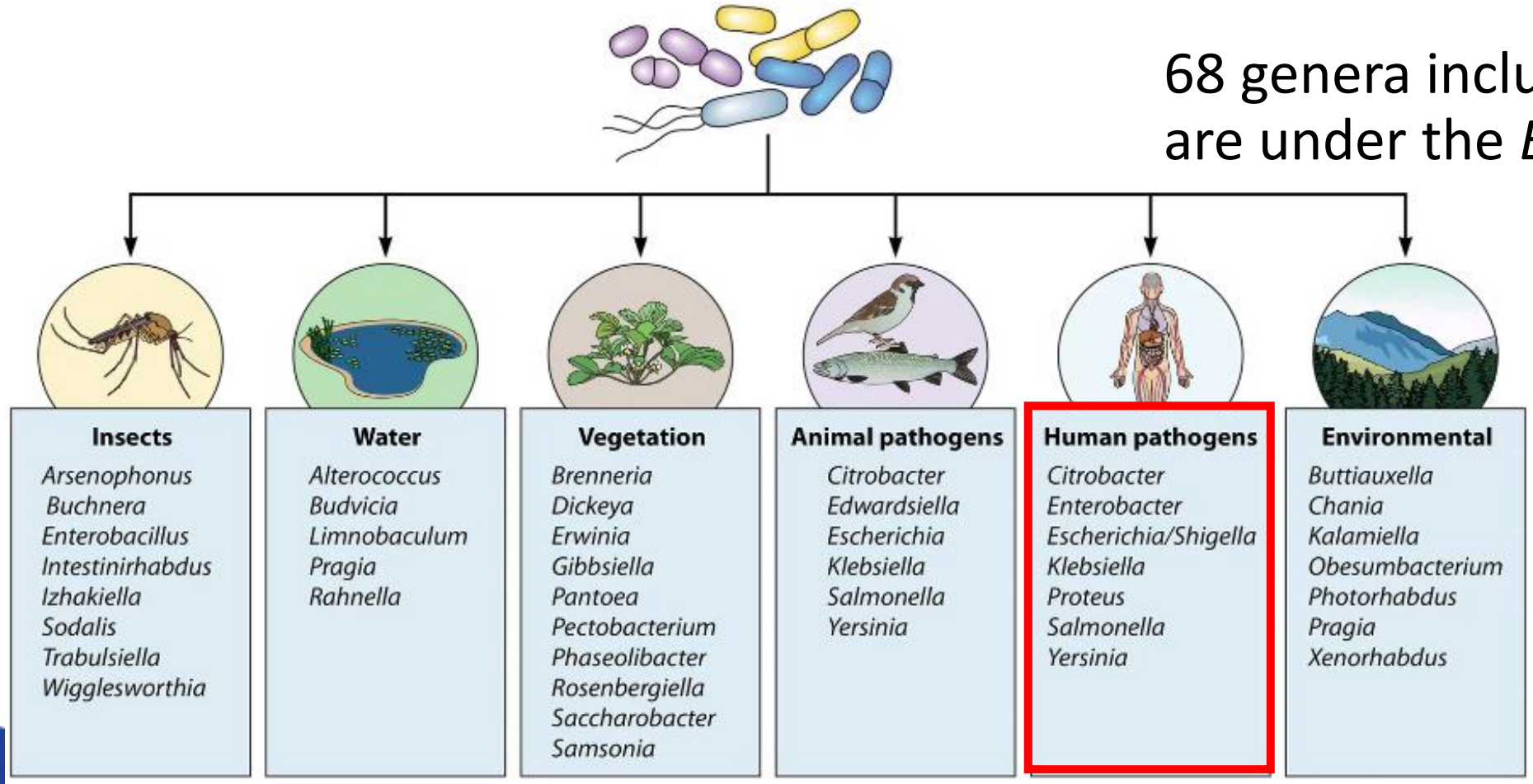
Objectives

- Describe the epidemiology of Carbapenem Resistant Enterobacterales (CRE)
- Explain the mechanisms of Resistance of Carbapenem Resistant Enterobacterales (CRE)
- Review diagnostic and treatment options for CRE

Outline

- Definition
- Epidemiology
- Transmission dynamics
- Therapeutics

Enterobacterales



68 genera including 355 species are under the *Enterobacterales*

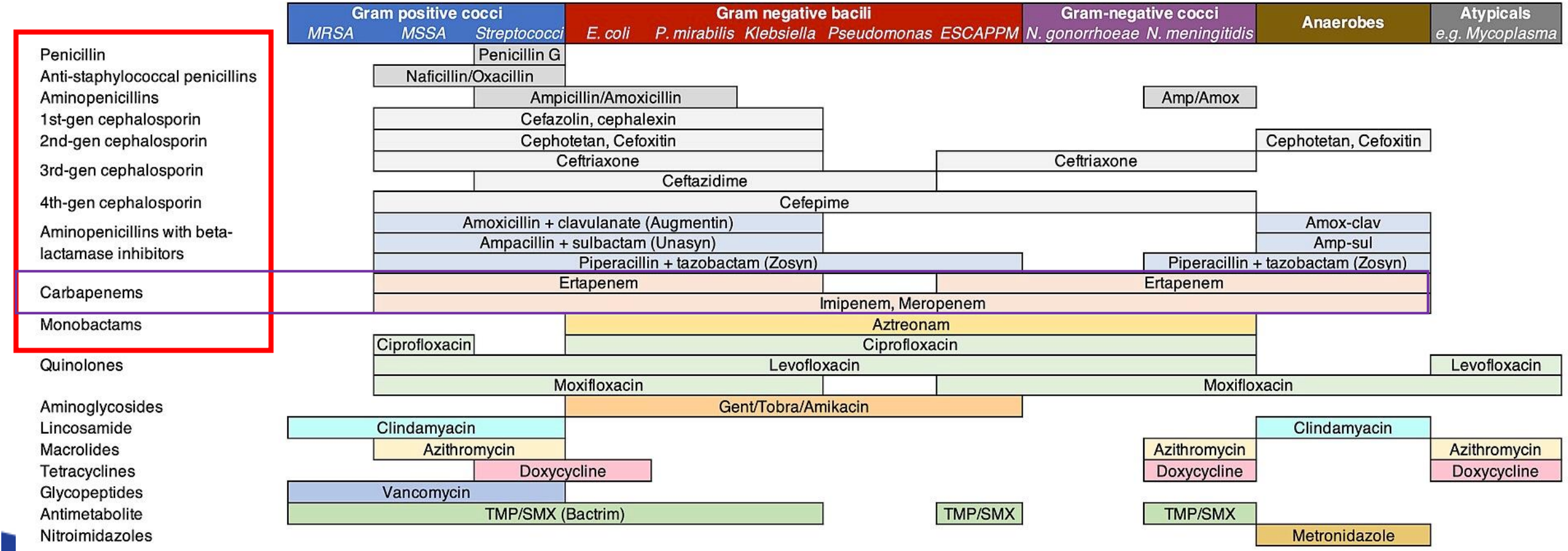
https://www.digicomply.com/blog/enterobacteriaceae-incidents-surge-again

