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# Antimicrobial Resistance in ESKAPE Pathogens

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# Objectives

- Recognize common patterns of multi-drug resistance (MDR) that emerge with the ESKAPE pathogens
- Identify common “susceptibility clues” in the antibiotic susceptibility report that are indicative of MRSA, VRE, ESBL and carbapenem resistance
- Compare and contrast treatment approaches in terms of site of infection, coverage of resistance mechanisms, and toxicity risks

**What is the current scope of the  
AMR problem?**

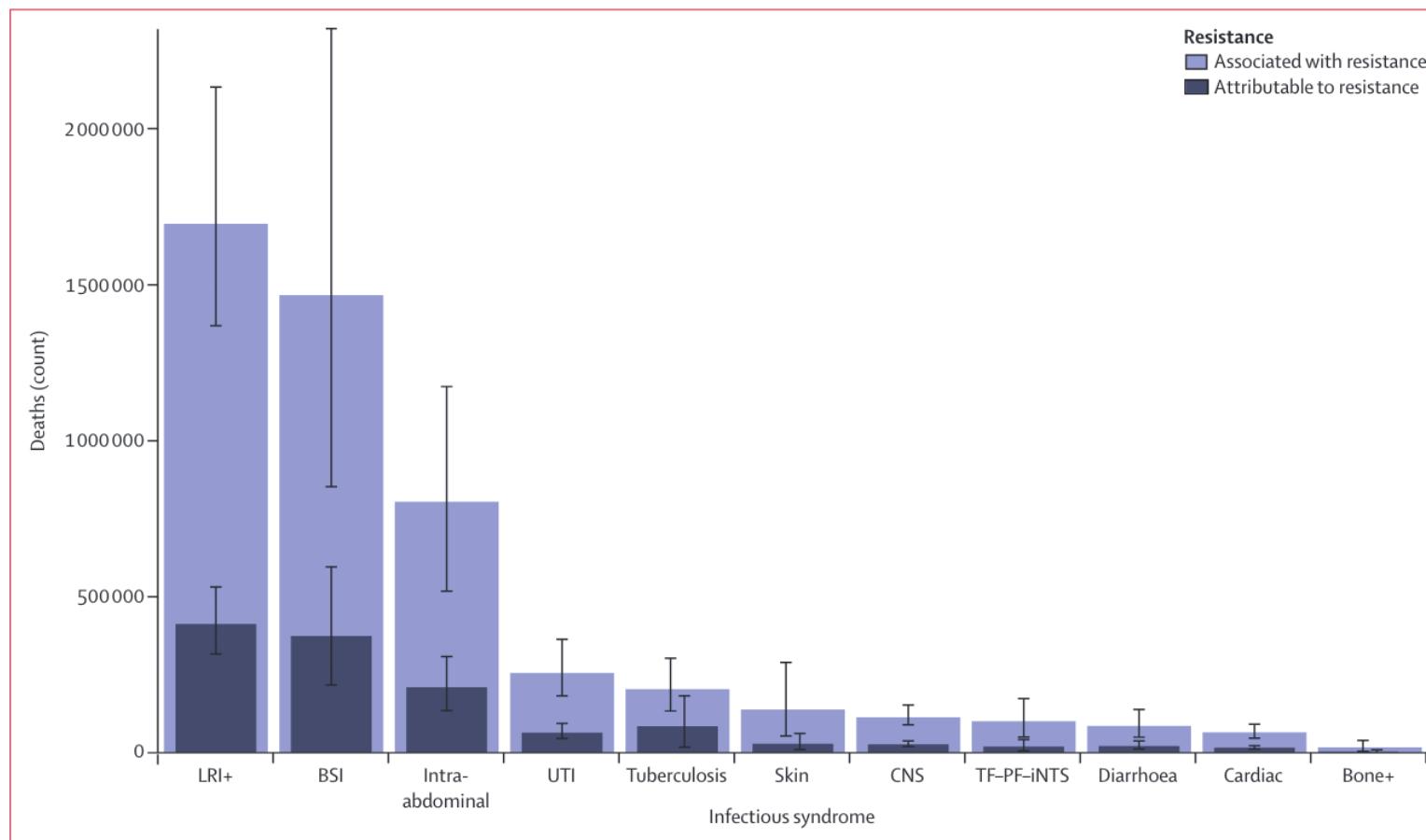
# Resistance definitions

Resistance type	Definition
Multidrug-resistance (MDR)	Resistance to one agent in at least 3 antibiotic categories
Extreme drug resistance (XDR)	Resistant except to 2 or fewer antibiotic categories
Pan-drug resistance (PDR)	Resistant to all agents in all agents in all antibiotic categories
Difficult-to-treat resistance (DTR)	Requires the use of less-effective or more toxic “reserve” antibiotics

Magiorakos A-P et al. Clinical Microbiology and Infection. 2012;268–81.

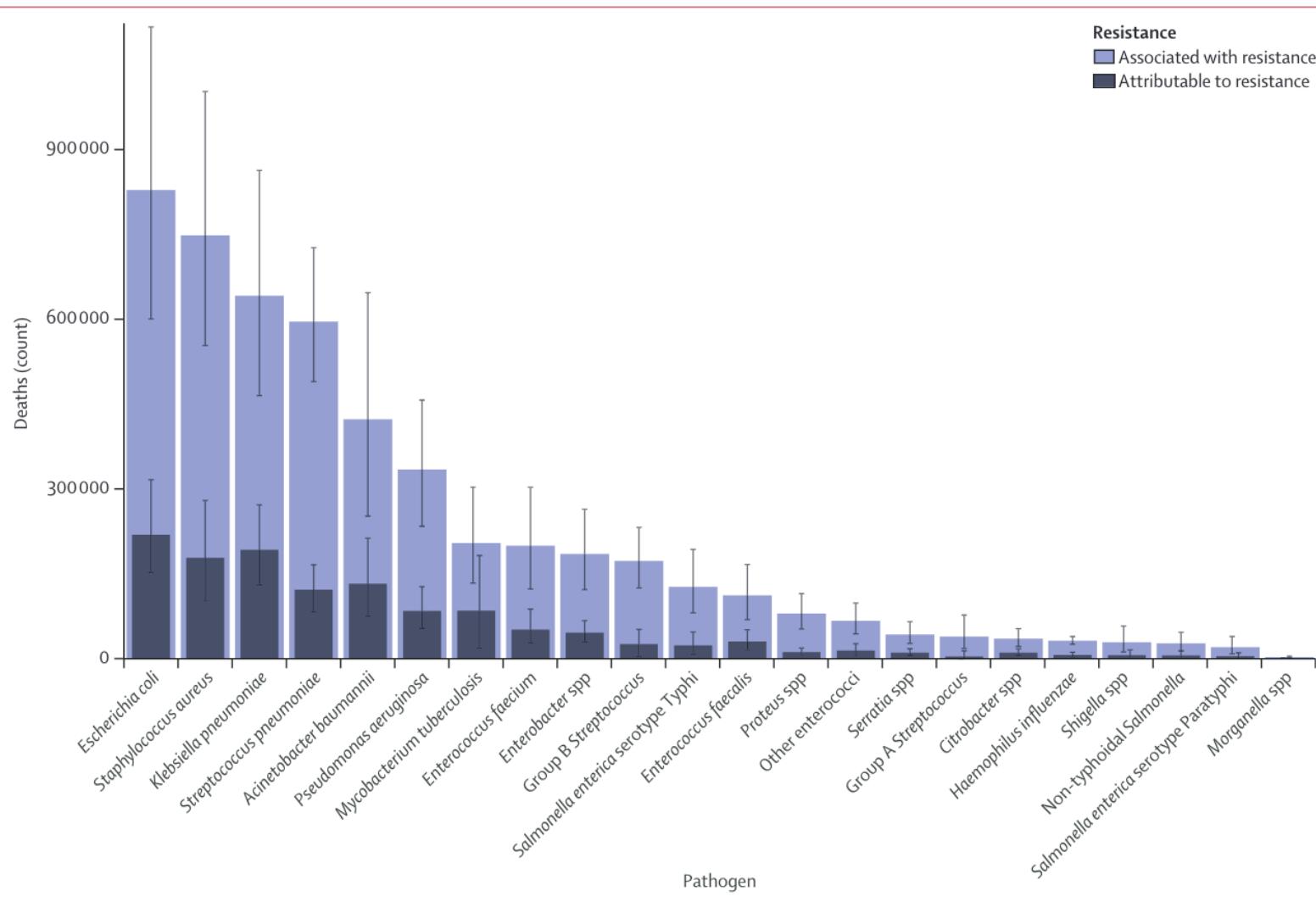
Kadri SS et al. Clinical Infectious Diseases. 2018;1803–14.

Murray CJ et al. The Lancet. 2022 Feb 12;399(10325):629–55.



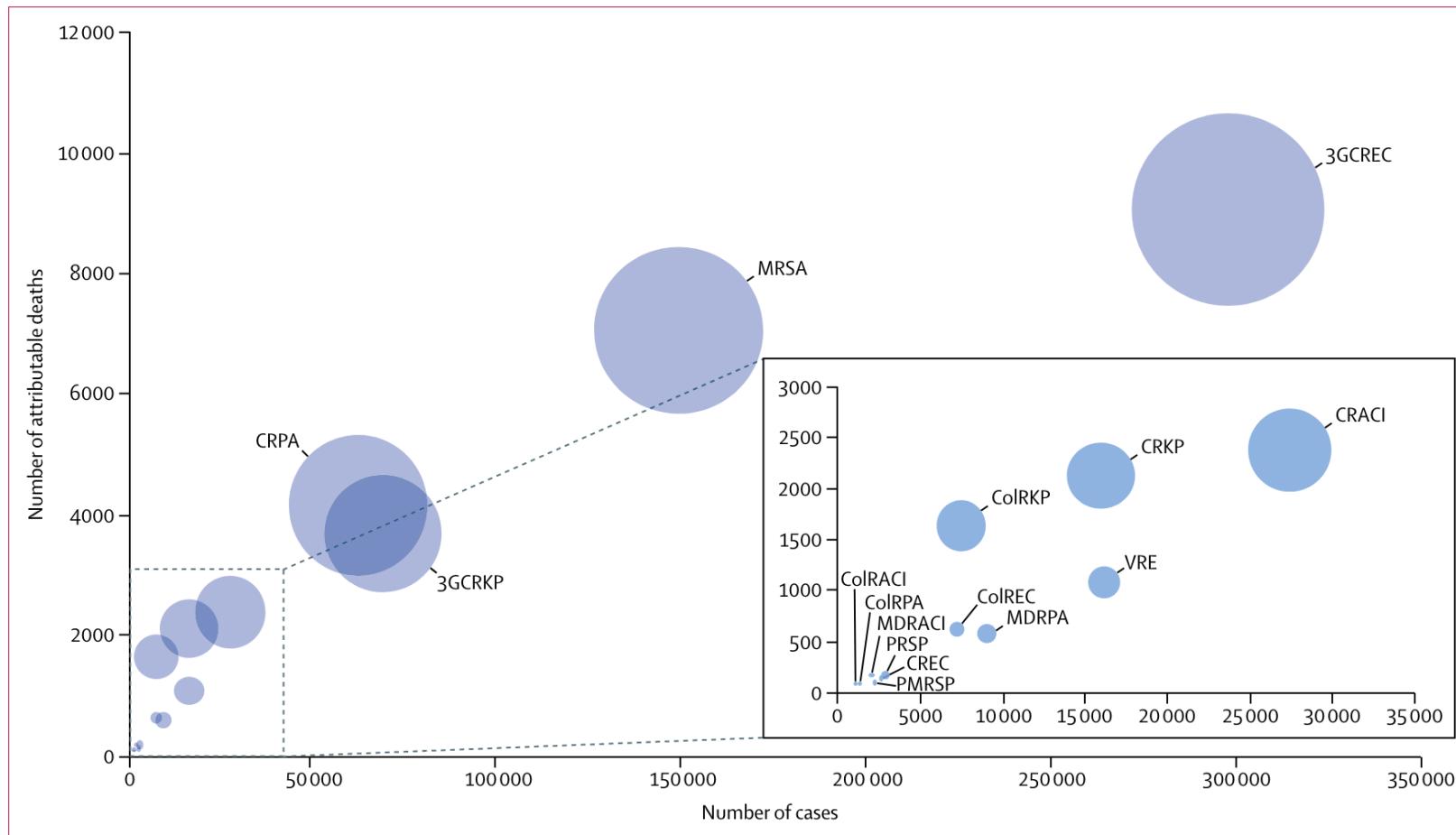
**Figure 3: Global deaths (counts) attributable to and associated with bacterial antimicrobial resistance by infectious syndrome, 2019**

Estimates were aggregated across drugs, accounting for the co-occurrence of resistance to multiple drugs. Error bars show 95% uncertainty intervals. Does not include gonorrhoea and chlamydia because we did not estimate the fatal burden of this infectious syndrome. Bone+=infections of bones, joints, and related organs. BSI=bloodstream infections. Cardiac=endocarditis and other cardiac infections. CNS=meningitis and other bacterial CNS infections. Intra-abdominal=peritoneal and intra-abdominal infections. LRI+=lower respiratory infections and all related infections in the thorax. Skin=bacterial infections of the skin and subcutaneous systems. TF-PF-iNTS=typhoid fever, paratyphoid fever, and invasive non-typhoidal *Salmonella* spp. UTI=urinary tract infections and pyelonephritis.



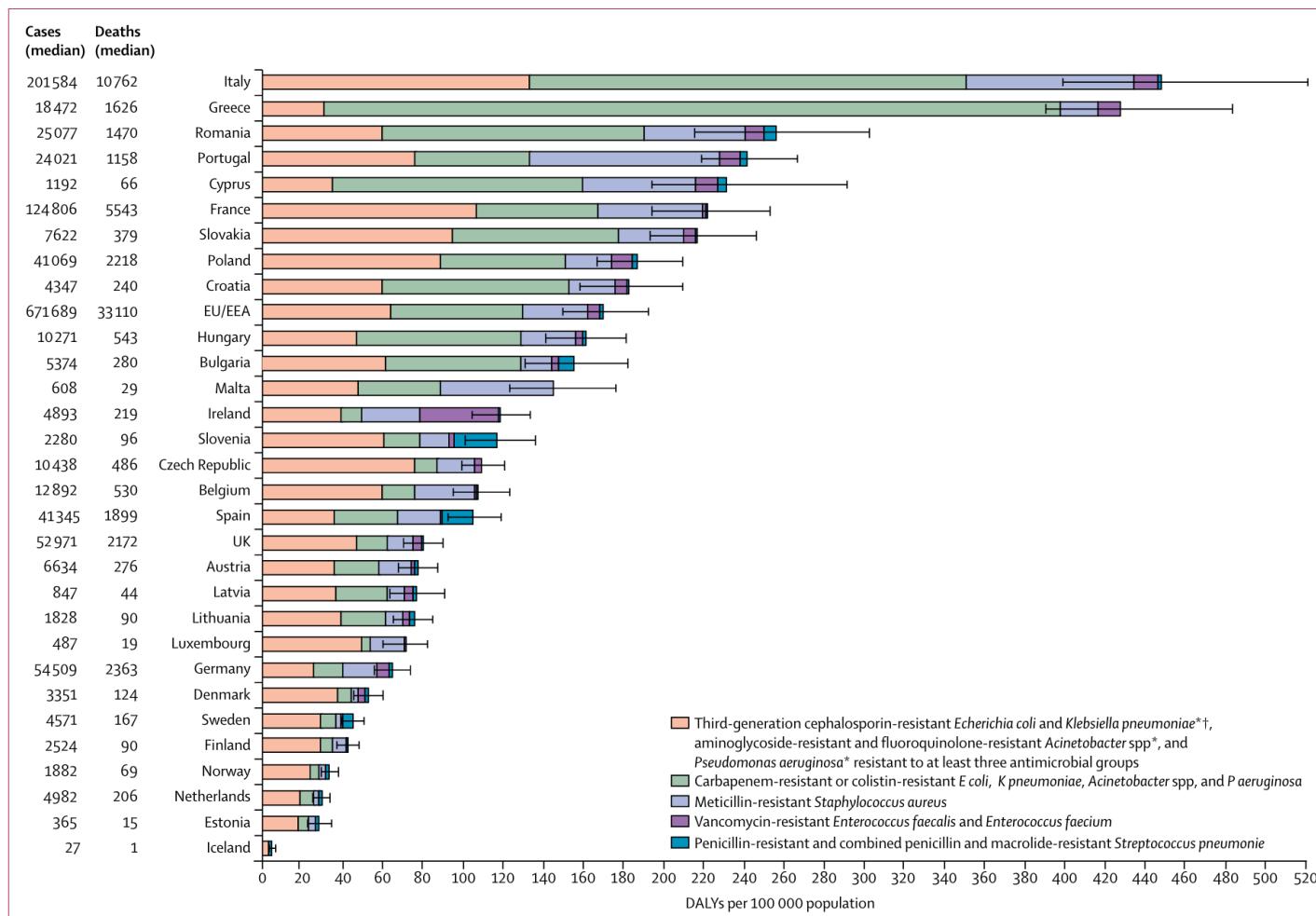
**Figure 4: Global deaths (counts) attributable to and associated with bacterial antimicrobial resistance by pathogen, 2019**

Estimates were aggregated across drugs, accounting for the co-occurrence of resistance to multiple drugs. Error bars show 95% uncertainty intervals.