Carbapenem Resistant Enterobacterales (CRE)

- **CRE:** Enterobacterales that are resistant to carbapenem antibiotics.
- **CP-CRE**:
  - Carbapenemases - enzymes that break down carbapenems and related antimicrobials making them ineffective
  - subset of all CRE.
- **CRO:** Carbapenem resistant Organisms
  - Non-enterobacterales carbapenem resistant organisms

- **ESBL – Extended spectrum beta-lactamase**
  - Defined as enzymes produced by certain bacteria that are able to hydrolyze extended spectrum cephalosporin.
  - Effective against beta-lactam antibiotics such as ceftazidime, ceftriaxone, cefotaxime
- **Amp C (beta lactamase)**
  - resistant to beta- lactamase inhibitors like clavulunate
  - mostly found on chromosomes
  - Enzyme is inducible with exposure to any antibiotic

Antibiotic classes



See github.com/aetherist/antibiogram for details. For educational purposes only. Consult your local antibiogram for clinical use.

TMP/SMX = Trimethoprim-sulfamethoxazole, MRSA = Methicillin-resistant Staphylococcus aureus, MSSA = Methicillin-sensitive Staphylococcus aureus, ESCAPPM = Enterobacter spp., Serratia spp., Citrobacter freundii, Aeromonas spp., Proteus spp., Providencia spp. and Morganella morganii.

https://github.com/alexgoodell/antibiogram

Epidemiology

HAZARD LEVEL
URGENT

These are high-consequence antibiotic-resistant threats because of significant risks identified across several criteria. These threats may not be currently widespread but have the potential to become so and require urgent public health attention to identify infections and to limit transmission.

Clostridium difficile (C. difficile), Carbapenem-resistant Enterobacteriaceae (CRE), Drug-resistant *Neisseria gonorrhoeae* (cephalosporin resistance)

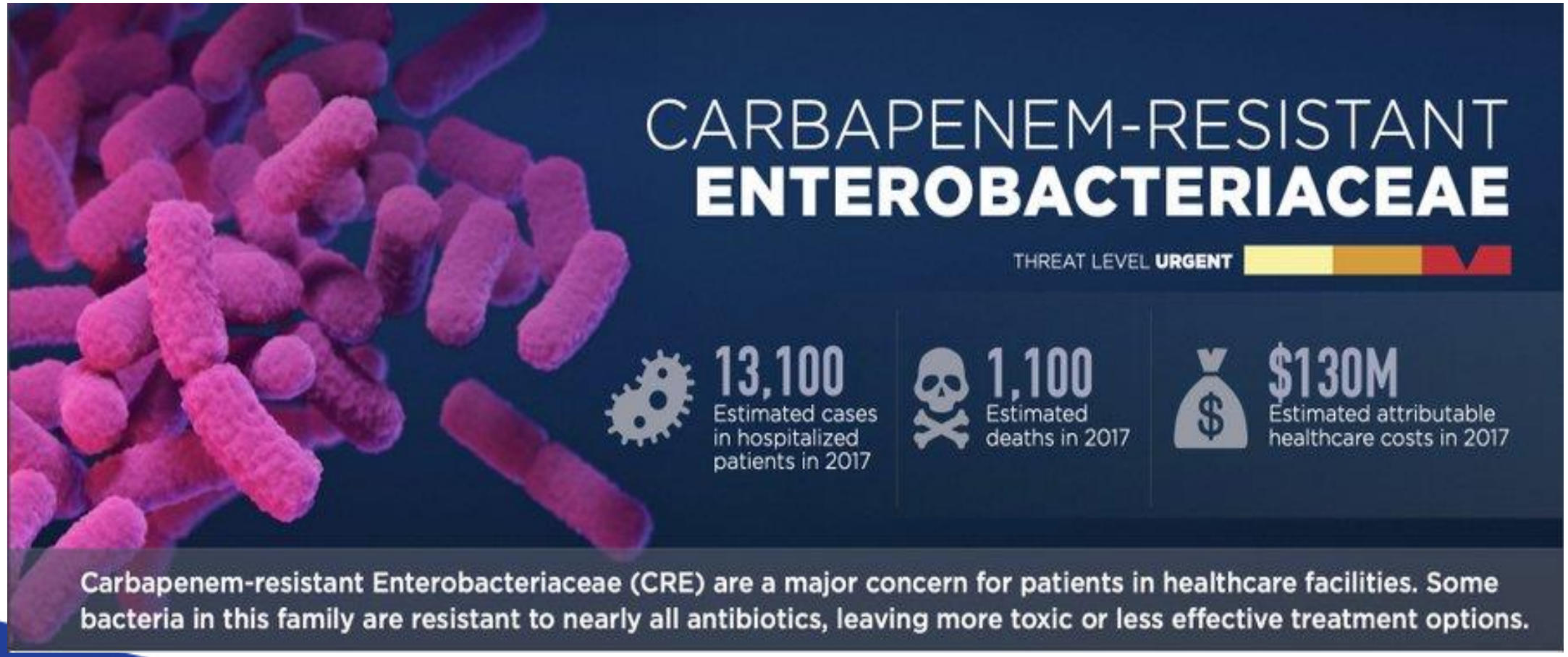
HAZARD LEVEL
SERIOUS

These are significant antibiotic-resistant threats. For varying reasons (e.g., low or declining domestic incidence or reasonable availability of therapeutic agents), they are not considered urgent, but these threats will worsen and may become urgent without ongoing public health monitoring and prevention activities.

Multidrug-resistant *Acinetobacter*, Drug-resistant *Campylobacter*, Fluconazole-resistant *Candida* (a fungus), Extended spectrum β-lactamase producing Enterobacteriaceae (ESBLs), Vancomycin-resistant *Enterococcus* (VRE), Multidrug-resistant *Pseudomonas aeruginosa*, Drug-resistant Non-typhoidal *Salmonella*, Drug-resistant *Salmonella* Typhi, Drug-resistant *Shigella*, Methicillin-resistant *Staphylococcus aureus* (MRSA), Drug-resistant *Streptococcus pneumonia*, Drug-resistant tuberculosis (MDR and XDR)

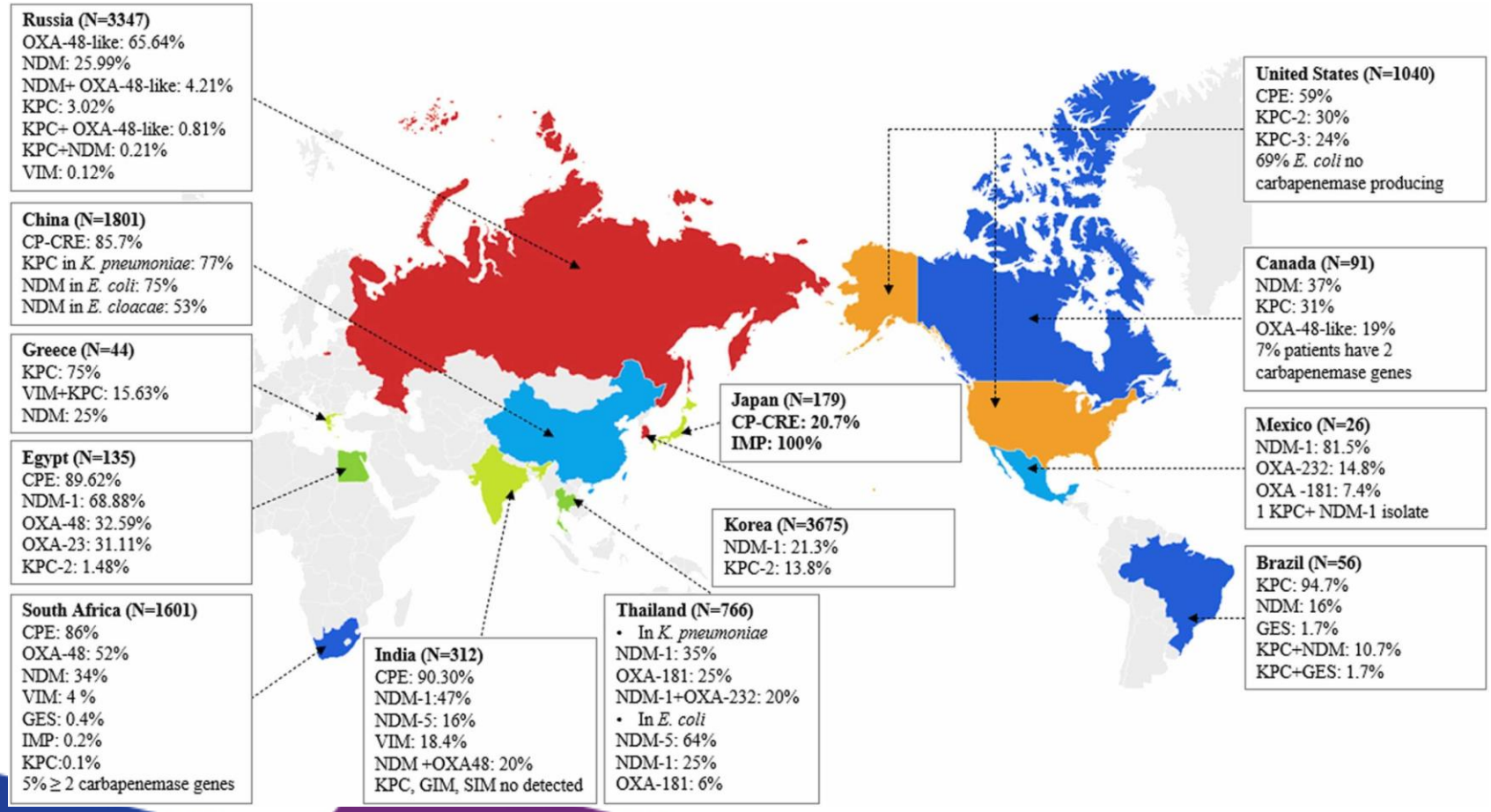
https://www.cdc.gov/hai/organisms/cre/cre-clinicians.html