**Figure 1: Infections with antibiotic-resistant bacteria, EU and European Economic Area, 2015**

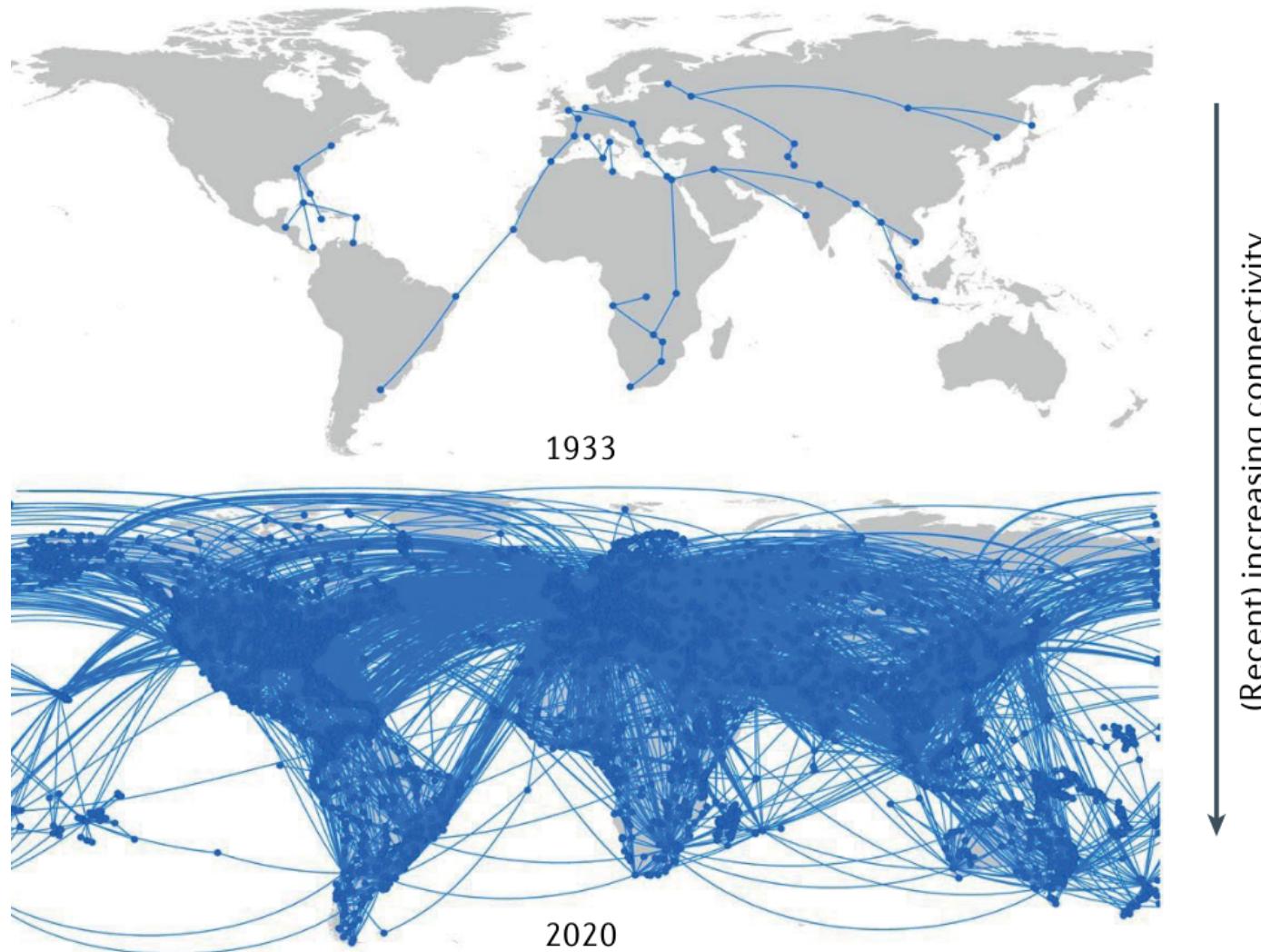
Diameter of bubbles represents the number of disability-adjusted life-years. ColRACI=colistin-resistant *Acinetobacter* spp. CRACI=carbapenem-resistant *Acinetobacter* spp. MDRACI=multidrug-resistant *Acinetobacter* spp. VRE=vancomycin-resistant *Enterococcus faecalis* and *Enterococcus faecium*. ColREC=colistin-resistant *Escherichia coli*. CREC=carbapenem-resistant *E. coli*. 3GCREC=third-generation cephalosporin-resistant *E. coli*. ColRKP=colistin-resistant *Klebsiella pneumoniae*. CRKP=carbapenem-resistant *K. pneumoniae*. 3GCRKP=third-generation cephalosporin-resistant *K. pneumoniae*. ColRPA=colistin-resistant *Pseudomonas aeruginosa*. CRPA=carbapenem-resistant *P. aeruginosa*. MDRPA=multidrug-resistant *P. aeruginosa*. MRSA=meticillin-resistant *Staphylococcus aureus*. PRSP=penicillin-resistant *Streptococcus pneumoniae*. PMRSP=penicillin-resistant and macrolide-resistant *S. pneumoniae*.



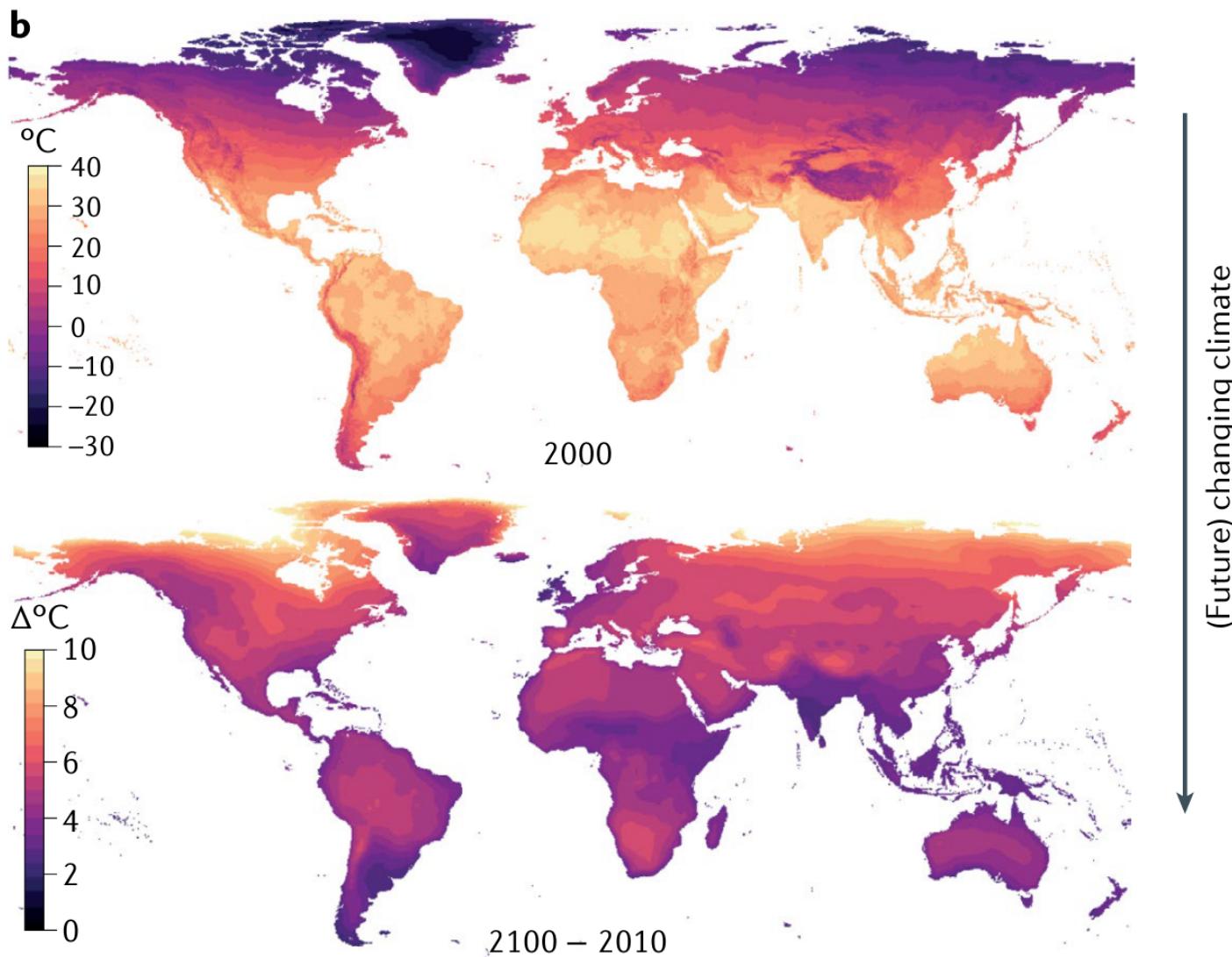
**Figure 3: Burden of infections with antibiotic-resistant bacteria in DALYs, EU and European Economic Area, 2015**

Error bars are 95% uncertainty intervals. Greece did not report data on *S pneumoniae* isolates to the European Antimicrobial Resistance Surveillance Network in 2015. DALY rates are age-standardised to limit the effect of demographic differences across countries; numbers of cases and deaths are not age-standardised. DALYs=disability-adjusted life-years. \*Excludes those resistant to carbapenem or colistin. †In 2015, most of the third-generation cephalosporin-resistant *E coli* (88·6%) and *K pneumoniae* (85·3%) isolates reported to the European Antimicrobial Resistance Surveillance Network produced an extended-spectrum β-lactamase.<sup>9</sup>

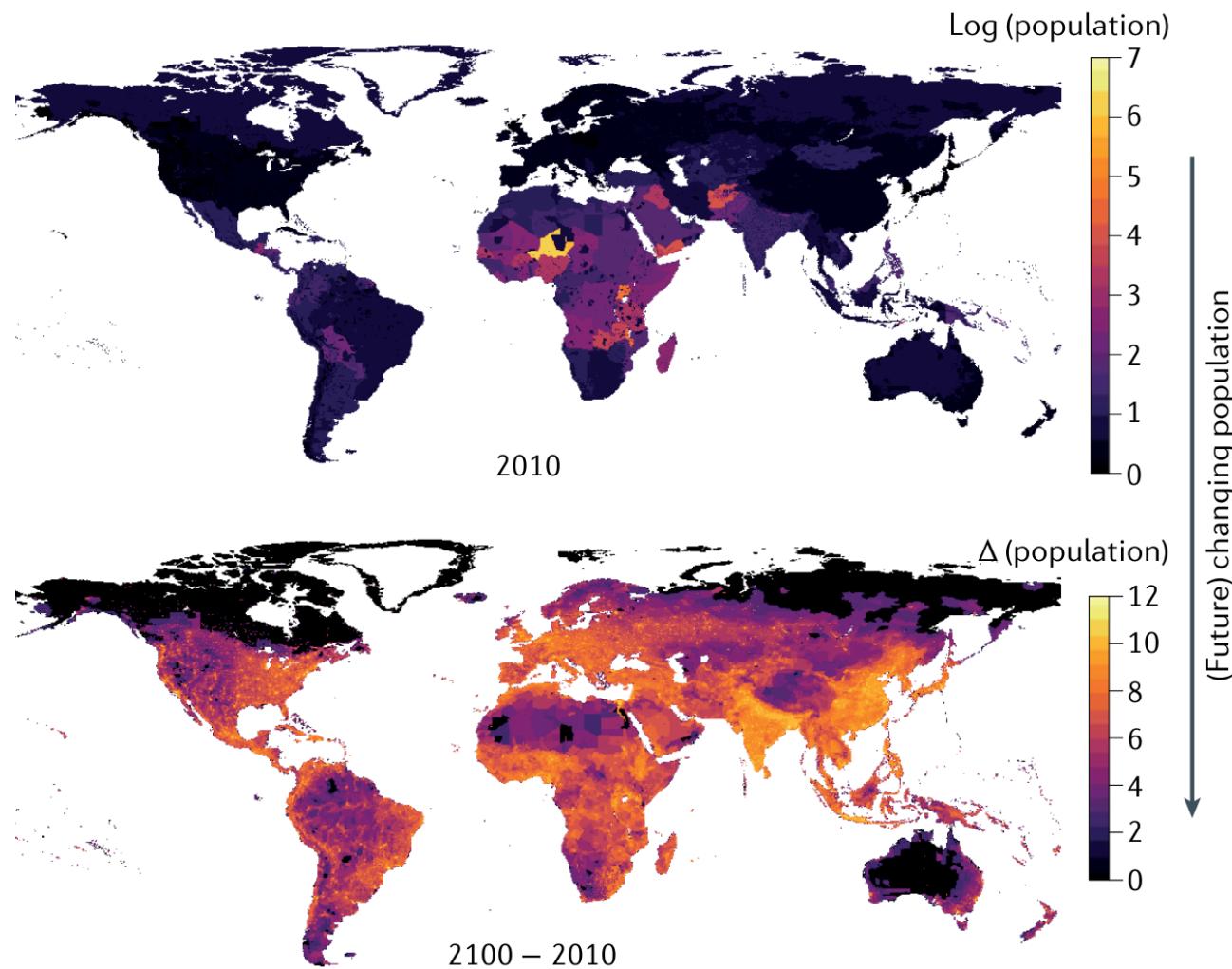
## Mapping changes in air travel

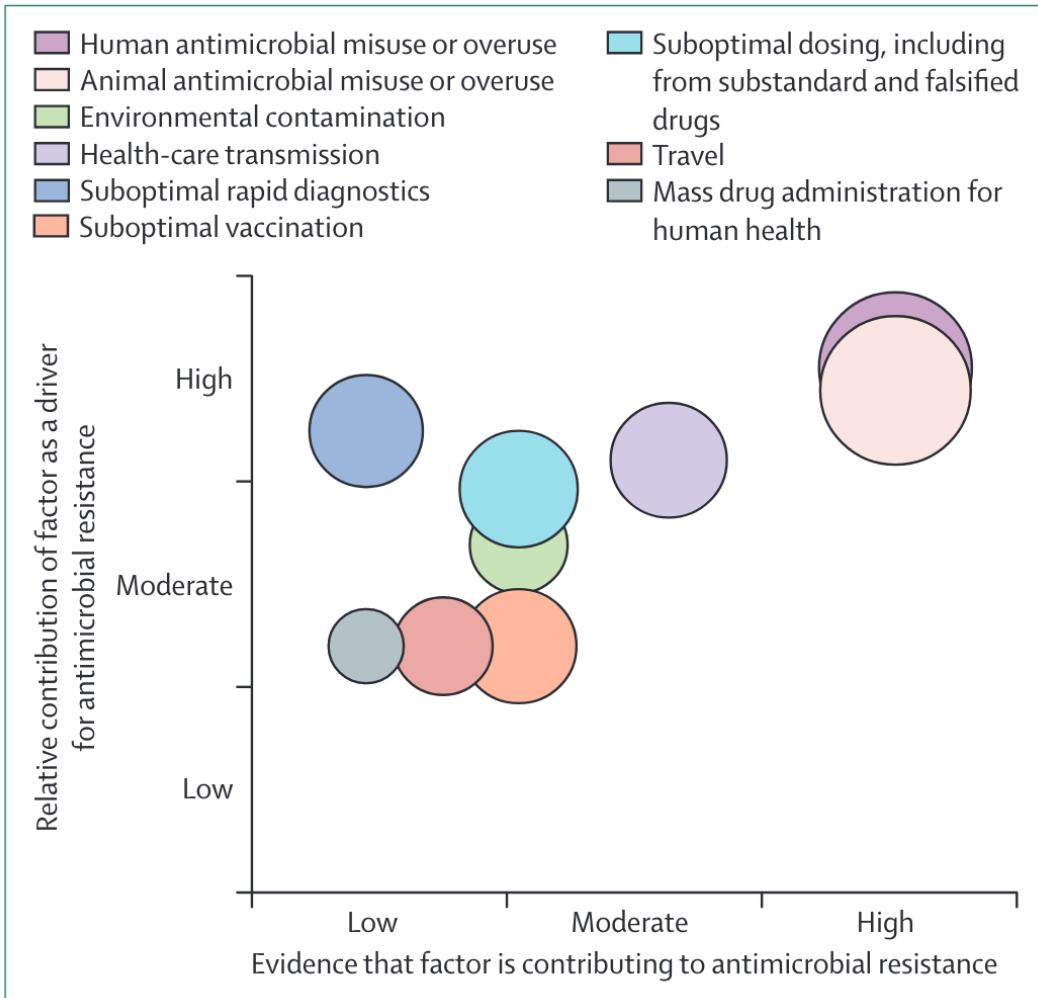


## Mapping changes in climate



## Mapping changes in population

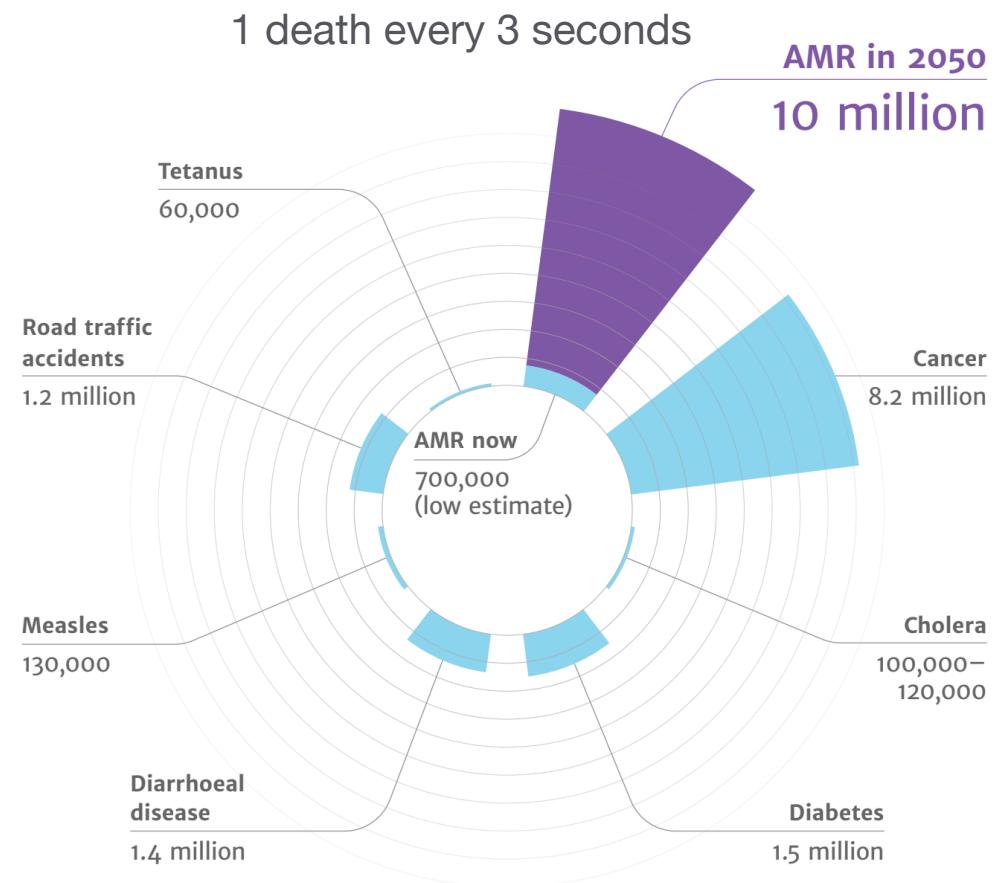




**Figure 3: Role of modifiable drivers for antimicrobial resistance: a conceptual framework**

Holmes AH, et al. The Lancet. 2016 Jan 9;387(10014):176–87.

# What future are we heading towards?



O'Neill J. Tackling drug-resistant infections globabally: Final report and recommendations [Internet]. 2016 [cited 2021 Nov 24]. 84 p.  
Available from: [https://amr-review.org/sites/default/files/160525\\_Final%20paper\\_with%20cover.pdf](https://amr-review.org/sites/default/files/160525_Final%20paper_with%20cover.pdf)

**What are the highest priority  
pathogens?**

# TUBERCULOSIS: A GLOBAL PRIORITY FOR RESEARCH AND DEVELOPMENT

## FIVE REASONS WHY



Tuberculosis (TB) is the number one global infectious disease killer today, causing 1.8 million deaths per year. Drug-resistant TB is the most common and lethal airborne AMR disease worldwide today, responsible for 250 000 deaths each year.



Patients with multidrug-resistant TB (MDR-TB<sup>1</sup>) need complex and prolonged multidrug treatment with costly, highly toxic, and much less effective second-line medicines. There is a limited number of second-line medicines to treat MDR-TB and only 52% of patients are successfully treated globally.



In about 50% of MDR-TB patients worldwide, treatment regimens are already compromised by second-line drug resistance. Treatment of extensively drug-resistant disease (XDR-TB<sup>2</sup>) is successful in only one in three patients at best.