Epidemiology



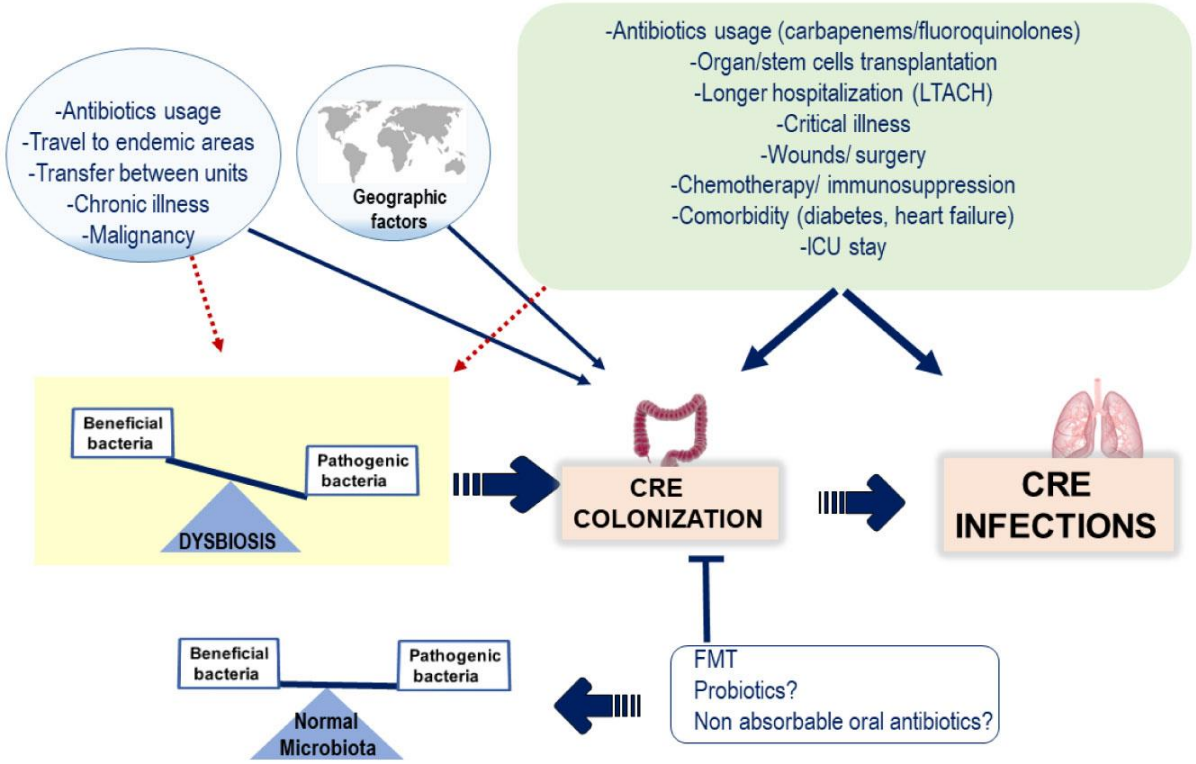
https://www.cdc.gov/hai/organisms/cre/cre-clinicians.html

Global Epidemiology



Ma J et. al. Microbiol Res . 2023 Jan:266:127249

Risk Factors for CRE



Risk Factors for CRE Infections

1. Elderly age
2. Hospitalization and prolonged hospital stay
3. Immunocompromised conditions
4. Prolonged antibiotic treatments
5. Recent surgery and open wounds
6. Invasive medical devices like IV catheters
7. Chronic diseases like Diabetic, cancer, AIDS

Dong LT, Espinoza HV, Espinoza JL.AIMS Microbiol. 2020 Jul 1;6(3):176-182.

Transport of Resistance

Mobile Genetic Elements

Plasmids

Circles of DNA that can move between cells.

Transposons

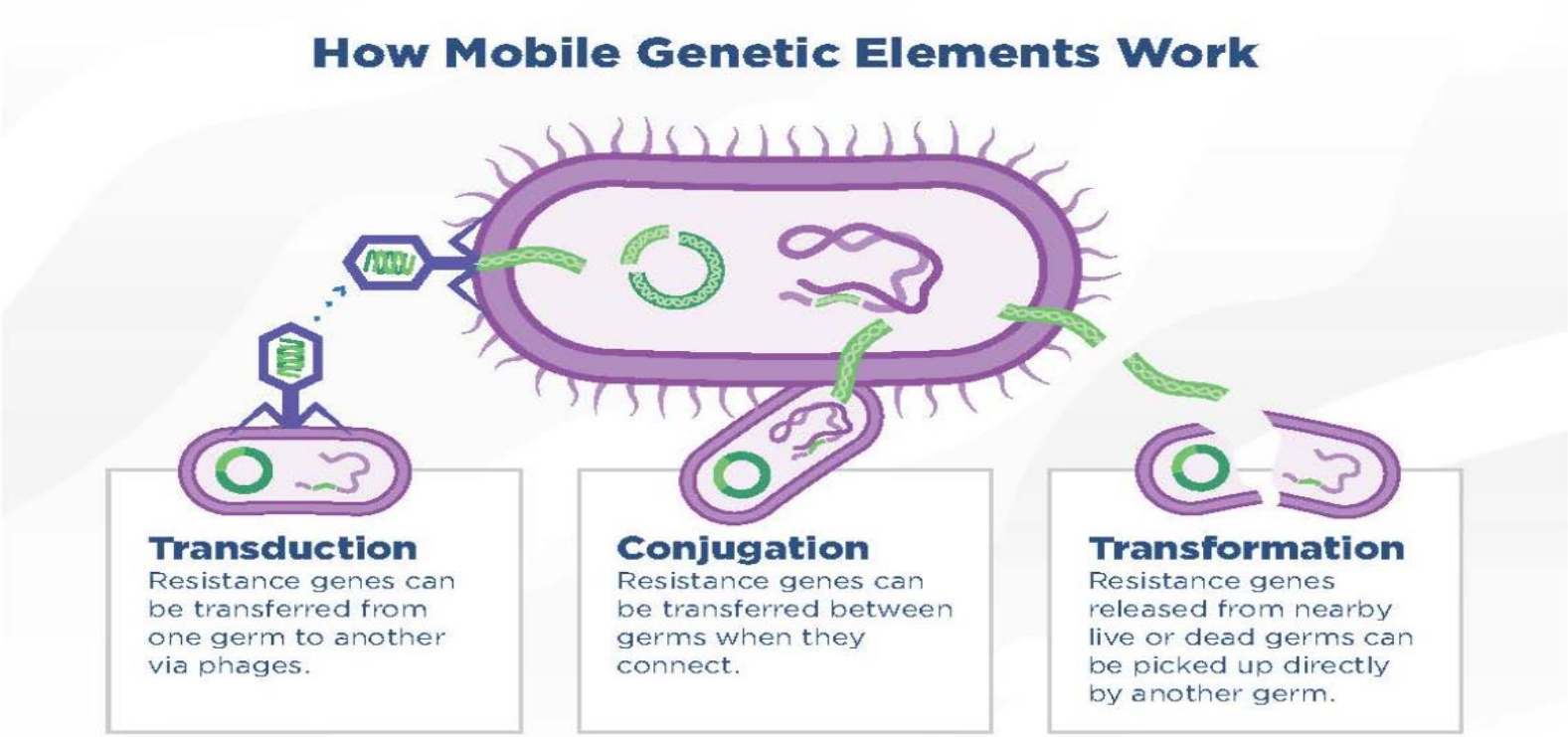
Small pieces of DNA that can go into and change the overall DNA of a cell. These can move from chromosomes (which carry all the genes essential for germ survival) to plasmids and back.