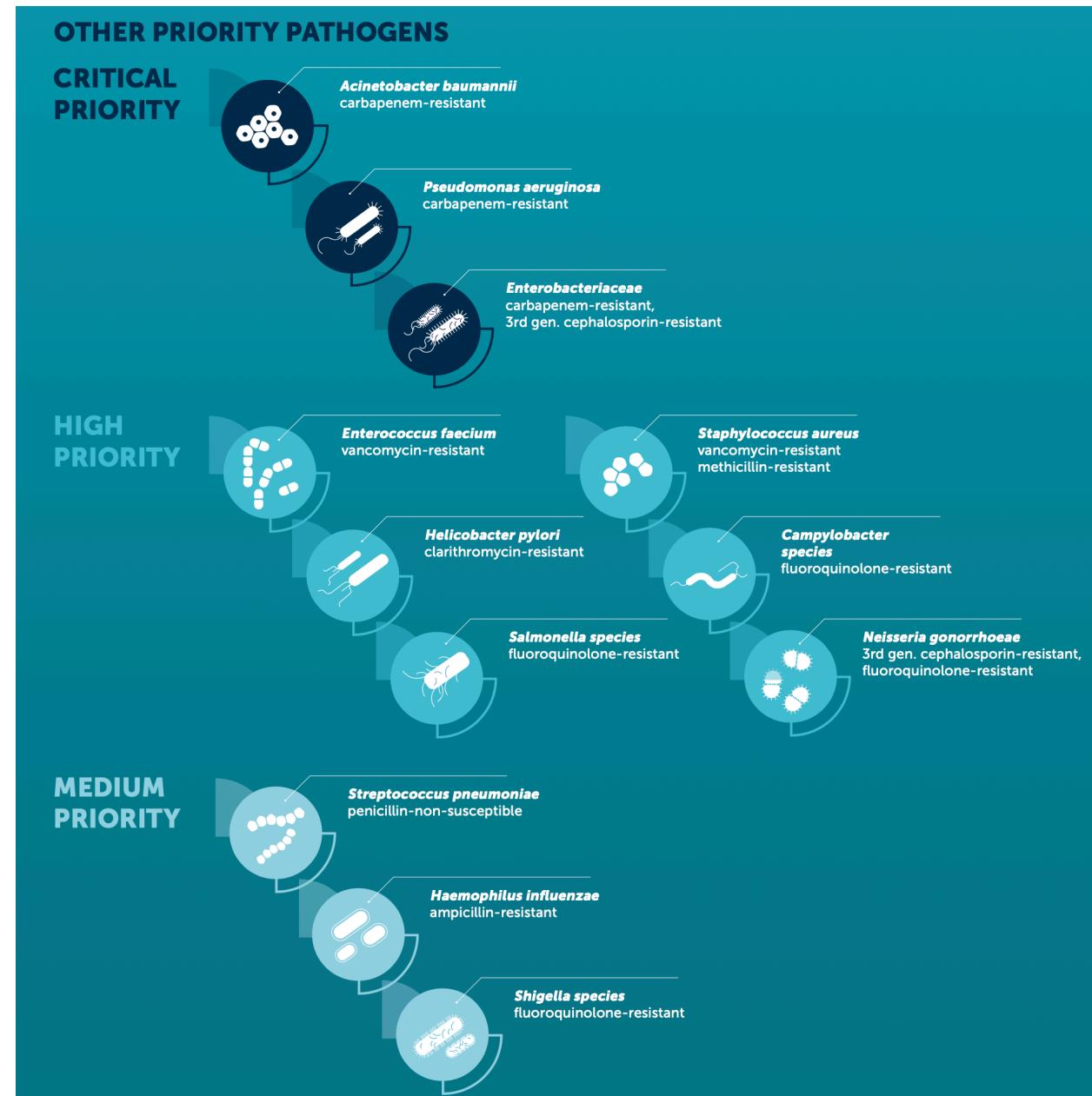
Patients with M/XDR-TB face agonising, prolonged suffering and often permanent disability while on treatment, compounded by devastating economic hardship, stigma and discrimination.



Only two new antibiotics for treatment of MDR-TB have reached the market in over 70 years. R&D investment in TB – seriously underfunded – is at its lowest level since 2008.

<sup>1</sup> MDR-TB – multidrug-resistant tuberculosis, that does not respond to at least isoniazid and rifampicin, the two most powerful first-line anti-TB medicines.

<sup>2</sup> XDR-TB – extensively drug-resistant tuberculosis, defined as MDR-TB plus resistance to fluoroquinolones and injectable second-line anti-TB medicines.



Source:  
WHO 2021 Priority Pathogens List



## The Critical Need for New Antibiotics

There are not enough antibiotics in development globally to meet current and anticipated patient needs.

There are only **43 antibiotics** in clinical development.\*



\* Total number of antibiotics in Phases 1-3 does not add up to 43 because new drug applications have been submitted for two drugs.

Historical data show that, generally, only

**1 in 5**

infectious disease drugs that enter Phase 1 trials will receive FDA approval.<sup>1</sup>

Products can fail to receive approval for many reasons, including lack of effectiveness or safety concerns.



### Critical threat pathogens

The World Health Organization considers three bacteria—all of which are resistant to last-line carbapenem antibiotics—to be critical threats to public health. These pathogens—carbapenem-resistant/ESBL-producing Enterobacteriaceae (CRE), *Pseudomonas aeruginosa* (CRPA), and *Acinetobacter baumannii* (CRAB)<sup>4</sup>—often cause severe complications in hospitalized patients, with up to 50 percent of patients dying from bloodstream infections caused by CRE.<sup>5</sup> There is an urgent need to address these critical threats, but only 15 antibiotics in development have the potential to treat infections caused by these bacteria.



**Only 15 antibiotics** in development have the potential to treat WHO's critical threat pathogens.



### Endnotes

- 1 Biotechnology Innovation Organization, "Clinical Development Success Rates 2006-2015" (2016), <https://www.bio.org/sites/default/files/Clinical%20Development%20Success%20Rates%202006-2015%20-%20BIO,%20Biomedtracker,%20Ampion%202016.pdf>.
- 2 The ESKAPE pathogens—*Enterococcus faecium*, *Staphylococcus aureus*, *Klebsiella pneumoniae*, *Acinetobacter baumannii*, *Pseudomonas aeruginosa*, and *Enterobacter* species—cause many infections in the United States and show resistance to many currently available antibiotics. Within the ESKAPE pathogens are key Gram-negative bacteria, including *K. pneumoniae*, *A. baumannii*, *P. aeruginosa*, and *Enterobacter* species. These pathogens are particularly concerning due to the difficulty in discovering new therapies that can overcome current resistance. Stakeholders often highlight the Gram-negative ESKAPE pathogens as an area in which drug innovation is urgently needed.
- 3 An antibiotic is considered to have potential to treat Gram-negative ESKAPE pathogens if the drug has *in vitro* or *in vivo* data showing both activity against one or more Gram-negative species that are considered ESKAPE pathogens and the potential for clinically significant improved coverage of isolates of these species relative to currently available antibiotics. For additional information, see <http://www.pewtrusts.org/en/multimedia/data-visualizations/2014/antibiotics-currently-in-clinical-development>.
- 4 World Health Organization, "Global Priority List of Antibiotic-Resistant Bacteria to Guide Research, Discovery, and Development of New Antibiotics" (2017), <https://www.who.int/medicines/publications/global-priority-list-antibiotic-resistant-bacteria/en/>.
- 5 U.S. Centers for Disease Control and Prevention, "Antibiotic Resistance Threats in the United States, 2019" (2019), <https://www.cdc.gov/drugresistance/pdf/threats-report/2019-ar-threats-report-508.pdf>.

This infographic was updated in March 2021 based on analysis as of December 2020.

### Antibiotics in Clinical Development With the Potential to Treat Infections Caused by Gram-Negative ESKAPE Pathogens<sup>†</sup>



There is a critical need for new therapies to treat deadly infections caused by Gram-negative ESKAPE pathogens<sup>2</sup>—bacteria that are often resistant to available antibiotics. Only a handful of new treatments with the potential to address these serious threats are currently in development.<sup>3</sup>

† One drug with a submitted new drug application also has the potential to treat Gram-negative ESKAPE pathogens.

**For further information, please visit:**  
[pewtrusts.org/antibiotic-pipeline](http://pewtrusts.org/antibiotic-pipeline)

Contact: Heather Cable, manager Email: [hcable@pewtrusts.org](mailto:hcable@pewtrusts.org) Phone: 202-552-2059

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# *ESKAPE Pathogens*

*Enterococcus faecium (vancomycin-resistant)*

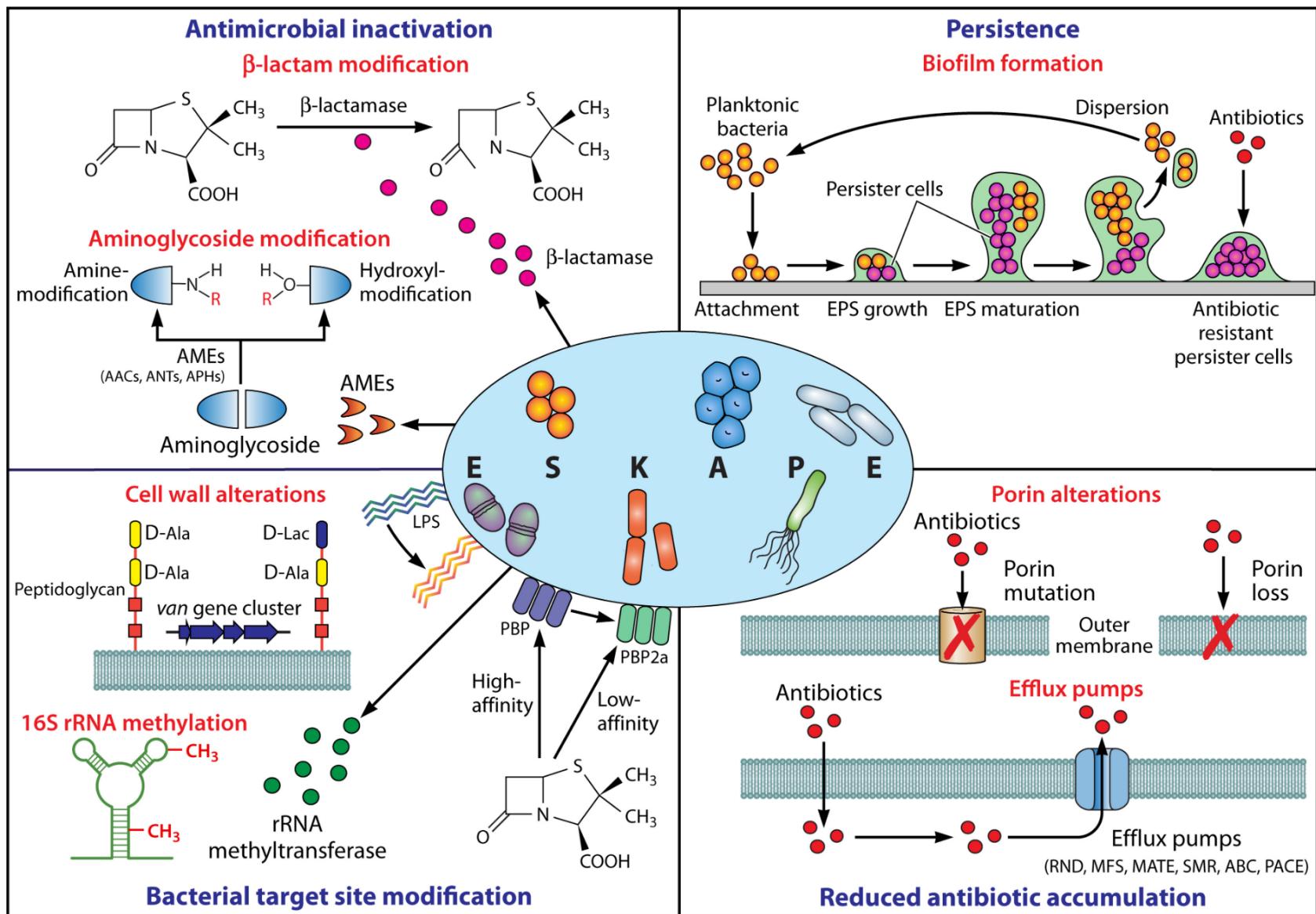
*Staphylococcus aureus (MRSA)*

*Klebsiella pneumoniae (ESBL, carbapenem-resistant)*

*Acinetobacter baumanii*

*Pseudomonas aeruginosa*

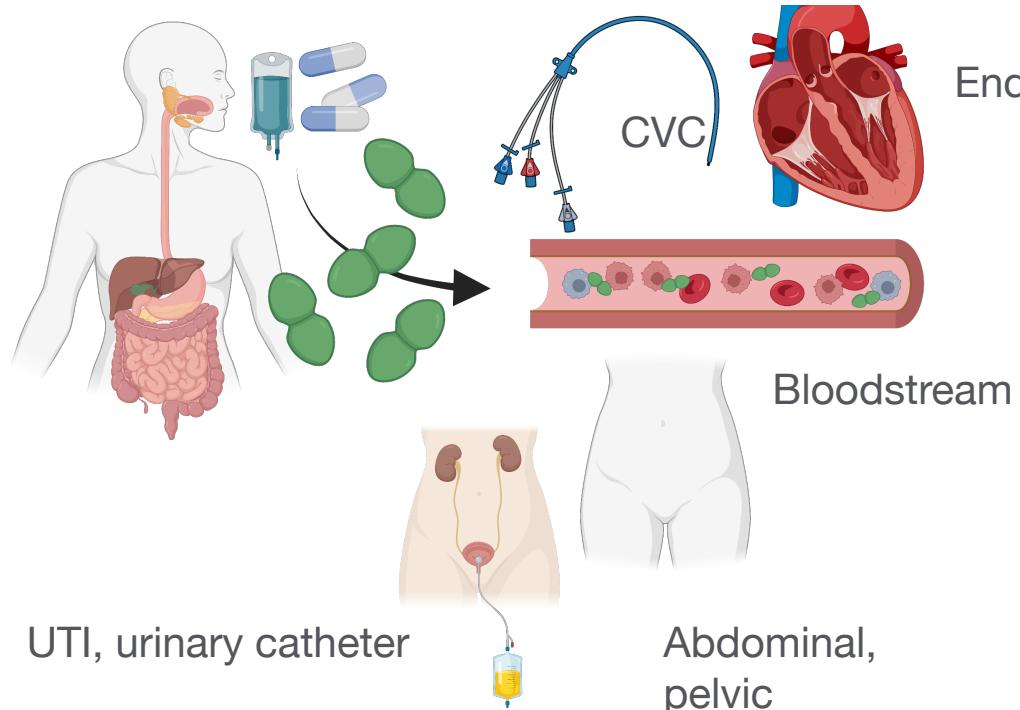
*Enterobacter spp.*



De Oliveira DMP, Forde BM, Kidd TJ et al. Antimicrobial Resistance in ESKAPE Pathogens. Clin Microbiol Rev. 2020;33

# Vancomycin-resistant *Enterococcus*

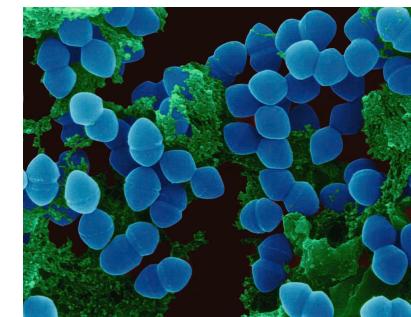
3rd generation cephalosporins  
selection pressure (**intrinsic resistance**)



Asymptomatic colonisation common; 30% mortality in bacteremia



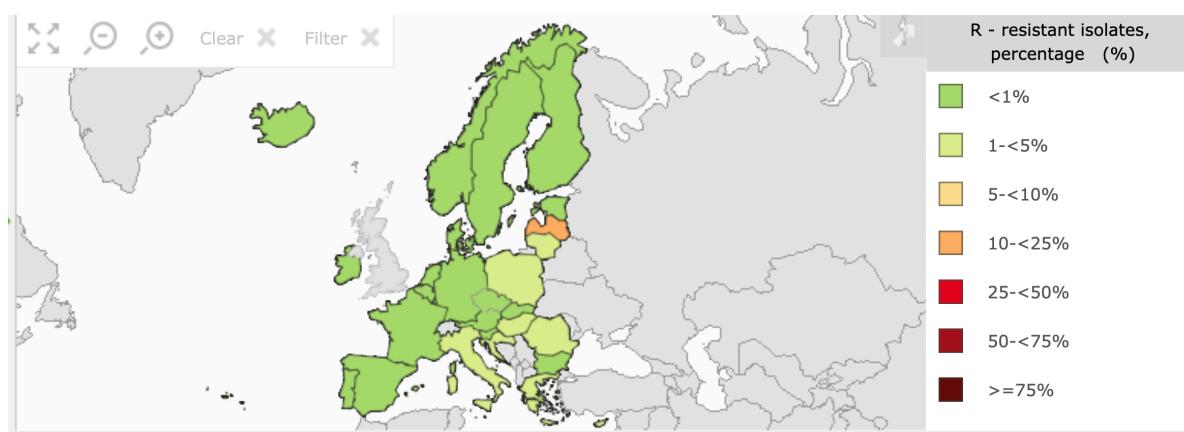
*Enterococcus faecalis*  
(Ampicillin-resistance)



*Enterococcus faecium*  
(Ampicillin and vancomycin resistance)

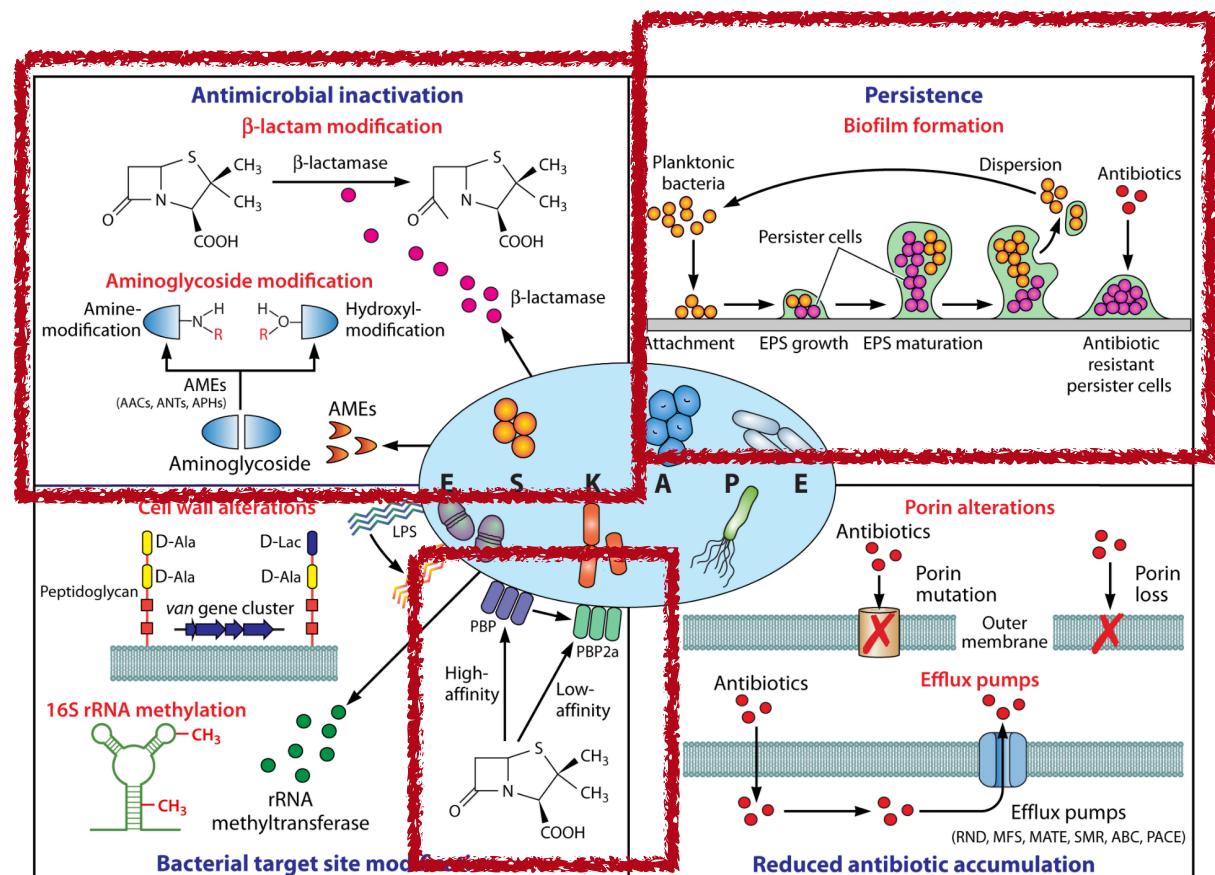
# *Enterococcus faecalis*

Aminopenicillin resistance



# Enterococcus faecalis

- Penicillin G and ampicillin are the most active drugs for susceptible strains
- Gentamicin was used in the past to improve bactericidal activity
- Susceptibility typically tested with 500 µg disk
  - Tobramycin and amikacin should not be used
- Ampicillin + ceftriaxone has shown similar efficacy regardless of gentamicin susceptibility- now preferred regimen (differential targeting of PBPs → synergy)<sup>1,2</sup>
- Most common resistance mechanism:** mutations in penicillin-binding proteins (PBP)
- Less common:** *blaZ*-encoded β-lactamases
  - Vancomycin
  - Ampicillin-Sulbactam (β-lactamase positive)
  - In urine only: Nitrofurantoin or Fosfomycin
- Vancomycin-resistant strains- treatment similar to VRE *E. faecium*

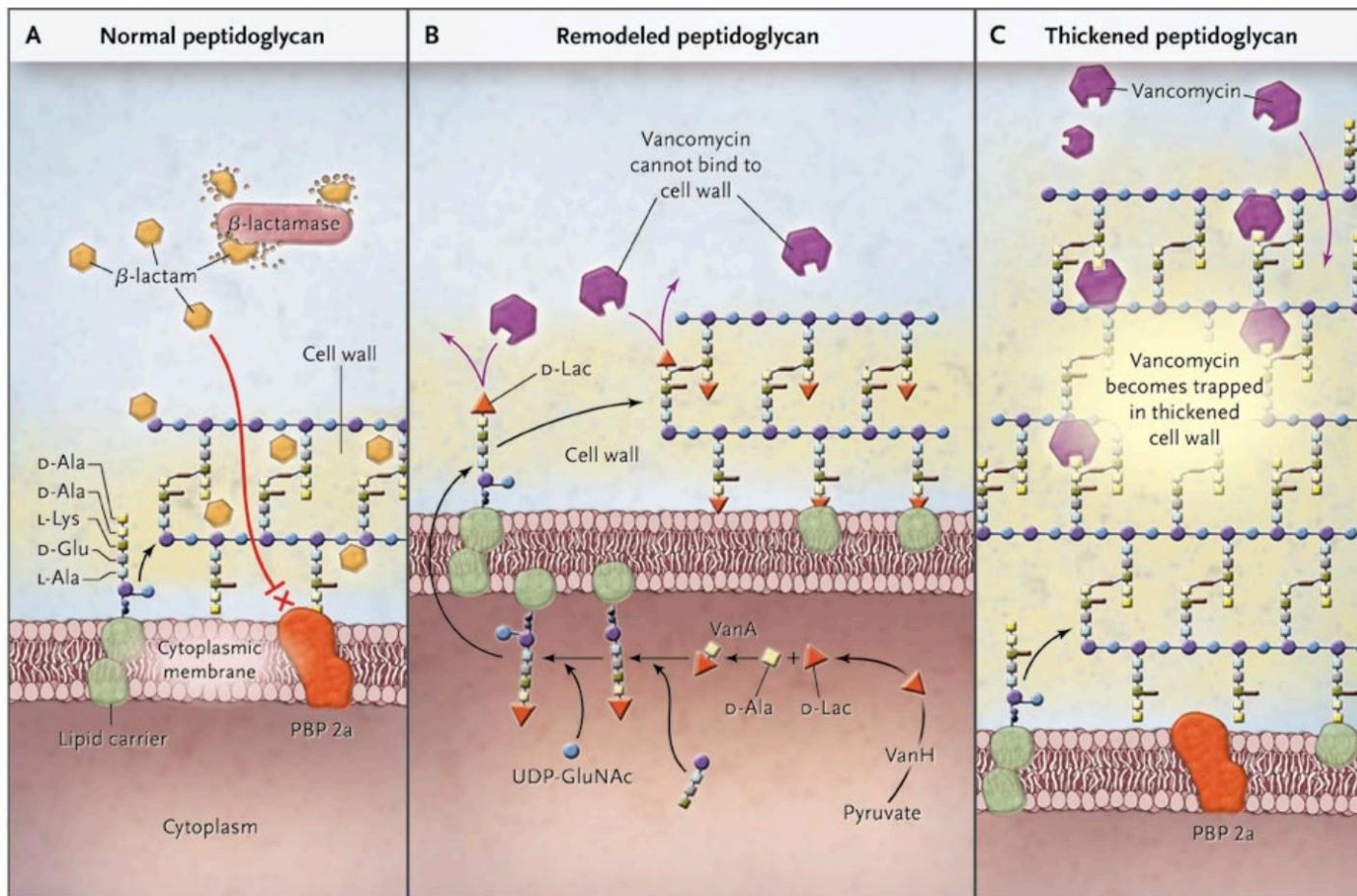


1 Sakoulas et al. Antimicrob Agent Chemother 2014;58:1494-1500.

1 Sakoulas et al. Antimicrob Agent Chemother 2012;56:838-44.

De Oliveira DMP et al. Clin Microbiol Rev. 2020;33

# *Vancomycin- Resistant Enterococcus faecium*



## Phenotypes of vancomycin-resistant enterococci (VRE)

Phenotype	Ligase gene	Ending of peptidoglycan*	MIC vancomycin (mcg/mL)	MIC teicoplanin (mcg/mL)	Transferability between strains	Species
VanA	<i>vanA</i>	D-Ala-D-Lac	64 to 1000	16 to 512	YES	<i>E. faecium</i> , <i>E. faecalis</i> , <i>E. durans</i> , <i>E. hirae</i> , <i>E. gallinarum</i> , <i>E. casseliflavus</i> , <i>E. raffinosus</i> , <i>E. avium</i> , <i>E. mundtii</i>
VanB	<i>vanB</i>	D-Ala-D-Lac	4 to 32	0.5 to 1	YES	<i>E. faecium</i> , <i>E. faecalis</i> , <i>E. durans</i> , <i>E. gallinarum</i>
VanC	<i>vanC</i>	D-Ala-D-Ser	8 to 32	0.5 to 1	NO	<i>E. gallinarum</i> , <i>E. casseliflavus</i>
VanD	<i>vanD</i>	D-Ala-D-Lac	64 to 128	4 to 64	NO	<i>E. faecium</i> , <i>E. faecalis</i> , <i>E. raffinosus</i>
VanE	<i>vanE</i>	D-Ala-D-Ser	8 to 32	0.5 to 1	NO	<i>E. faecalis</i>
VanG	<i>vanG</i>	D-Ala-D-Ser	8 to 16	0.5 to 1	YES	<i>E. faecalis</i>
VanL	<i>vanL</i>	D-Ala-D-Ser¶	8	0.5	NO	<i>E. faecalis</i>
VanM	<i>vanM</i>	D-Ala-D-Lac¶	>256	64 to >256	YES	<i>E. faecium</i>
VanN	<i>vanN</i>	D-Ala-D-Ser¶	8	0.5	YES	<i>E. faecium</i>

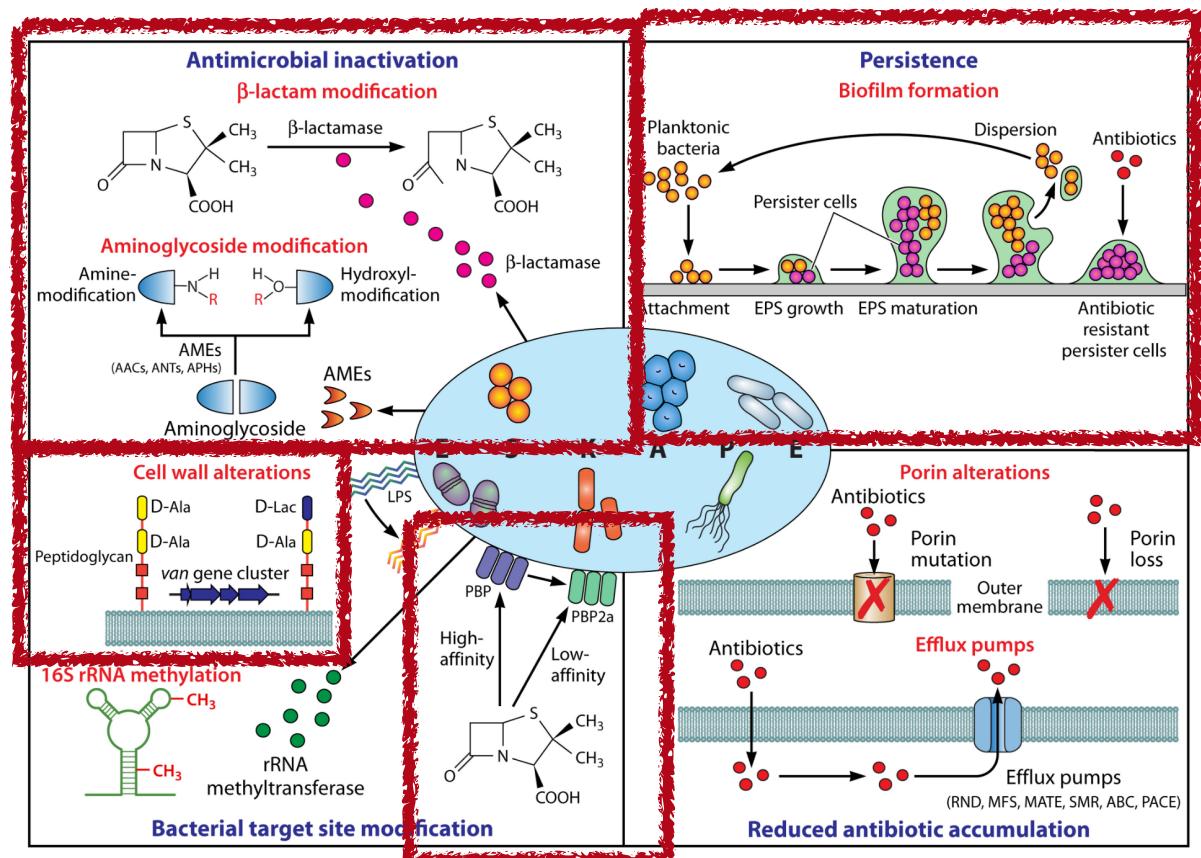
D-Ala-D-Lac: D-alanine-D-lactate; D-Ala-D-Ser: D-alanine-D-serine; MIC: minimal inhibitory concentration.

\* Refers to the last two amino acids of peptidoglycan precursors, which are normally D-Ala-D-Ala; in some phenotypes, the ending is deduced from the amino acid sequence of the corresponding ligase.

¶ Predicted but not actually confirmed.

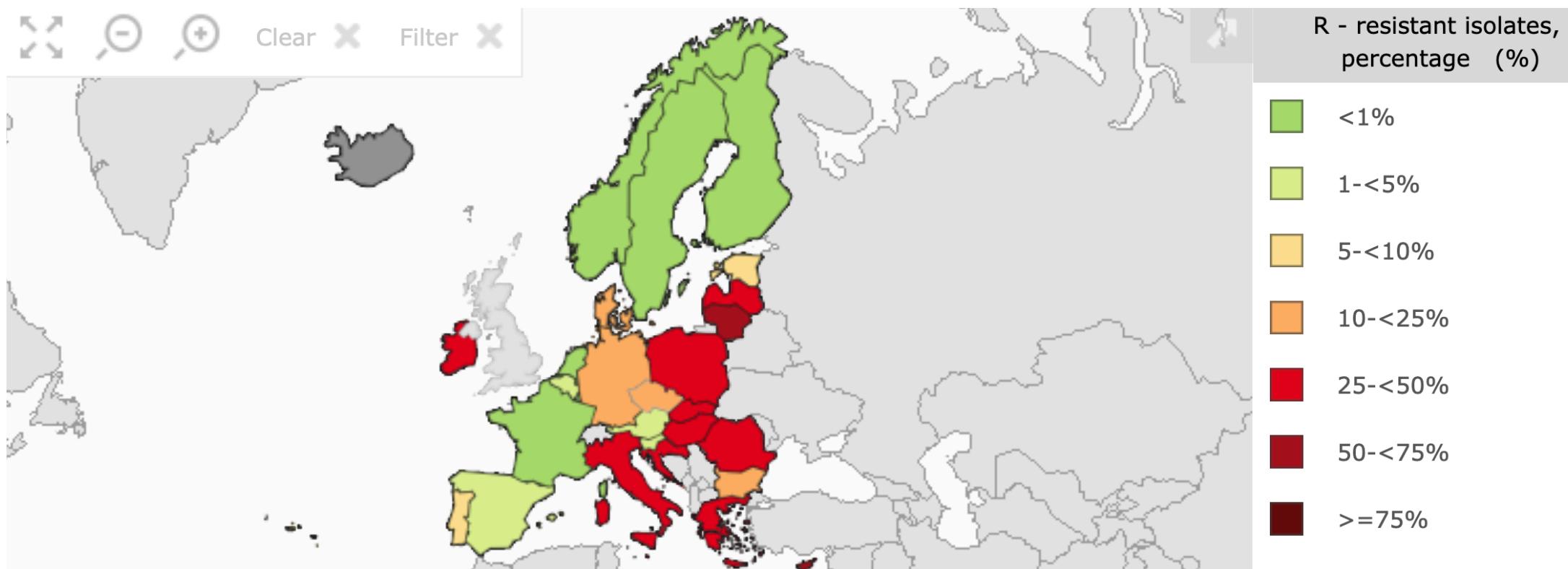
# Enterococcus faecium

- Often resistant to penicillin, aminoglycosides and vancomycin
- Alteration in cell-wall precursors:
  - VanA- High level resistance to vancomycin AND teicoplanin
  - VanB- Lower level resistance, can be treated *WITH* teicoplanin



De Oliveira DMP et al. Clin Microbiol Rev. 2020;33

# Vancomycin-Resistant *Enterococcus faecium*



# Patient case

- 33 year old female diagnosed with acute myeloid leukemia → induction chemotherapy → achieved CR then relapsed and underwent rescue chemotherapy
- Surveillance stool cultures for VRE were negative before admission
- Patient developed painful erythematous rash and hands and feet (ARA-C hand-foot) but was treated with vancomycin and ceftazidime
- Patient underwent MUD Allogeneic HSCT → complicated by Grade II/III mucositis and *S. epidermidis* bacteria treated with vancomycin and exchange of her CVC. She remained febrile, so she was continued on vancomycin + cefepime + liposomal amphotericin B
- On day +10 of vancomycin therapy, blood cultures were positive for VRE

# VRE treatment

- Refractory infections: Daptomycin 10-12 mg/kg q24h + ampicillin 2 grams IV q4h or ceftriaxone 2 gm IV q12h or ceftaroline 600 mg IV q8h)
  - Higher than licensed daptomycin doses (6 mg/kg q24h) recommended; doses > 9 mg/kg associated with lower mortality<sup>1</sup>
  - Combination therapy slows the development of resistance
- Linezolid 600 mg IV/PO q12h
- Cystitis: nitrofurantoin 100 mg po q6h or fosfomycin 3 gram PO x1 dose
- If VanB phenotype and teicoplanin susceptible:
  - Teicoplanin + Gentamicin (if gentamicin susceptible)

<sup>1</sup> Chuang YC et al. Clin Infect Dis. 2017;64:1026-1034.