Phages

Viruses that attack germs and can carry DNA from germ to germ.

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

Transport of Resistance



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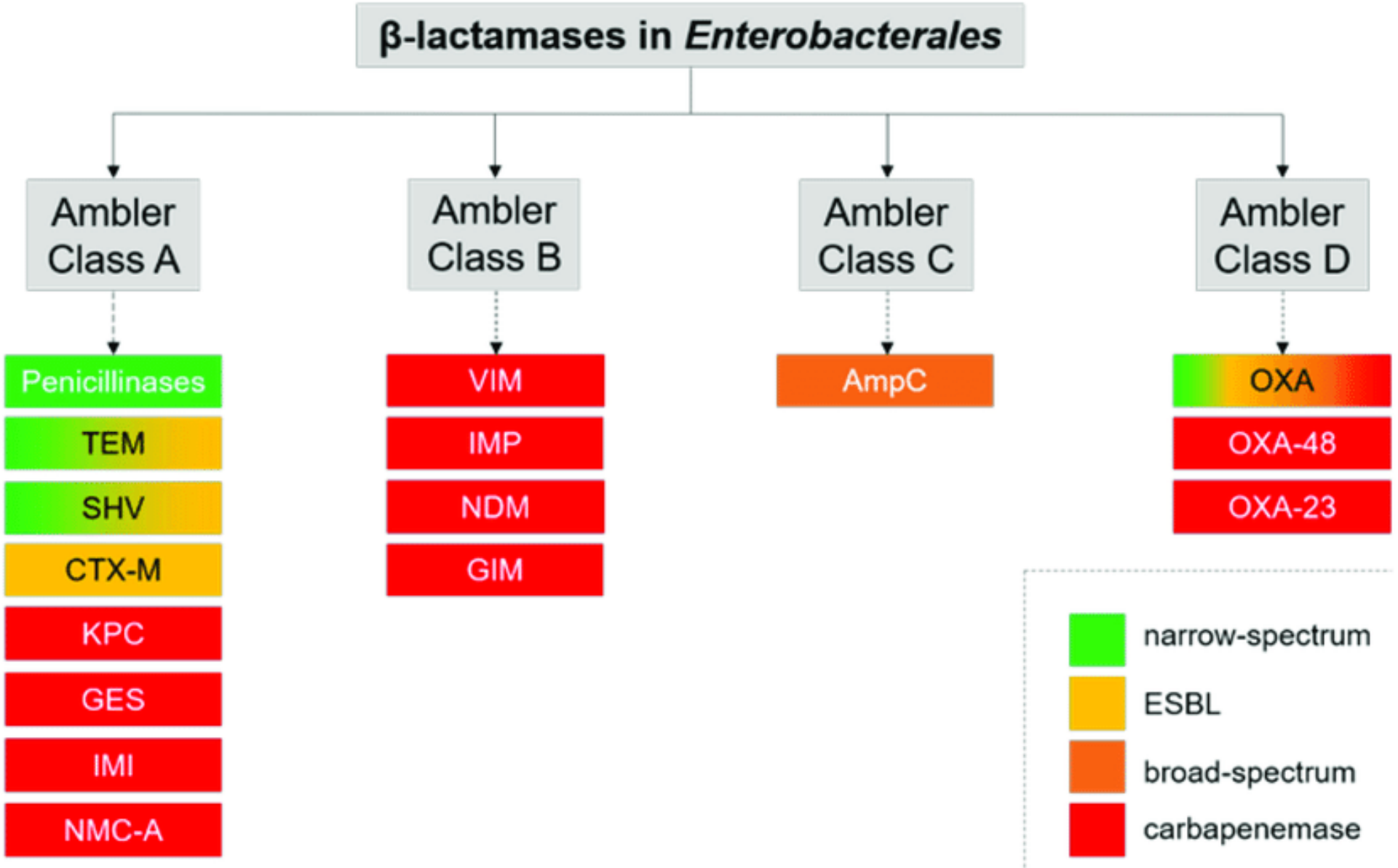


Noster J. et.al. Antibiotics (Basel). 2021 Sep 21;10(9):1140.