# ***ESKAPE Pathogens***

***Enterococcus faecium (vancomycin-resistant)***

***Staphylococcus aureus (MRSA)***

***Klebsiella pneumoniae (ESBL, carbapenem-resistant)***

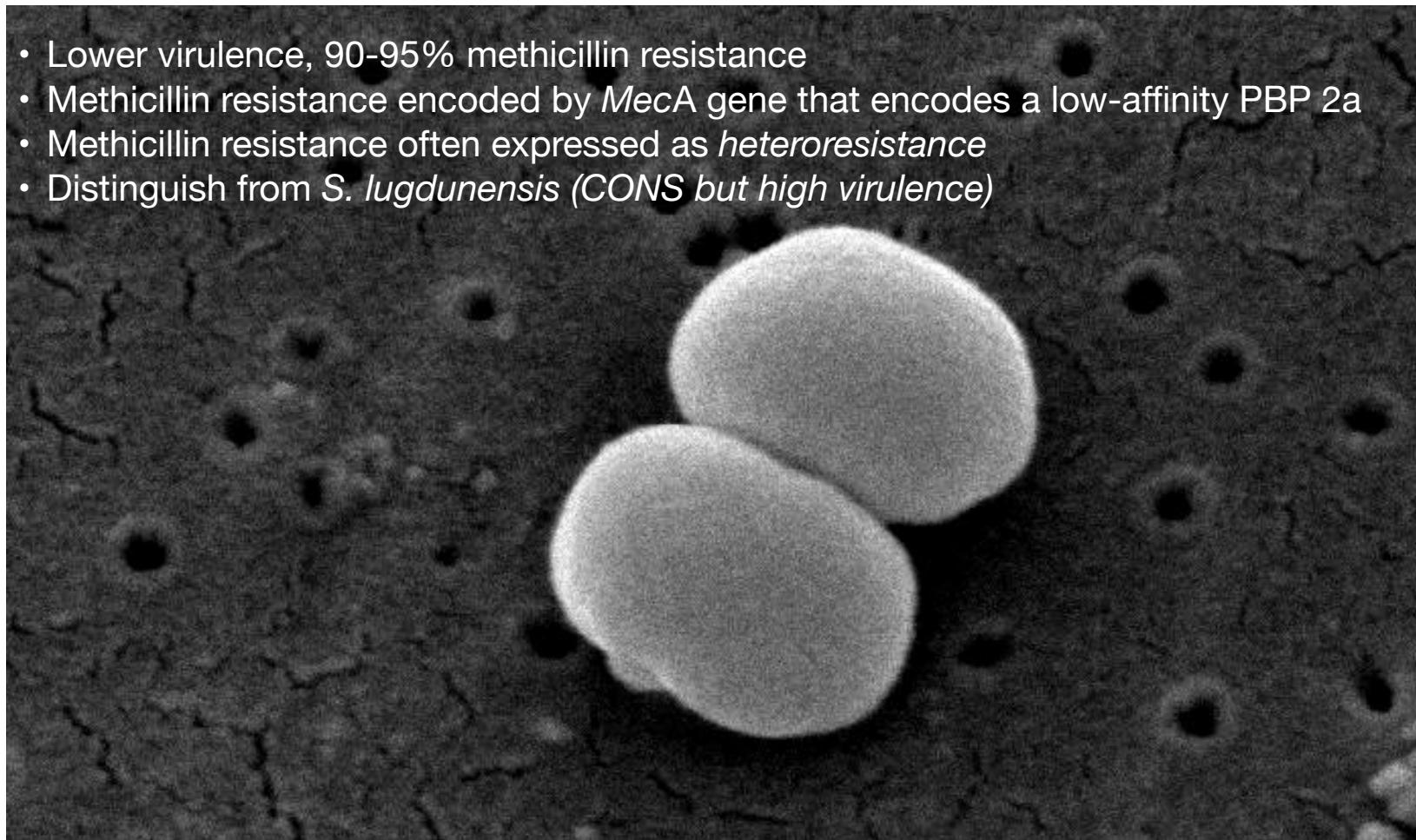
***Acinetobacter baumanii***

***Pseudomonas aeruginosa***

***Enterobacter spp.***

# Methicillin-resistant *Staphylococcus epidermidis*

- Lower virulence, 90-95% methicillin resistance
- Methicillin resistance encoded by *MecA* gene that encodes a low-affinity PBP 2a
- Methicillin resistance often expressed as *heteroresistance*
- Distinguish from *S. lugdunensis* (*CONS* but *high virulence*)



# ID physicians respect *S. aureus* (MRSA)



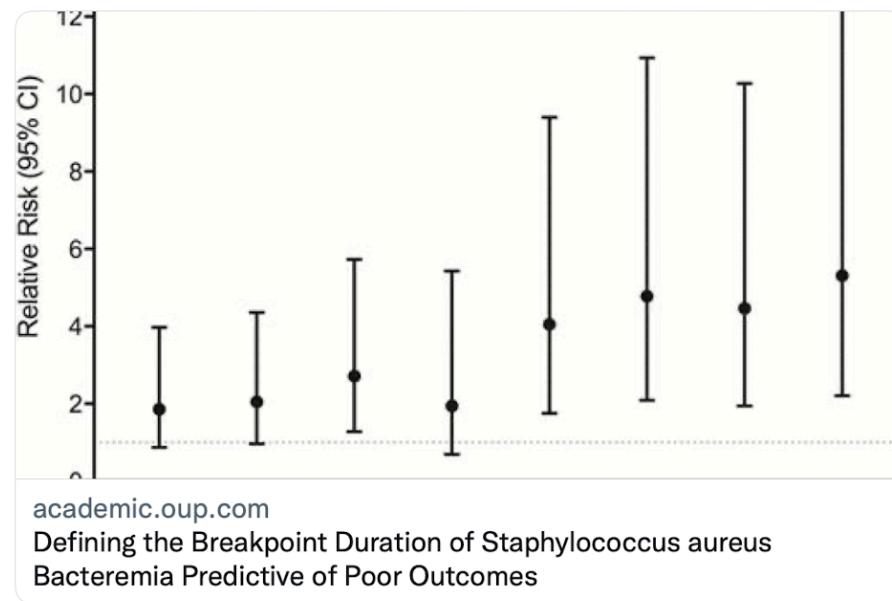
Dr David Griffin 🚑🦠😊🦉 @drdavidwjt · 05/04/19

I have the utmost respect (fear) for Staph. aureus.

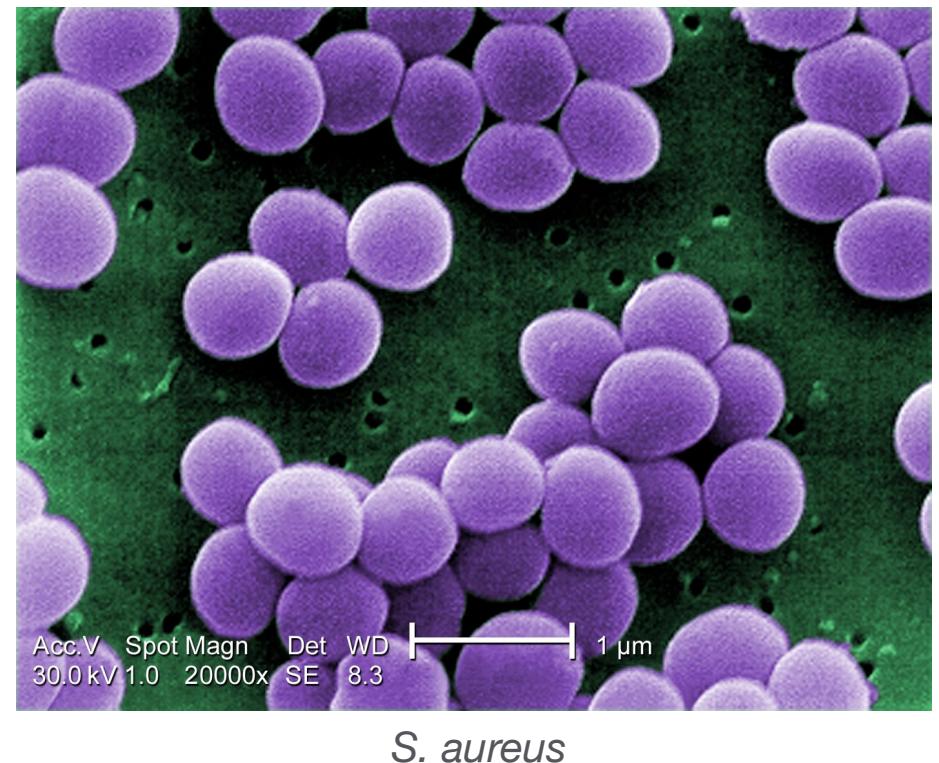
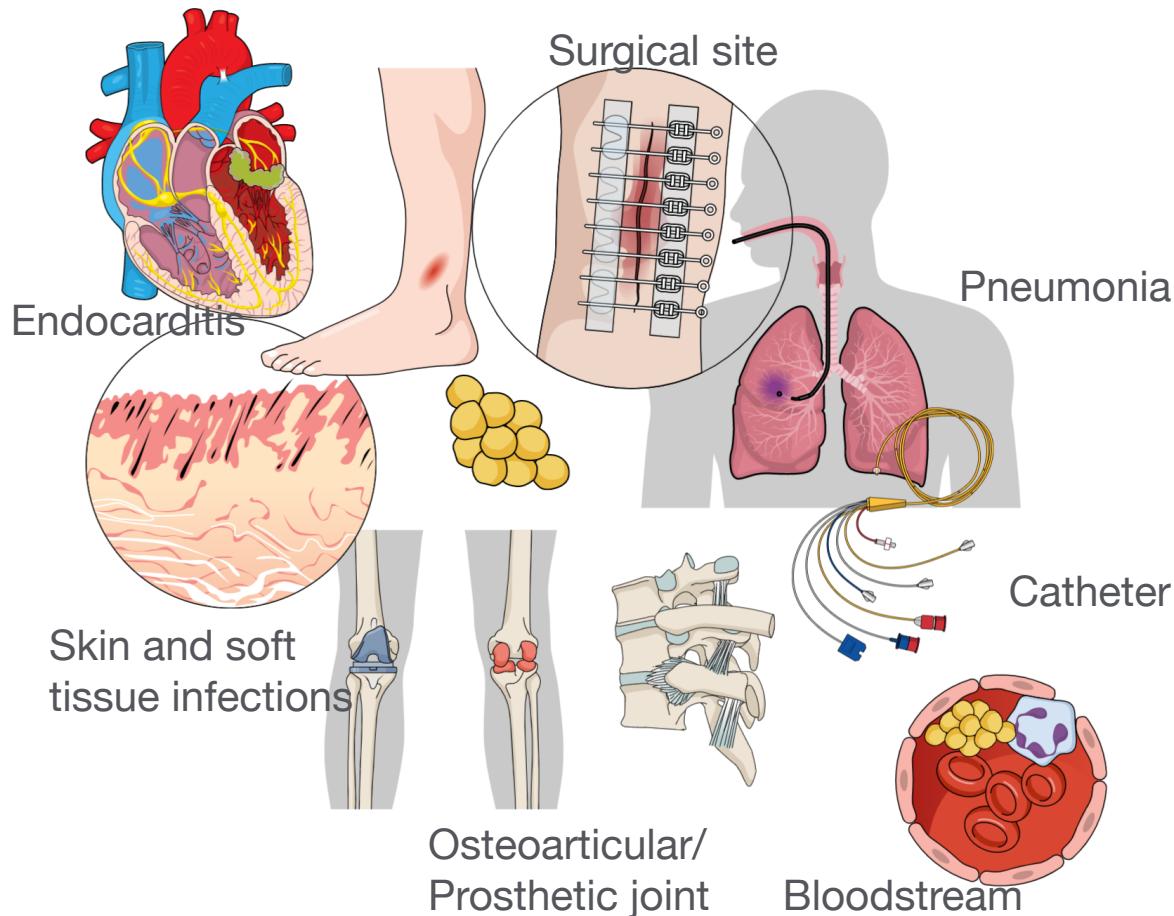
...

Defining the Breakpoint Duration of **Staphylococcus aureus**  
Bacteremia Predictive of Poor Outcomes [academic.oup.com/cid/  
advance-ar...](https://academic.oup.com/cid/advance-ar...)

Each day of bacteraemia was associated with an additional 16% relative mortality risk! #IDTwitter

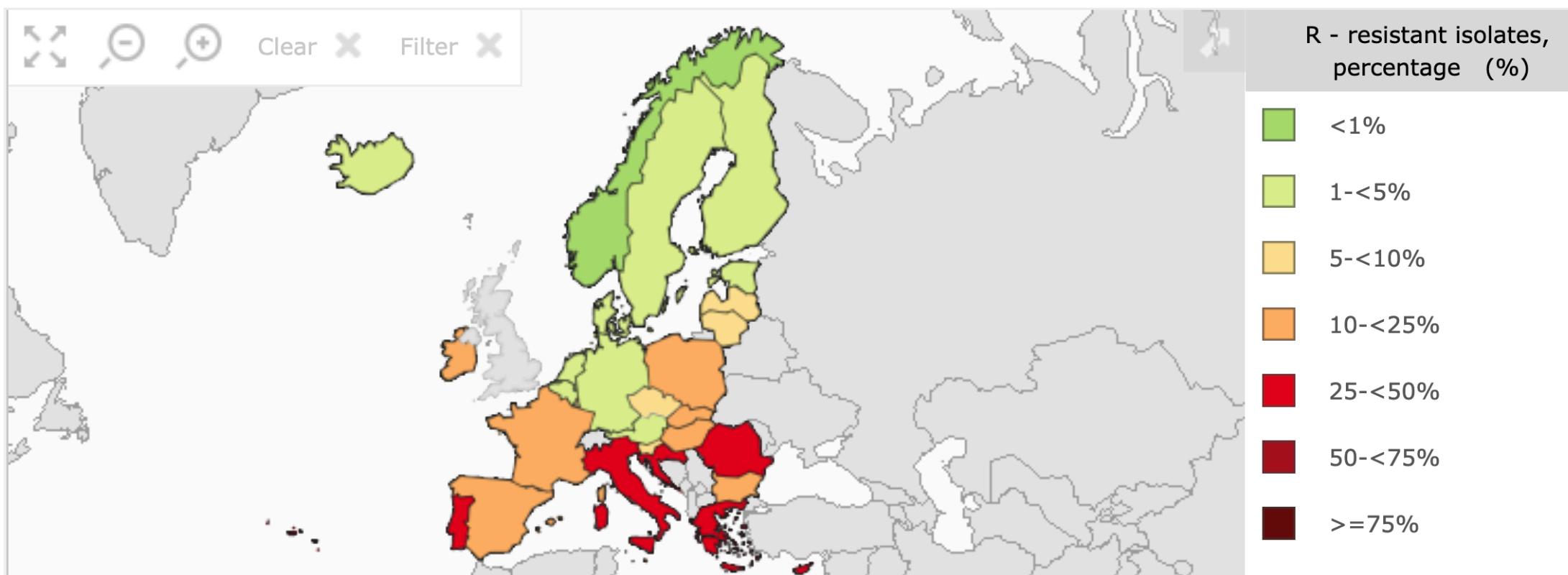


# Methicillin-resistant *Staphylococcus aureus*



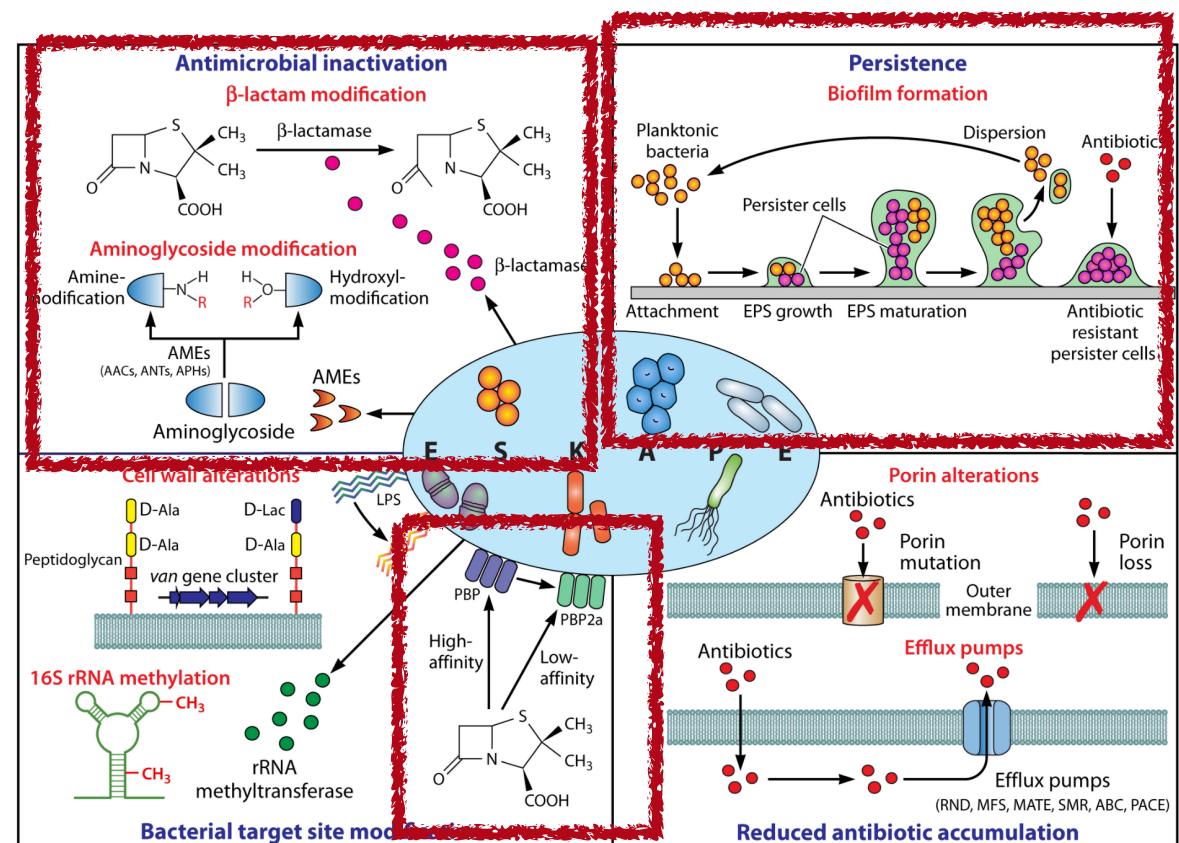
Overall mortality 10-50%; 20% for bloodstream infections

# Methicillin-resistant *Staphylococcus aureus*



# *S. aureus* (MRSA)

- Methicillin resistance encoded by two genes, *mecA*, *MecC*, which code for a low-affinity PBP2A, and PBP2c, respectively.
- Genes can be detected by latex agglutination or PCR tests; including in nasal swabs of MRSA colonized patient



# Patient case

- 71 y/o male undergoes right hip arthroplasty at a hospital in Rome, received prophylaxis with cefazolin and low molecular weight heparin.
- At discharge, no local signs of inflammation or infection were evident
- After 20 days from discharge, patient re-admitted with secretion from wound. A surgical debridement was performed, cultures collected and patient was started on teicoplanin + amikacin. The patient had elevated serum C reactive protein (131 mg/dL, normal < 3).
- Multiple cultures were positive for *S. Aureus* (identified by MALDI-TOF). Presence of sccMecA and sccmecC was confirmed by PCR.
- AST Oxacillin > 4mg/L (R), vancomycin < 0.5 mg/L (S), teicoplanin > 8 mg/L (R), erythromycin 2 mg/L ( R), linezolid 0.25 mg/L (S), clindamycin 0.25 (S), <8 mg/L amikacin (S), rifampin <0.03 mg/L (S), doxycycline < 1 mg/L (S).
- The patient was switched to vancomycin 1 gram twice daily and amikacin 1 gram daily

*Is this optimal treatment? What are the problems?*

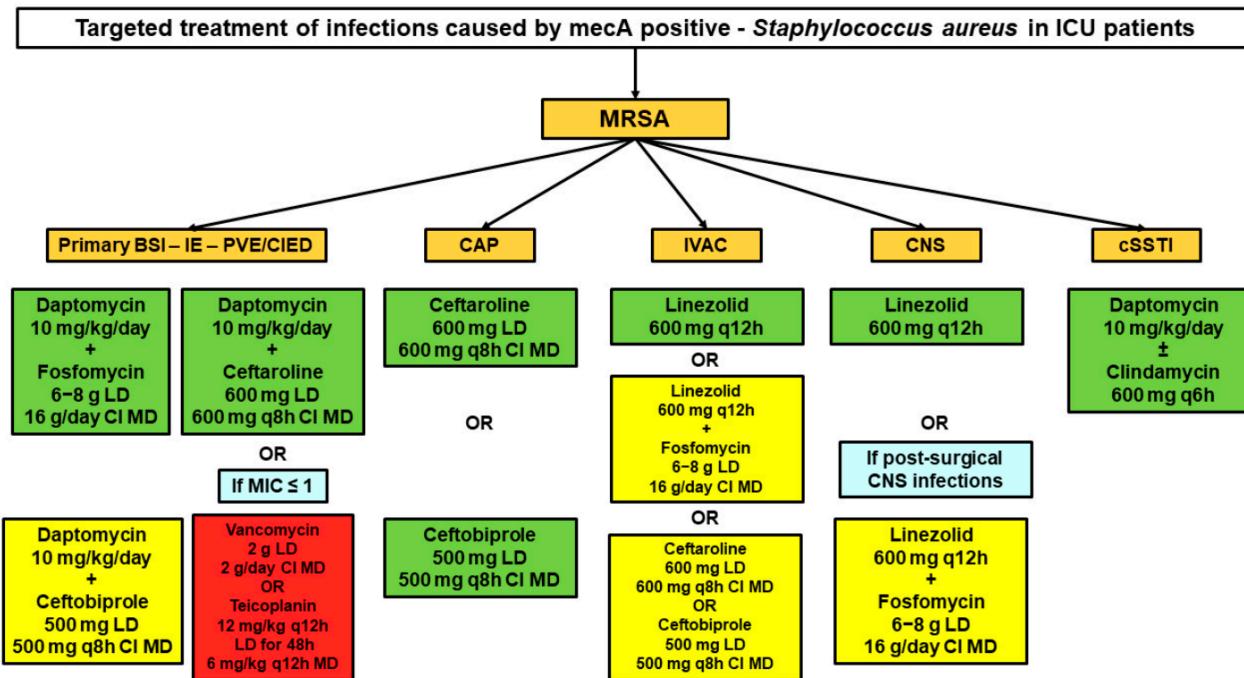
## ***MRSA treatment options***

- **Vancomycin 15-20 mg/kg IV q12h to achieve AUC<sub>24</sub> of 400-600**
  - AUC dosing calculator in Sanfords, or can use computerized model
  - Only use vancomycin if MIC < 4 µg/mL, cannot achieve PK/PD target at higher MICs
  - Monitor renal function, TDM, slow killing(?), risk of nephrotoxicity
- **Teicoplanin 12 mg/kg q12h 3-5 doses then 12 mg/kg q24h**
  - Target trough 15- 30 µg/mL
  - Less nephrotoxicity than vancomycin, cytopenias with high dose therapy