Beta-lactamase classification	Antibiotic resistance	Common organisms	Antibiotics affected
Serine Beta-lactamase (Ambler Class A)	- penicillinases and cephalosporinase - extended-spectrum beta-lactamases (ESBLs) - TEM and SHV - Plasmid CTX-M – hydrolysis - Carbapenemase KPC, GES, IMI, NMC-A	*E. Coli* *Klebsiella pneumoniae,* *Haemophilus influenzae,* *Proteus mirabilis* *Klebsiella oxytoca* *Serratia marcescens,* *Citrobacter* *Enterobacter* *Salmonella spp.*	1st and 2nd generation cephalosporins Penicillins, cephalosporins except cefoxitin and carbapenems Carbapenems
Metallo-B-lactamases (Ambler Class B)	- require zinc for activity - Hydrolysis of a wide range of beta- lactam antibiotics including carbapenems - Plasmid vectors - VIM, IMP, NDM, GIM	*Escherichia coli* *Klebsiella pneumoniae* other *Enterobacteriacae* *Pseudomonas aeruginosa* *Acinetobacter* species	Wide range of beta-lactams and Carbapenems

Beta-lactamase classification	Antibiotic resistance	Common organisms	Antibiotics affected
Serine β-lactamase (Ambler Class C)	- Predominant enzyme is Amp C - Found on the chromosome or can occur as a plasmid	*Enterobacter Cloacae* *Klebsiella aerogenes* *Citrobacter freundii* *Serratia marcescens* *Providencia stuartii* *Pseudomonas aeruginosa* *Hafnia alvei* *Morganella morganii*	- Active against all beta-lactam agents EXCEPT Cefepime and Carbapenems
Oxacillinases (Ambler Class D)	- Oxacillinase (OXA) – Penicillinase/Oxacillinase and ESBL - Carbapenemase genes (OXA48, OXA-23) - secondary resistance - porin deficiencies or overexpressed efflux pumps.	*Enterobacteriaceae, Acinetobacter baumannii, Klebsiella pneumoniae*	- Active against nearly all beta-lactam agents including carbapenems (weak) - Exceptions may include 3rd and 4th gen cephalosporins

Mechanism of CRE Resistance

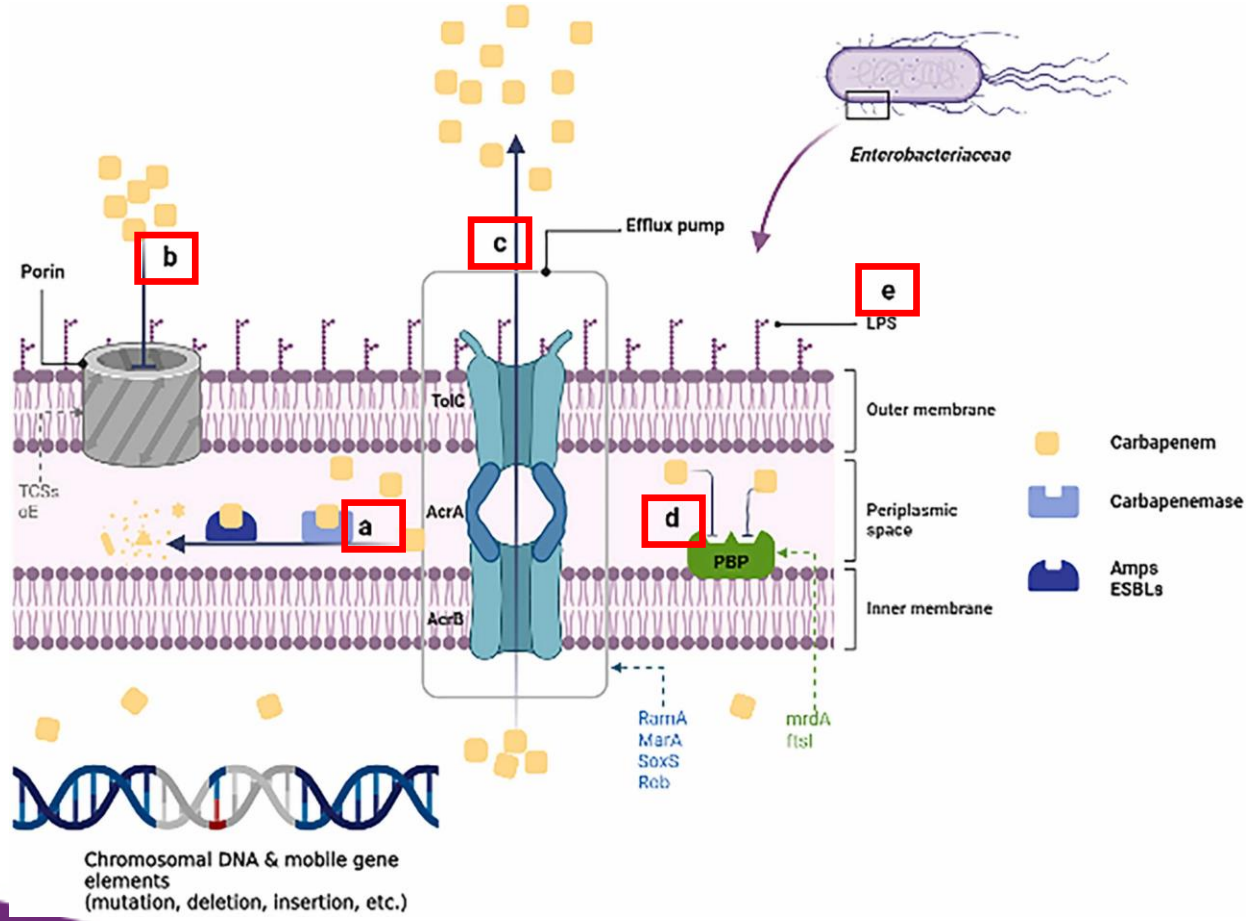
a. **Carbapenemase** production

b. **Altered pore proteins:** inability of carbapenems to enter the bacteria

c. **Efflux pump** excretes carbapenems

d. Changes in the **structure of the penicillin-binding protein (PBP**) – carbapenems unable to bind

e. Alteration of **biofilm** components leads to drug resistance, (e.g. Lipopolysaccharide)