## ***MRSA treatment options***

- **Linezolid 600 mg po/IV q12h** for pneumonia (drug of choice) or acute skin and soft tissue infection
  - Thrombocytopenia with prolonged therapy, TDM?
- **Daptomycin 4-6 mg/kg q12h IV once daily** (consider 8-12 mg/kg q24h in bacteremia).
  - Monitor CPK enzymes, renal function
- **Televancin:** Not active if vancomycin-resistant
- **Ceftaroline 600 mg q8-12h IV** (q8h for treatment of bacteremia)
  - Alternatives: Dalbavancin, Oritavancin, Tedizolid, TMP/SMX (not as monotherapy)
  - MRSA Treatment failure: Daptomycin 8-12 mg/kg + Ceftaroline → source control
    - Note must use hydrophilic β lactic (i.e not flucloxacillin, oxacillin, cloxacillin → higher nephrotoxicity risk)

# Bologna MRSA treatment approaches



**Figure 2.** Algorithms for targeted therapy of BSIs or IE caused by methicillin-resistant *Staphylococcus aureus*. Green box: best therapeutic regimen according to current evidence; yellow box: alternative therapeutic regimen according to current evidence; red box: therapeutic regimen recommended only in specific situations. BSI: bloodstream infection; CAP: community-acquired pneumonia; CI: continuous infusion; CIED: cardiac implantable electronic device infections; CNS: central nervous system; cSSTI: complicated skin and soft tissue infection; ICU: intensive care unit; IE: infective endocarditis; IVAC: infective ventilator-associated complications; LD: loading dose; MD: maintenance dose; PVE: prosthetic valve endocarditis.

# ***ESKAPE Pathogens***

***Enterococcus faecium (vancomycin-resistant)***

***Staphylococcus aureus (MRSA)***

***Klebsiella pneumoniae (ESBL, carbapenem-resistant)***

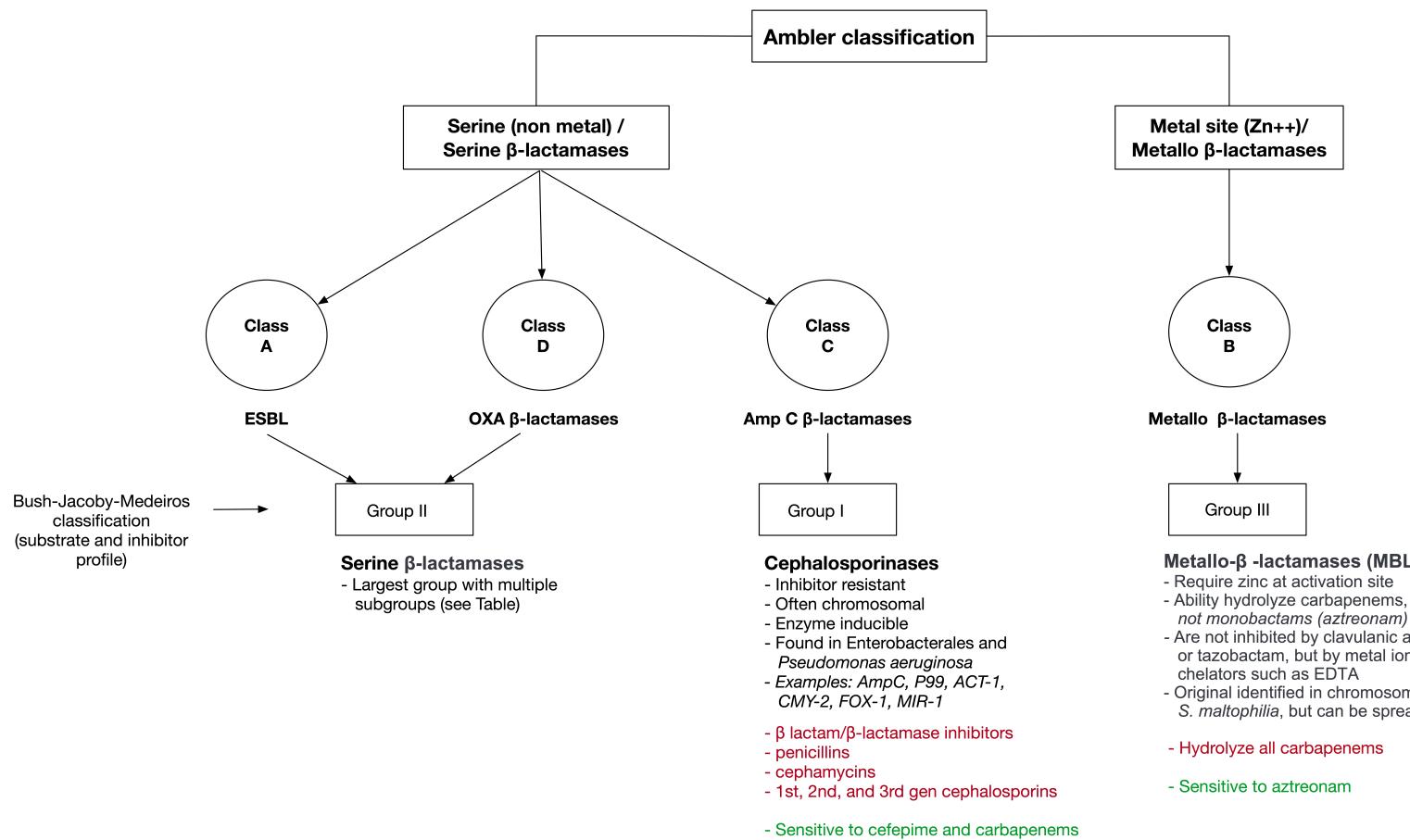
***Acinetobacter baumanii***

***Pseudomonas aeruginosa***

***Enterobacter spp.***

**Know your β-lactamases!**

# B-lactamase classification



## Group II serine $\beta$ -lactamases

Sub group	Substrate	Defining character	Examples
2a	Penicillin	<ul style="list-style-type: none"> <li>1. Predominant penicillinase in Staphylococci and enterococci</li> <li>2. Preferentially hydrolyze benzylpenicillin and many penicillin derivatives, with poor hydrolysis of cephalosporins, carbapenems, or monobactams except nitrocefin hydrolysis</li> <li>3. Are inhibited by clavulanic acid and tazobactam</li> <li>4. Majority are chromosomal, although some staphylococcal penicillinases are plasmid-encoded</li> </ul>	PC1
2b	Penicillins and early cephalosporins	<ul style="list-style-type: none"> <li>1. Readily hydrolyze penicillins and early cephalosporins, such as cephaloridine and cephalothin</li> <li>2. Strongly inhibited by clavulanic acid and tazobactam</li> <li>3. Most common plasmid-mediated <math>\beta</math> lactamases</li> </ul>	TEM-1, TEM-2, SHV-1
2be*	Extended-spectrum cephalosporins, monobactams	<ul style="list-style-type: none"> <li>1. Increased hydrolysis of oxyimino-<math>\beta</math>-lactams (cefotaxime, ceftazidime, ceftriaxone, cefepime, aztreonam)</li> <li>2. Are sensitive to inhibition by clavulanic acid, a feature used in their detection by clinical laboratories</li> </ul>	TEM-3, SHV-2, CTX-M-15
2br	Penicillin	Have acquired resistance to clavulanic acid, sulbactam and tazobactam	TEM-30,S HV-10
2ber	Extended-spectrum cephalosporins, monobactams	<ul style="list-style-type: none"> <li>1. Increased hydrolysis of oxyimino-<math>\beta</math>-lactams combined with resistance to clavulanic acid, sulbactam and tazobactam</li> <li>2. Also known as CMT (complex mutant TEM) <math>\beta</math>-lactamases</li> </ul>	TEM-50 (CMT-1)
2c	Carbenicillin	Ability to hydrolyze carbenicillin or ticarcillin Easily inhibited by clavulanic acid or tazobactam	PSE-1, CARB-3
2ce	Extended-spectrum cephalosporins	Increased hydrolysis of carbenicillin, cefepime, and cefpirome Inhibited by clavulanic acid or tazobactam	RTG-4 (CARB-10 )
2d	Cloxacillin	Hydrolyze cloxacillin or oxacillin, also carbenicillin hence are termed OXA enzymes OXA-related enzymes now comprise the second largest family of $\beta$ -lactamases	OXA-1 OXA-10
2df	Carbapenems	<ul style="list-style-type: none"> <li>1. Hydrolyze cloxacillin or oxacillin and carbapenems</li> <li>2. The enzymes, and their producing organisms, are typically unresponsive to inhibition by clavulanic acid</li> </ul>	OXA-23 OXA-48
2e	Extended-spectrum cephalosporins	<ul style="list-style-type: none"> <li>1. Hydrolyze cephalosporins.</li> <li>2. Inhibited by clavulanic acid but not aztreonam</li> </ul>	CepA
2f	Carbapenems	Increased hydrolysis of carbapenems, oxyimino- $\beta$ lactams, cephemycins	KPC-2, IMI-1, SME-1

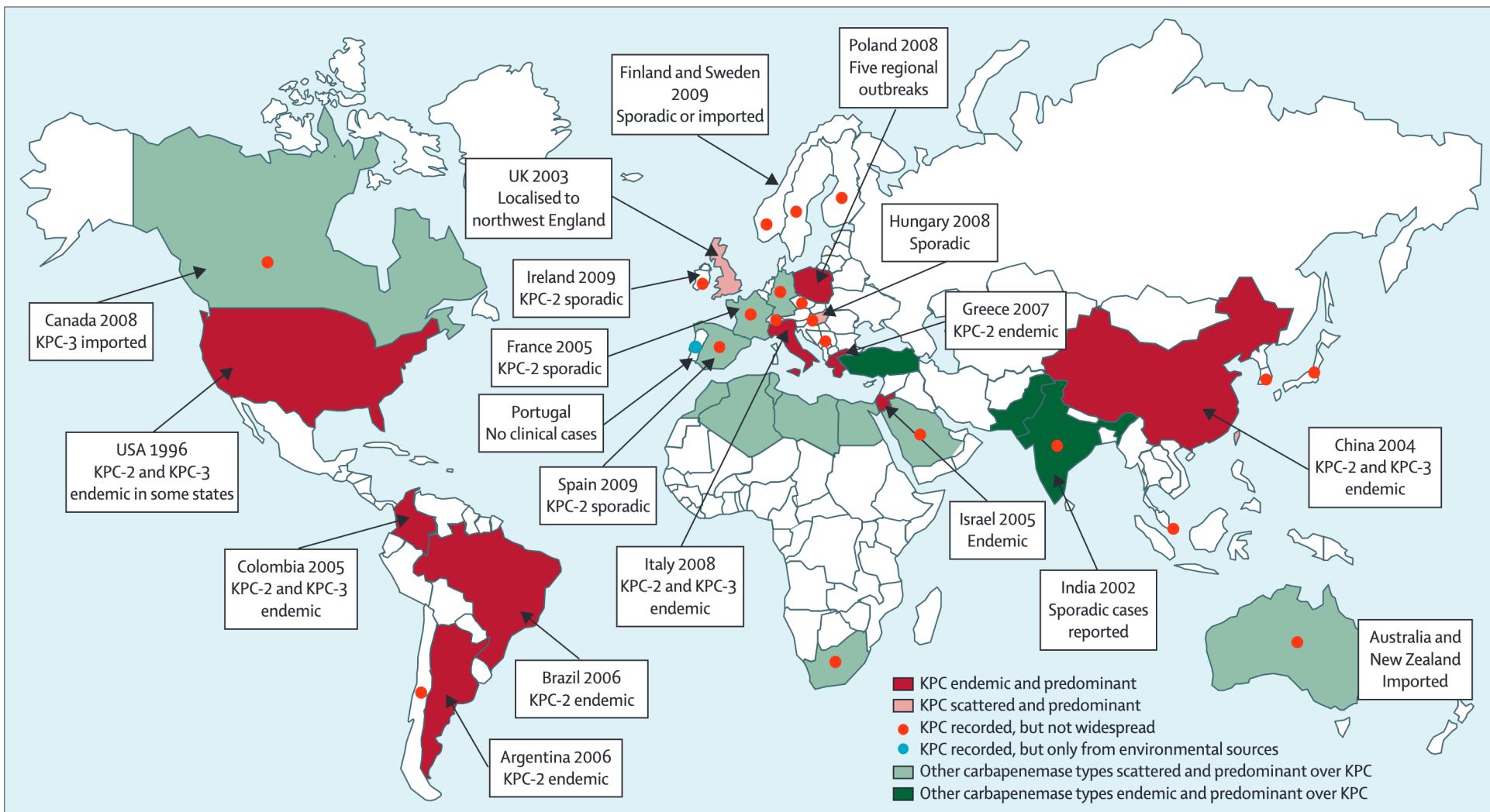
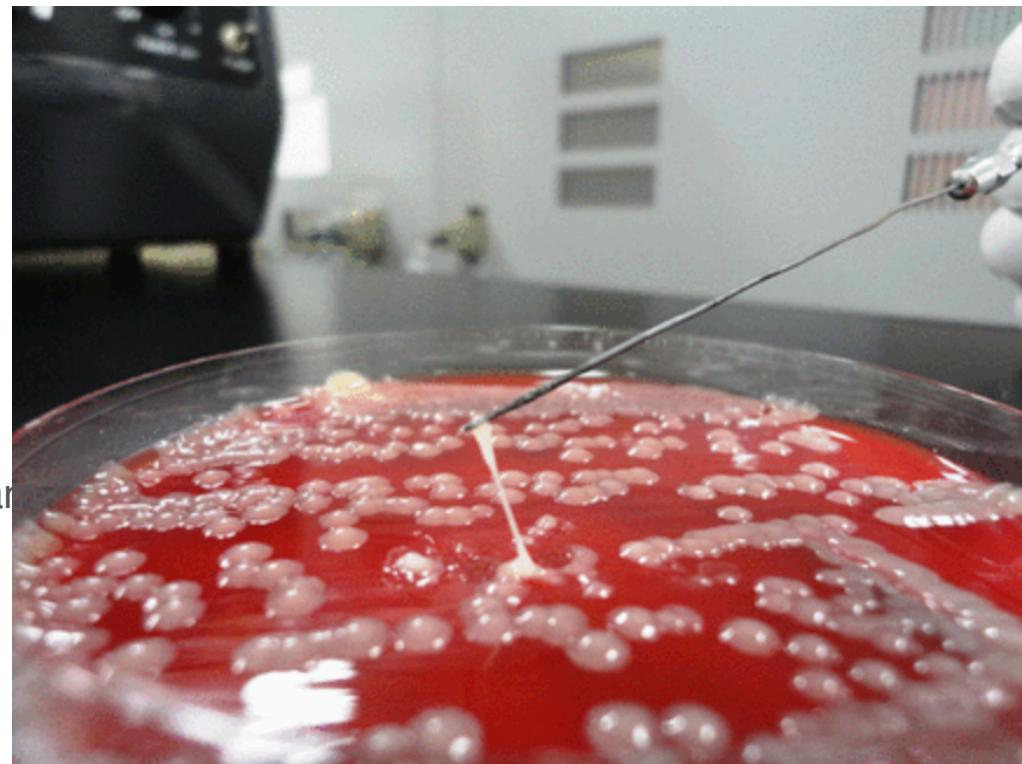
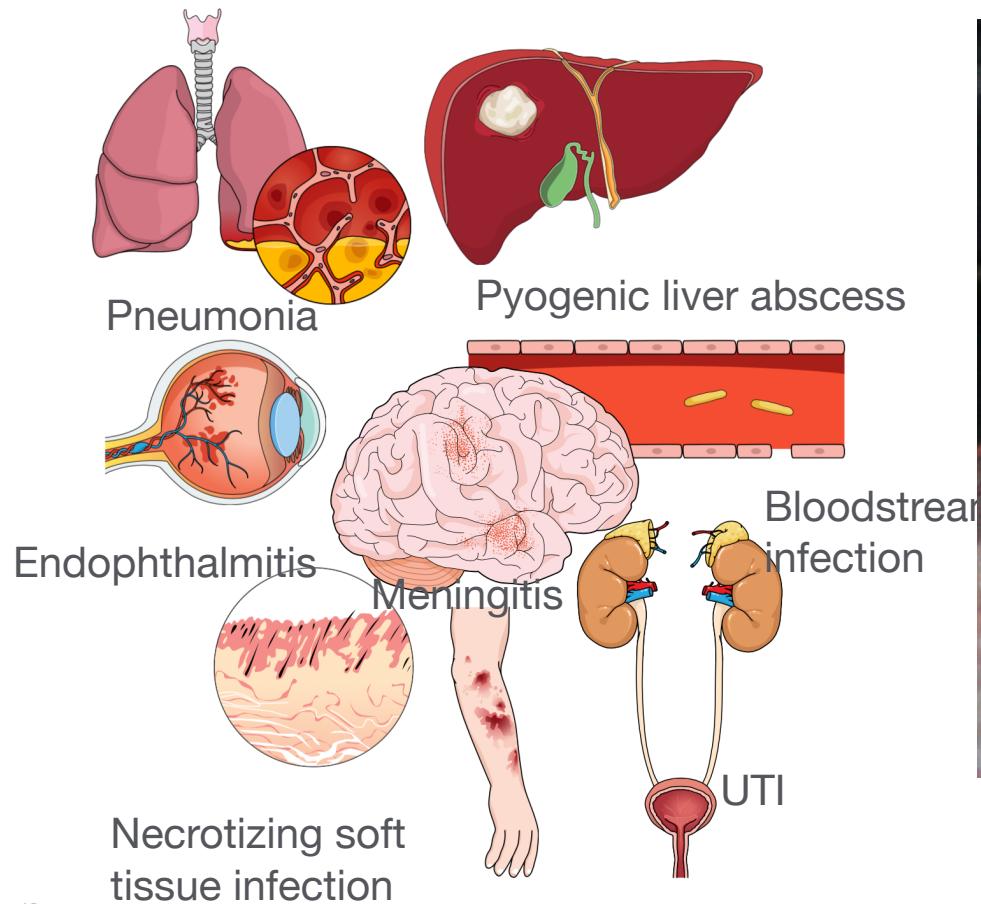


Figure: Epidemiological features of producers of *Klebsiella pneumoniae* carbapenemases by country of origin

Other carbapenemase types include VIM, OXA-48, or NDM. KPC= *Klebsiella pneumoniae* carbapenemase.

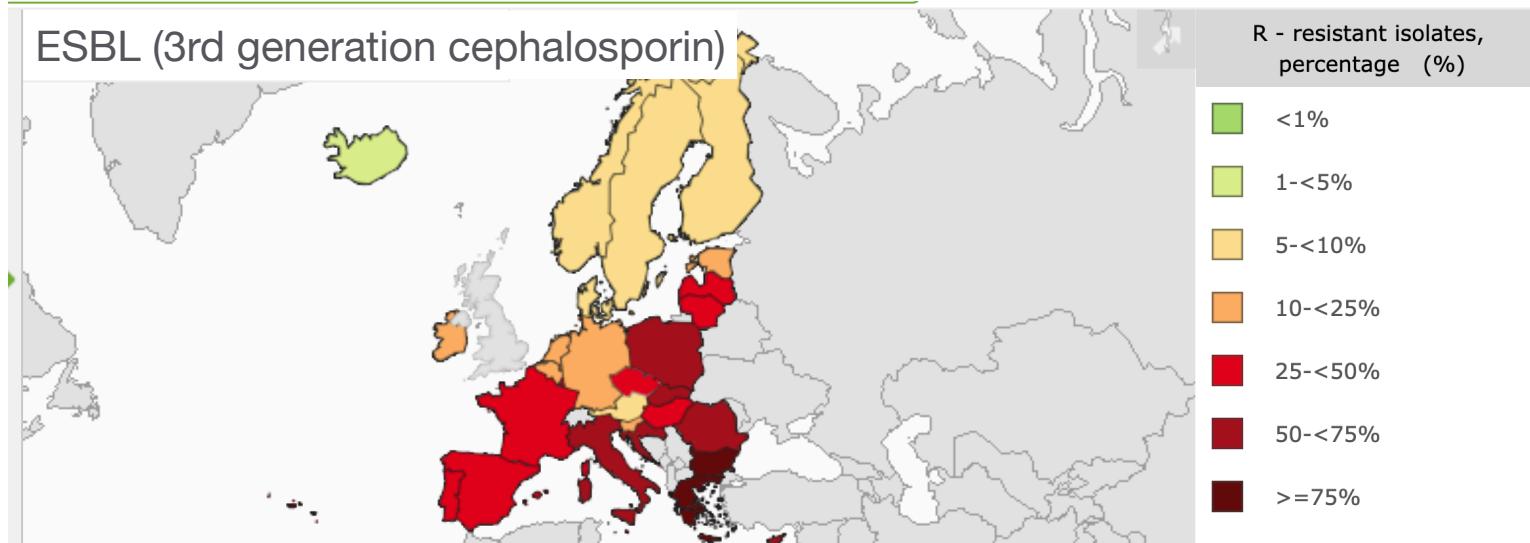
# *Klebsiella pneumoniae*



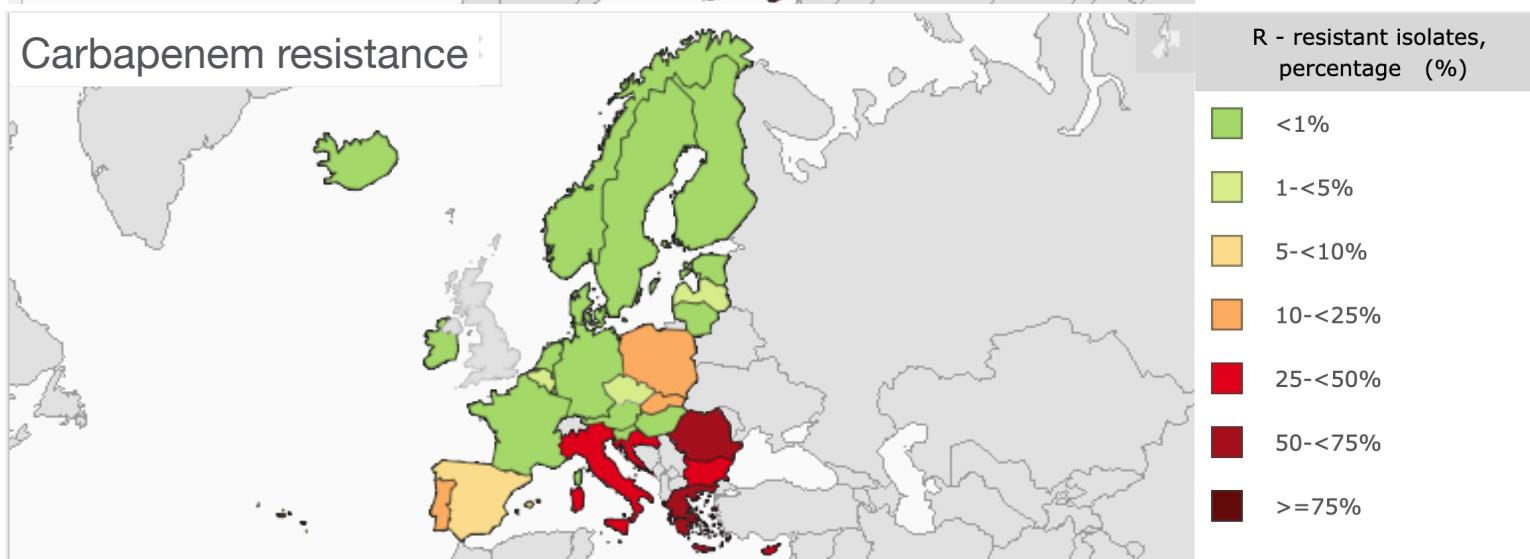
*K. pneumoniae* positive string test

# *Klebsiella pneumoniae* resistance

ESBL (3rd generation cephalosporin)



Carbapenem resistance



40-60% mortality rate  
for carbapenem-resistant  
*K. pneumoniae*

## Extended-spectrum $\beta$ -lactamase producing Enterobacteriales

*Escherichia coli, Klebsiella pneumonia, Klebsiella oxytoca, Proteus mirabilis*

Typically identified by non-susceptibility to ceftriaxone (i.e. MIC  $\geq$  2  $\mu\text{g/mL}$ )

**Table 2. Recommended Antibiotic Treatment Options for Presumed or Confirmed Extended-spectrum  $\beta$ -Lactamase-Producing Enterobacteriales, Assuming In Vitro Susceptibility to Agents in Table**

Source of Infection	Preferred Treatment	Alternative Treatment if First-line Options not Available or Tolerated
Cystitis	Nitrofurantoin, trimethoprim-sulfamethoxazole	Amoxicillin-clavulanate, single-dose aminoglycosides, fosfomycin ( <i>Escherichia coli</i> only) Ciprofloxacin, levofloxacin, ertapenem, meropenem, imipenem-cilastatin
Pyelonephritis or complicated urinary tract infection <sup>a</sup>	Ertapenem, meropenem, imipenem-cilastatin, ciprofloxacin, levofloxacin, or trimethoprim-sulfamethoxazole	
Infections outside of the urinary tract	Meropenem, imipenem-cilastatin, ertapenem  Oral step-down therapy to ciprofloxacin, levofloxacin, or trimethoprim-sulfamethoxazole should be considered <sup>b</sup>	

<sup>a</sup>A complicated urinary tract infection (UTI) is defined as a UTI that occurs in association with a structural or functional abnormality of the genitourinary tract, or any UTI in a male patient.

<sup>b</sup>Oral step-down therapy can be considered after susceptibility to the oral agent is demonstrated, patients are afebrile and hemodynamically stable, appropriate source control is achieved, and there are no issues with intestinal absorption.

## Extended-spectrum $\beta$ -lactamase producing Enterbacteriales

*Escherichia coli, Klebsiella pneumonia, Klebsiella oxytoca, Proteus mirabilis*

Typically identified by non-susceptibility to ceftriaxone (i.e. MIC  $\geq 2 \mu\text{g/mL}$ )

- Areas of controversy:
  - Can you use piperacillin-tazobactam if micro report says “S”?
    - Answer: Not recommended, based on MERINO Trial that demonstrated superiority of carbapenem vs. piperacillin-tazobactam for ESBL infections<sup>1</sup>
    - Possible exceptions: Patient with UTI, started empirically, already responding clinically
  - Can we use ceftipime if the micro report says “S” ?
    - Answer: Not recommended, outcomes poorer vs. carbapenems

Tamma PD et al. Clin Infect Dis 2021; 72:e169–e183.

<sup>1</sup>Harris PNA et al. JAMA. 2018;320:984-994.



**Use carbapenems to treat ESBL Enterbacterales →**  
**Carbapenem resistance increases in Enterbacterales**

# The question now is which carbapenemase...which drug?

Not available  
in Europe



Agent	KPC-producer	NDM-producer	OXA-48-like-producer	Carbapenem-resistant <i>Pseudomonas aeruginosa</i>	Carbapenem-resistant <i>Acinetobacter baumannii</i>	<i>Stenotrophomonas maltophilia</i>
Aztreonam-avibactam				Yellow	Red	
Cefiderocol				Green	Green	
Ceftazidime-avibactam <sup>1</sup>	Green	Red	Green	Yellow	Red	Red
Ceftolozane-tazobactam <sup>1</sup>	Red	Red	Red	Yellow	Red	Yellow
Ervacycline <sup>1,2</sup>	Green	Green	Green	Red	Green	Green
Fosfomycin (intravenous)	Yellow	Yellow	Yellow	Yellow	Red	Red
Imipenem-relebactam <sup>3</sup>	Green	Red	Yellow	Green	Red	Red
Meropenem-vaborbactam <sup>1</sup>		Red	Red	Red	Red	Red
Plazomicin <sup>1,4</sup>	Green	Yellow	Green	Yellow	Red	Red
Polymyxin B <sup>1,5</sup> or Colistin <sup>1,5</sup>	Yellow	Yellow	Yellow	Yellow	Yellow	Yellow
Tigecycline <sup>1,2</sup>	Green	Green	Green	Red	Green	Green

**Figure 1.** Select antibiotics with activity against carbapenem-resistant organisms. Green, susceptibility anticipated to be >80%; yellow, susceptibility anticipated to be 30% to 80%; red, intrinsic resistance or susceptibility anticipated to be <30%. <sup>1</sup>, US Food and Drug Administration-approved agent; <sup>2</sup>, synthetic tetracycline derivative; <sup>3</sup>, imipenem-cilastatin-relebactam; <sup>4</sup>, synthetic aminoglycoside; <sup>5</sup>, polymyxin class. Abbreviations: KPC, *Klebsiella pneumoniae* carbapenemase; NDM, New Delhi metallo-β-lactamase.

# The question now is which carbapenemase?

## A word of warning about cefiderocol



In a clinical trial where 51% of patients were infected with CRE, mortality at 28 days was higher in the cefiderocol arm when compared to best-available therapy (colistin-based combination therapy). These findings were most striking for the treatment of pneumonia and bloodstream infections.



Generally reserved for intraabdominal infections—poor PK/PD target attainment in blood

Agent	KPC-producer	NDM-producer	OXA-48-like-producer	Carbapenem-resistant <i>Pseudomonas aeruginosa</i>	Carbapenem-resistant <i>Acinetobacter baumannii</i>	<i>Stenotrophomonas maltophilia</i>
Aztreonam-avibactam	Green	Green	Yellow	Yellow	Red	Green
Cefiderocol	Green	Green	Yellow	Yellow	Green	Green
Ceftazidime-avibactam <sup>1</sup>	Green	Red	Green	Yellow	Red	Red
Ceftolozane-tazobactam <sup>1</sup>	Red	Red	Red	Yellow	Red	Yellow
Ervacycline <sup>1,2</sup>	Green	Green	Green	Red	Green	Green
Fosfomycin (intravenous)	Yellow	Yellow	Yellow	Yellow	Red	Red
Imipenem-relebactam <sup>3</sup>	Green	Red	Yellow	Green	Red	Red
Meropenem-vaborbactam <sup>1</sup>	Green	Red	Red	Red	Red	Red
Razekacin <sup>1,4</sup>	Green	Yellow	Green	Yellow	Red	Red
Polymyxin B <sup>1,5</sup> or Colistin <sup>1,5</sup>	Yellow	Yellow	Yellow	Yellow	Yellow	Yellow
Tigecycline <sup>1,2</sup>	Green	Green	Green	Red	Green	Green

**Figure 1.** Select antibiotics with activity against carbapenem-resistant organisms. Green, susceptibility anticipated to be >80%; yellow, susceptibility anticipated to be 30% to 80%; red, intrinsic resistance or susceptibility anticipated to be <30%. <sup>1</sup>, US Food and Drug Administration–approved agent; <sup>2</sup>, synthetic tetracycline derivative; <sup>3</sup>, imipenem-cilastatin–relebactam; <sup>4</sup>, synthetic aminoglycoside; <sup>5</sup>, polymyxin class. Abbreviations: KPC, *Klebsiella pneumoniae* carbapenemase; NDM, New Delhi metallo-β-lactamase.

# Treatment of carbapenem-resistant Enterobacterales (i.e. KPC-2 producing *K. pneumonia*)

Source of Infection	Preferred Treatment	Alternative Treatment if First-line Options not Available or Tolerated
Cystitis	<p>Ciprofloxacin, levofloxacin, trimethoprim-sulfamethoxazole, nitrofurantoin, or a single dose of an aminoglycoside</p> <p>Meropenem<sup>a</sup> (standard infusion): only if ertapenem-resistant, meropenem-susceptible, AND carbapenemase testing results are either not available or negative</p>	<p>Ceftazidime-avibactam, meropenem-vaborbactam, imipenem-cilastatin-relebactam, and cefiderocol</p> <p>Colistin (when no alternative options are available)</p>
Pyelonephritis or complicated urinary tract infection <sup>b</sup>	<p>Ceftazidime-avibactam, meropenem-vaborbactam, imipenem-cilastatin-relebactam, and cefiderocol</p> <p>Meropenem<sup>a</sup> (extended-infusion): only if ertapenem-resistant, meropenem-susceptible, AND carbapenemase testing results are either not available or negative</p>	Once-daily aminoglycosides

Tamma PD et al. Clin Infect Dis. 2021;72:e169-e183.

# Treatment of carbapenem-resistant Enterobacteriales (i.e. KPC-2 producing *K. pneumonia*)

Infections outside of the urinary tract  Resistant to ertapenem, susceptible to meropenem, AND carbapenemase testing results are either not available or negative	Meropenem <sup>a</sup> (extended-infusion)  Ceftazidime-avibactam	
Infections outside of the urinary tract  Resistant to ertapenem, resistant to meropenem, AND carbapenemase testing results are either not available or negative	Ceftazidime-avibactam, meropenem-vaborbactam, and imipenem-cilastatin-relebactam	Cefiderocol  Tigecycline, eravacycline (generally limited to intra-abdominal infections)
<i>Klebsiella pneumoniae</i> carbapenemases identified (or carbapenemase positive but identify of carbapenemase unknown <sup>b</sup> )	Ceftazidime-avibactam, meropenem-vaborbactam, imipenem-cilastatin-relebactam	Cefiderocol  Tigecycline, eravacycline (generally limited to intra-abdominal infections)
Metallo-β-lactamase (ie, NDM, VIM, IMP) carbapenemase identified	Ceftazidime-avibactam + aztreonam, cefiderocol	Tigecycline, eravacycline (generally limited to intra-abdominal infections)
OXA-48-like carbapenemase identified	Ceftazidime-avibactam	Cefiderocol  Tigecycline, eravacycline (generally limited to intra-abdominal infections)

<sup>a</sup>The majority of infections caused by carbapenem-resistant Enterobacteriales (CRE) resistant to ertapenem but susceptible to meropenem are caused by organisms that do not produce carbapenemases.

<sup>b</sup>A complicated urinary tract infection (UTI) is defined as a UTI that occurs in association with a structural or functional abnormality of the genitourinary tract, or any UTI in a male patient.

The vast majority of carbapenemase-producing Enterobacteriales infections in the United States are due to bacteria that produce *Klebsiella pneumoniae* carbapenemases (KPC). If a disease-causing Enterobacteriales is carbapenemase-producing but the specific carbapenemase enzyme is unknown, it is reasonable to treat as if the strain is a KPC producer. If a patient is infected with a CRE strain with an unknown carbapenemase status and the patient has recently traveled from an area where metallo-β-lactamases are endemic (eg, Middle East, South Asia, Mediterranean), treatment with ceftazidime-avibactam plus aztreonam or cefiderocol as monotherapy is recommended. Preferred treatment approaches for infections caused by metallo-β-lactamase producers also provide activity against KPC and OXA (oxacillinase)-48-like enzymes.

# *ESKAPE Pathogens*

*Enterococcus faecium (vancomycin-resistant)*

*Staphylococcus aureus (MRSA)*

*Klebsiella pneumoniae (ESBL, carbapenem-resistant)*

*Acinetobacter baumanii*

*Pseudomonas aeruginosa*

*Enterobacter spp.*

Know your  $\beta$ -lactamases!