Ma J. et. Al. Microbiological Research. January 2023, Vol 266

Enzymes Conferring Carbapenem Resistance

TABLE 1

Enzymes conferring carbapenem resistance in Enterobacteriaceae

Enzyme	Common genetic platform	Species distribution in Enterobacteriaceae	Geographic distribution
KPC (*Klebsiella pneumoniae* carbapenemase)	*K pneumoniae* sequence type 258, various plasmids types, transposon Tn*4401*x	*K pneumoniae, Escherichia coli, Enterobacter* species, diverse Enterobacteriaceae	Endemic in the United States, Greece, Israel, Italy, Puerto Rico, China, and South America
NDM (New Delhi metallo-beta-lactamase)	Various plasmid types	*K pneumoniae* and *E coli* predominantly, diverse Enterobacteriaceae	Indian subcontinent and the Balkan region, and around the world
OXA-48 (oxacillinase)	IncI/M-type plasmid	*K pneumoniae* predominantly, diverse Enterobacteriaceae	Southern and Western Europe, Turkey and North Africa; rare in the United States
VIM (Verona integron-encoded metallo-beta-lactamase)	Gene cassettes in class 1 integrons	*K pneumoniae* predominantly	Common in Italy, Greece, and the Far East, sporadic globally
IMP	Gene cassettes in class 1 integrons	*K pneumoniae* predominantly	Common in the Far East and South America, sporadic globally
SME	Chromosome	*Serratia marcescens*	Sporadic in North America and South America

BASED ON INFORMATION IN TZOUVELEKIS LS, MARKOGIANNAKIS A, PSICHOGIOU M, TASSIOS PT, DAIKOS GL. CARBAPENEMASES IN *KLEBSIELLA PNEUMONIAE* AND OTHER ENTEROBACTERIACEAE: AN EVOLVING CRISIS OF GLOBAL DIMENSIONS. CLIN MICROBIOL REV 2012; 25):682–707.

- **Transposons:** chromosomal segment that can transfer from a plasmid to other plasmids or from a DNA chromosome to plasmid and vice versa
- **Plasmid:** small, circular, double-stranded DNA molecule distinct from a cell's chromosomal DNA
- **Gene cassette**: mobile genetic element that can transpose into or out of a specific receptor site
- **Chromosome**: spontaneous, random, and relatively rare alterations in the DNA

Perez F. et. al. Cleveland Clinic Journal of Medicine. Vol 80; 4; April 2013

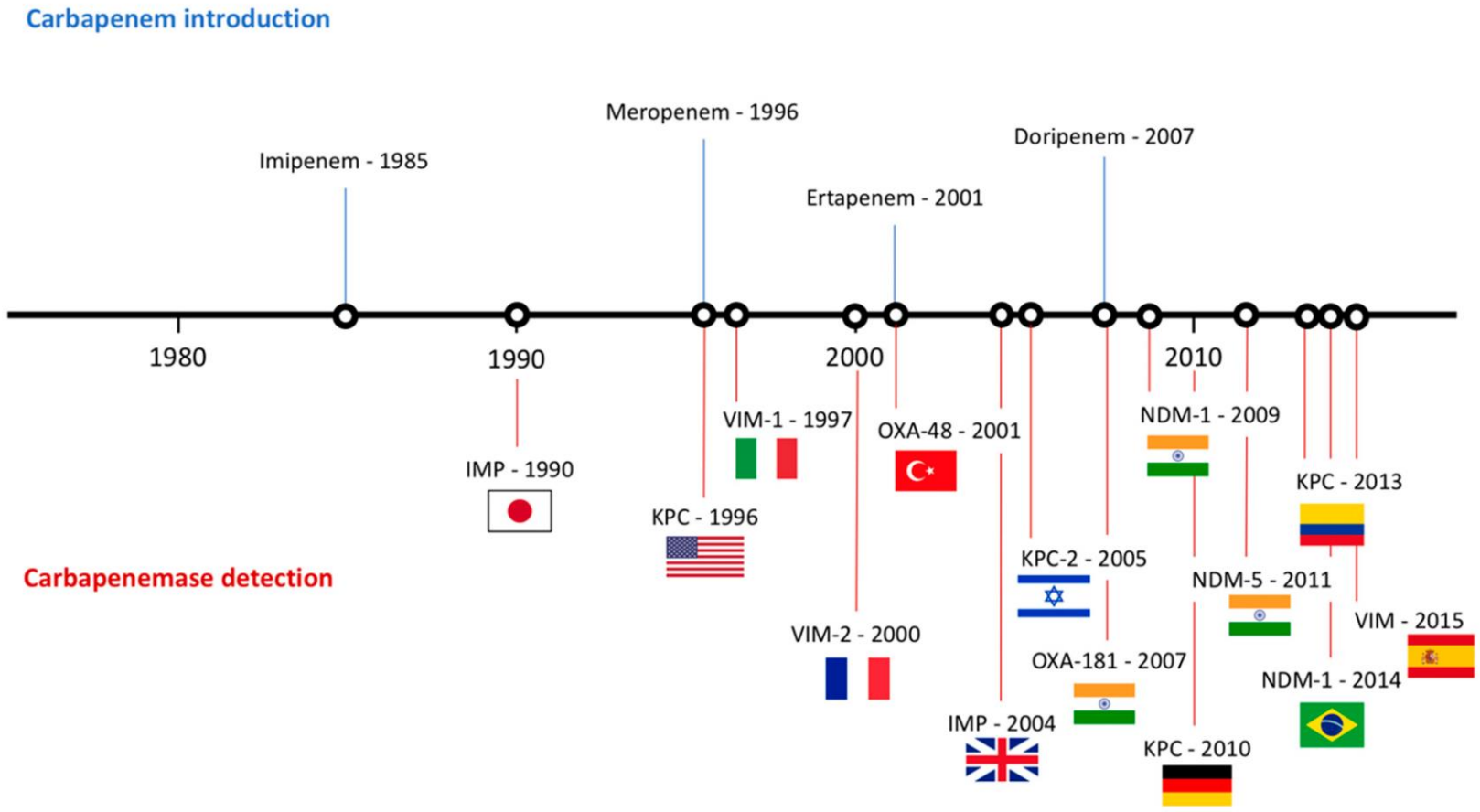
Laboratory Tests

- Traditional sensitivities
- Modified Hodge Test
- **Carbapenem Inactivation Method**
- EDTA Inhibition Test
- Boronic Acid Inhibition Test
- Carba NP Test
- Matrix-assisted laser desorption/ionization time-of-flight mass spectrometry (MALDI-TOF MS)

- **Polymerase Chain Reaction (PCR)**
- Duplex multiple cross displacement amplification combined with lateral flow biosensor (MCDA-LFB) method.
- Verigene Gram-negative blood culture assay: nucleic acid non-amplification test
- **DNA Microarray is another commonly used method.**
- **BioFire Film Array Method (PCR)**
- **Xpert Carba-R**
- Whole Genome Sequencing

Smith H. Carbapenem-Resistant Enterobacterales. StatPearls Publishing; 2024 Feb 2.

Carbapenem timeline



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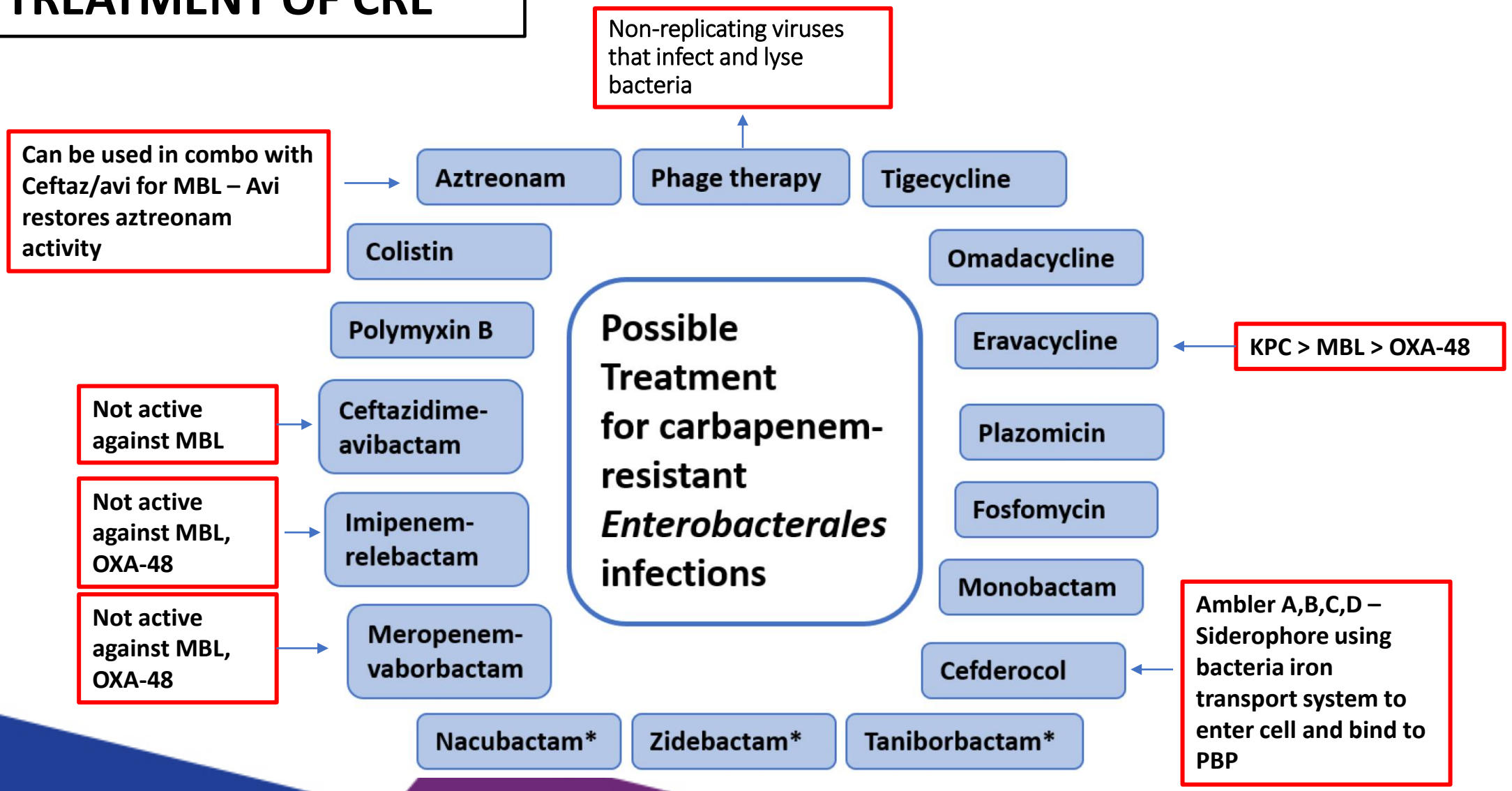
ANTIBIOTIC TREATMENT OF CRE



Rabaan AA et. al (Kaunas). 2022 Nov 19;58(11):1675.

Key Takeaways

- CRE is an urgent public health threat which needs to be addressed globally
- Multiple mechanisms of resistance exist for CRE which dictates treatment options
- Development of laboratory testing, especially PCR is a critical piece of the diagnosis and treatment of CRE
- Lack of effective antibiotics remains a challenge for treatment of CRE
- Antibiotic stewardship is an important part of preventing the emergence of CRE

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