# **Enterobacter spp. (Old mnemonic- SPICE, SPACE organisms)\***

- Inducible resistance via chromosomally encoded **ampC** genes (eg, Enterobacter cloacae, Klebsiella aerogenes, Serratia marcescens, Citrobacter freundii, Pseudomonas aeruginosa, etc.) **may test susceptible to ceftriaxone or ceftazidime**
- Non-inducible chromosomal resistance due to promoter and/or attenuator mutations (eg, *Escherichia coli*, *Shigella* species, *Acinetobacter baumannii*), **will test resistant to ceftriaxone or ceftazidime**
- Plasmid mediated resistance (eg, *Klebsiella pneumoniae*, *E. coli*, *Salmonella* species, etc.) **will test resistant to ceftriaxone or ceftazidime**

# **Enterobacter spp. (SPICE, SPACE organisms)\***

**Which drugs can be used?**

	<b>Strong Inducers</b>	<b>Weak Inducers</b>
<b>Good Substrates</b>	Aminopenicillins, first-generation cephalosporins, cefoxitin, cefotetan	Ceftazidime, ceftriaxone, cefotaxime, piperacillin, ticarcillin, aztreonam
<b>Poor Substrates</b>	Imipenem	Cefepime, meropenem

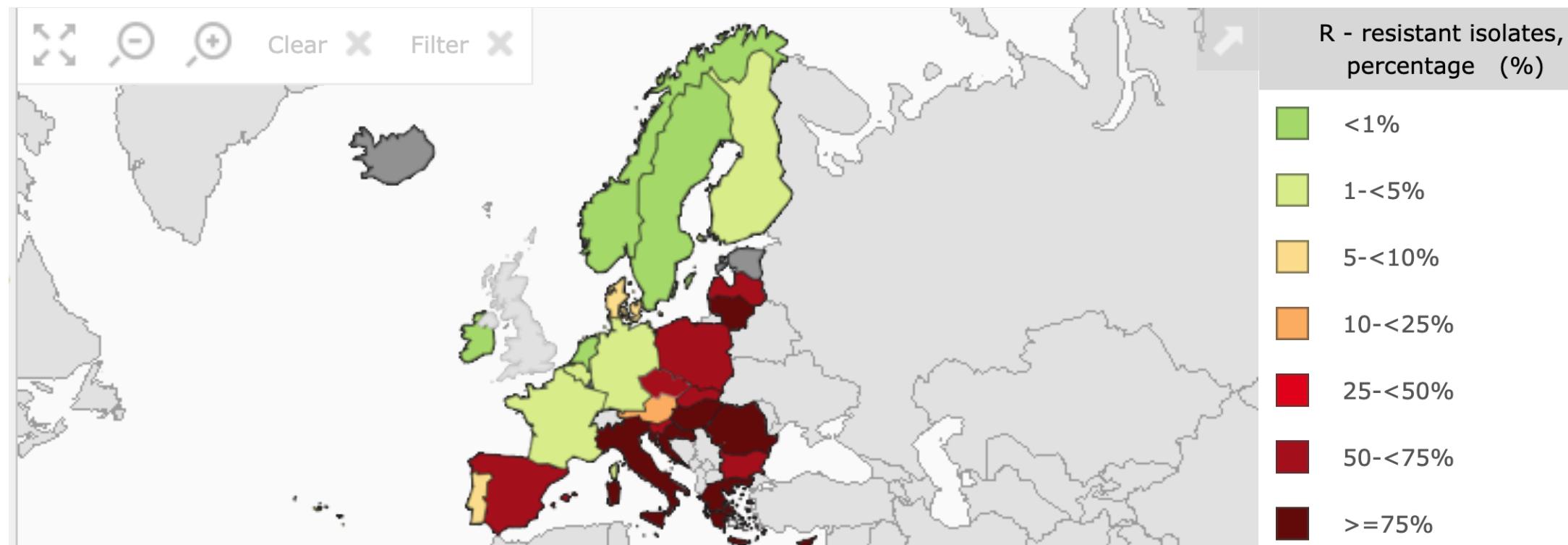
Do not consider cefepime if MIC ≥ 2; indicates presence of ESBL

Tazobactam is less effective at inhibiting AmpC hydrolysis than newer  $\beta$ -lactamase inhibitors, such as avibactam, relebactam, and vaborbactam

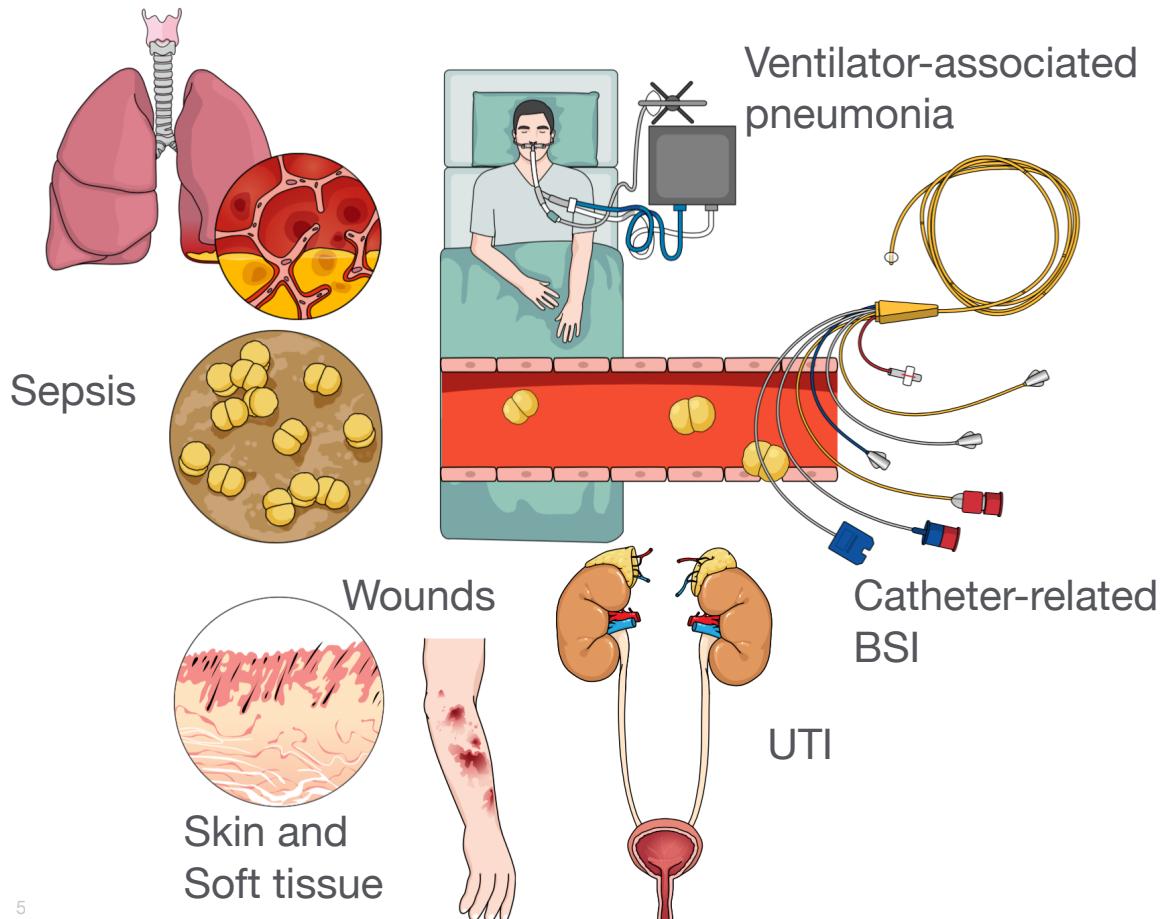
Fluoroquinolones, aminoglycosides, trimethoprim-sulfamethoxazole (TMP- SMX), tetracycline, and other non- $\beta$ -lactam antibiotics do not induce *ampC* and are also not substrates for AmpC hydrolysis

# *Acinetobacter baumanii* 2021

Combined resistance to carbapenems, fluoroquinolone and aminoglycosides



# *Acinetobacter baumanii*

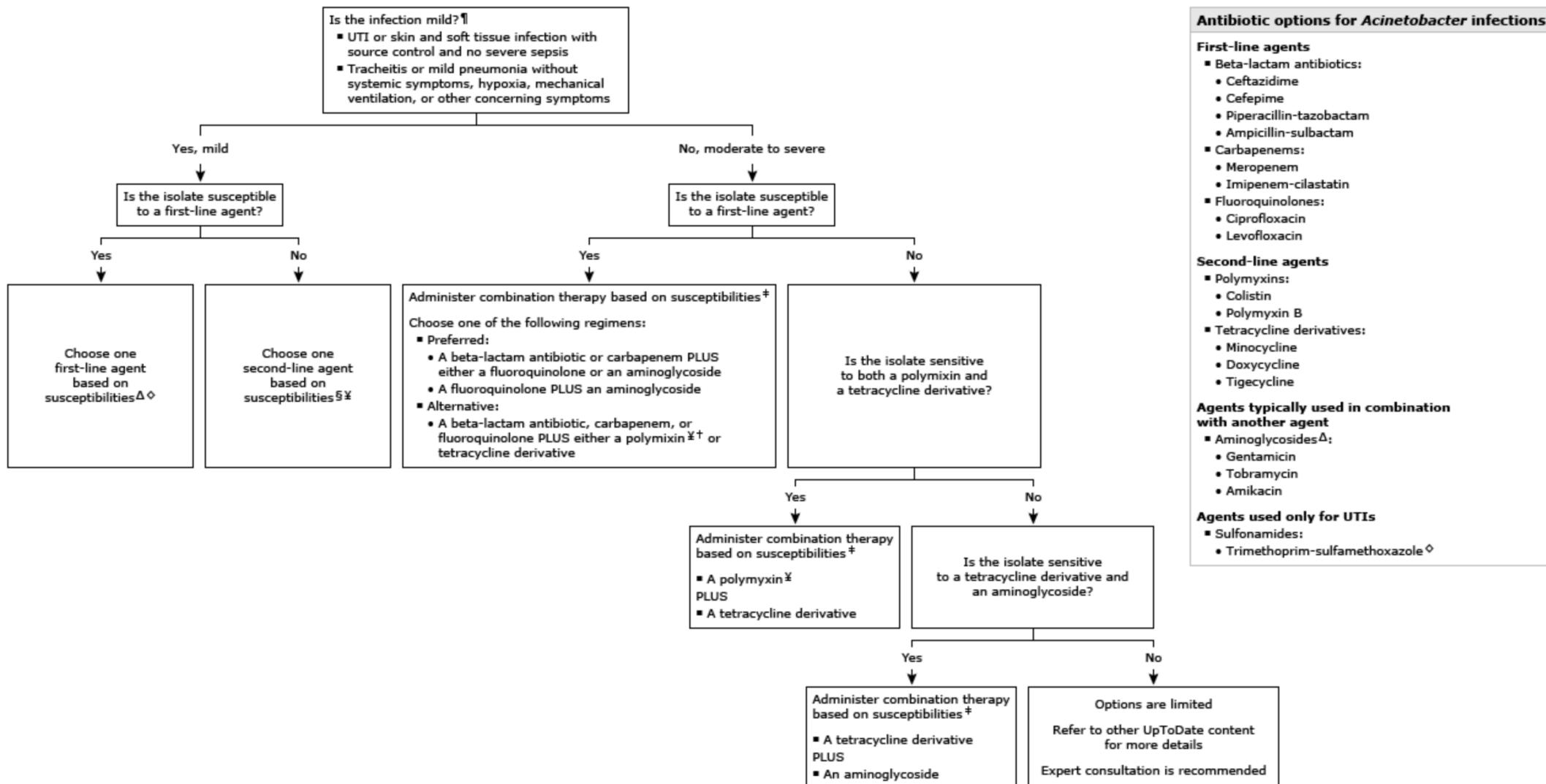


# What makes *Acinetobacter* difficult to treat?

- Commonly recovered from respiratory specimens or wounds in critically-ill patients— *colonizer or pathogen?*
- *A. baumanii* has considerable genomic plasticity- it can readily take up exogenous DNA and mutate, persist on hospital surfaces
- Once *A. baumannii* exhibits carbapenem resistance, it generally has acquired resistance to most other anti- biotics leaving few remaining therapeutic options.
  - OXA-24/40-like carbapenemases and OXA-23-like carbapenemases
- There is no clear “standard of care” antibiotic regimen for CRAB infections against which to estimate the effectiveness of various treatment regimens.



## Antibiotic selection for *Acinetobacter* infections, excluding central nervous system infections\*



UTI: urinary tract infection.

## Treatment of carbapenem-resistant *Acinetobacter spp.*

- **Preferred treatment:** Ampicillin/sulbactam: 9g IV q8h over 4 hours or 27g IV q24h as a continuous infusion
  - Sulbactam inhibits PBP1, PBP3
- For mild infections caused by CRAB isolates susceptible to ampicillin-sulbactam, it is reasonable to administer 3g IV q4h—particularly if intolerance or toxicities precludes the use of higher dosages.
- **Combination therapy:** additional agents include minocycline, tigecycline, cefedirocol, or polymyxin B/E (colistin).

## Cause for optimism: Sulbactam-durlobactam

- Sulbactam-durlobactam (diazabicyclooctane class of  $\beta$ -lactamase inhibitors, with broad spectrum activity against Ambler class A, C and D serine  $\beta$ -lactamases, resulting in the restoration of the susceptibility of CRAB isolates to  $\beta$ -lactams)
- Phase 3 ATTACK trial (ClinicalTrials.gov Identifier: [NCT03894046](#)), which evaluated sulbactam-durlobactam vs colistin in patients with documented *Acinetobacter baumannii* hospital-acquired bacterial pneumonia, ventilator-associated bacterial pneumonia, ventilated pneumonia, or bacteremia
- Sulbactam-durlobactam was found to be statistically non/inferior to colistin for the primary endpoint of 28-day all-cause mortality in patients with carbapenem-resistant *Acinetobacter* infections.
- The mortality rate was 19.0% (12/63) in the sulbactam-durlobactam arm and 32.3% (20/62) in the colistin arm (treatment difference, 13.2%; 95% CI, -30.0, 3.5).
- A statistically significant difference in clinical cure rates was observed (61.9% with sulbactam-durlobactam vs 40.3% with colistin).

# *ESKAPE Pathogens*

*Enterococcus faecium (vancomycin-resistant)*

*Staphylococcus aureus (MRSA)*

*Klebsiella pneumoniae (ESBL, carbapenem-resistant)*

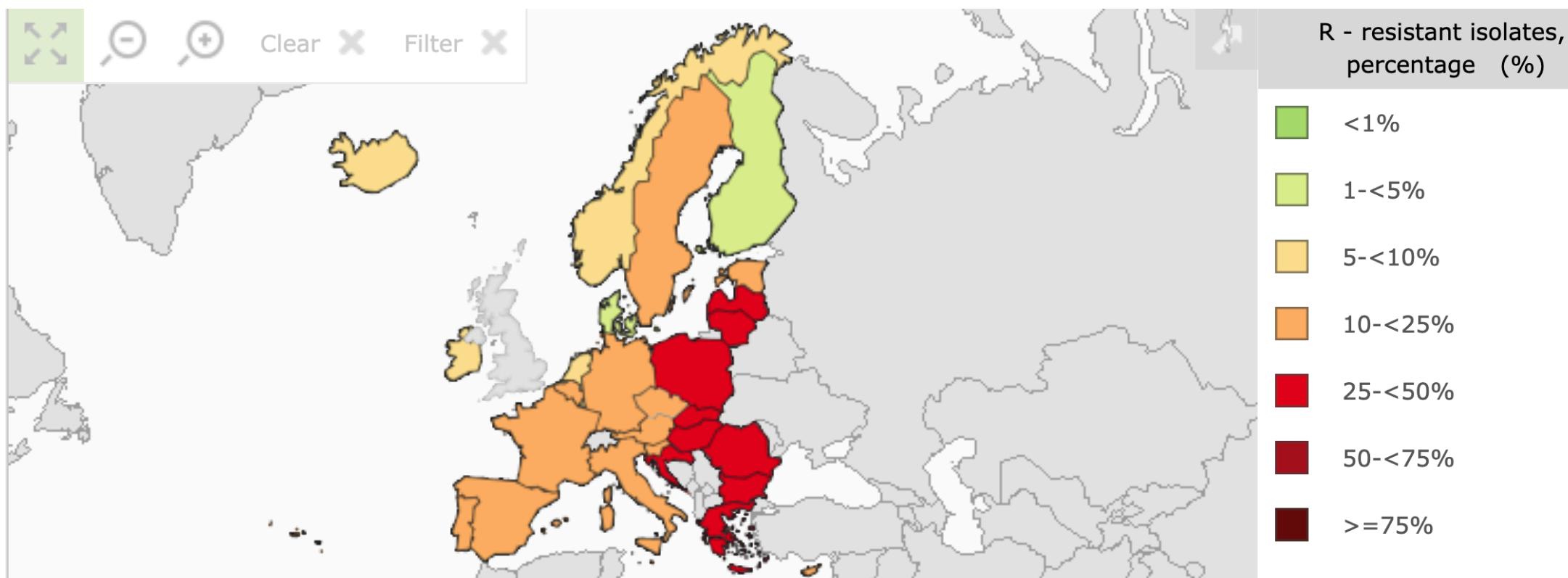
*Acinetobacter baumanii*

*Pseudomonas aeruginosa*

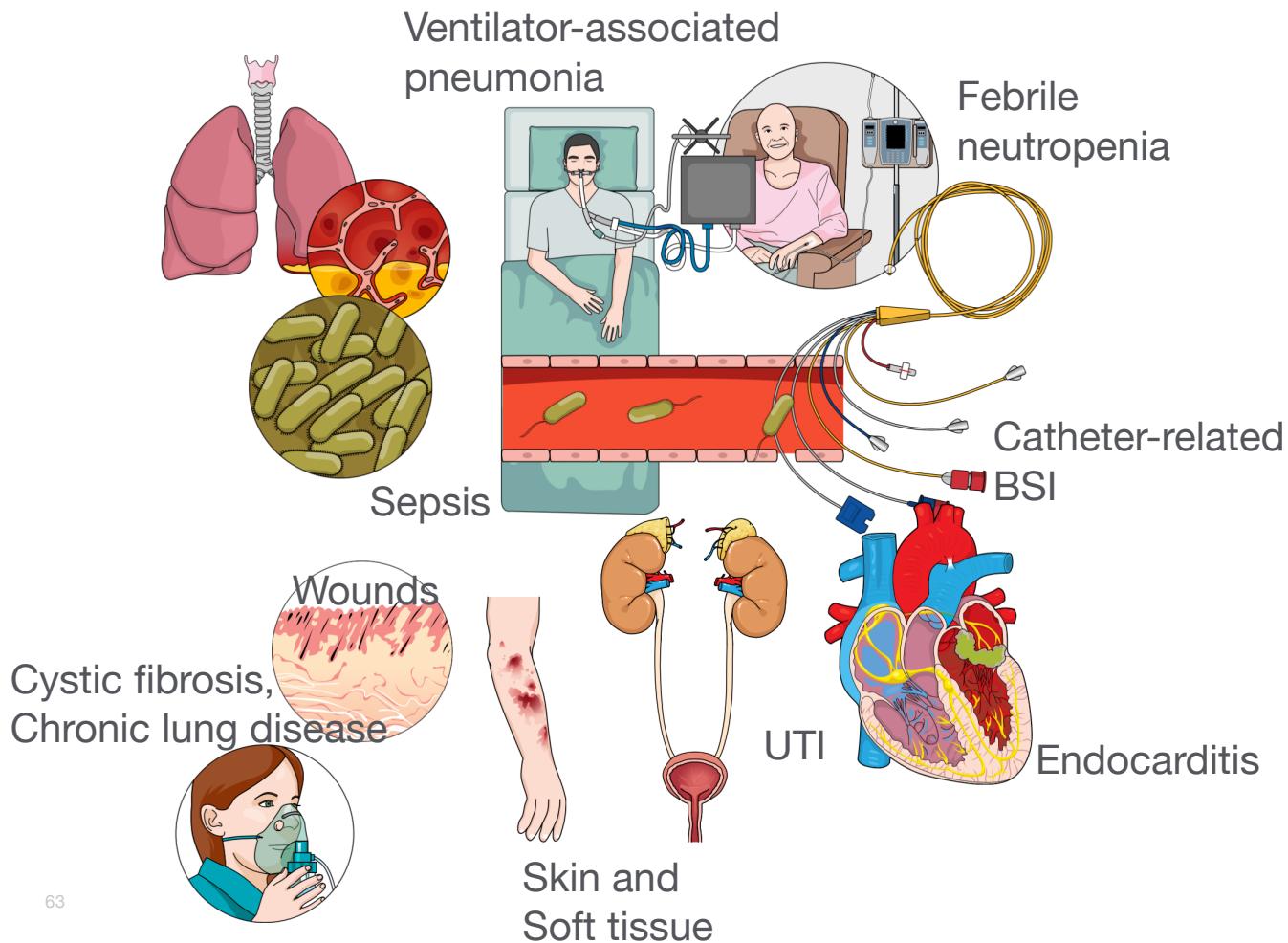
*Enterobacter spp.*

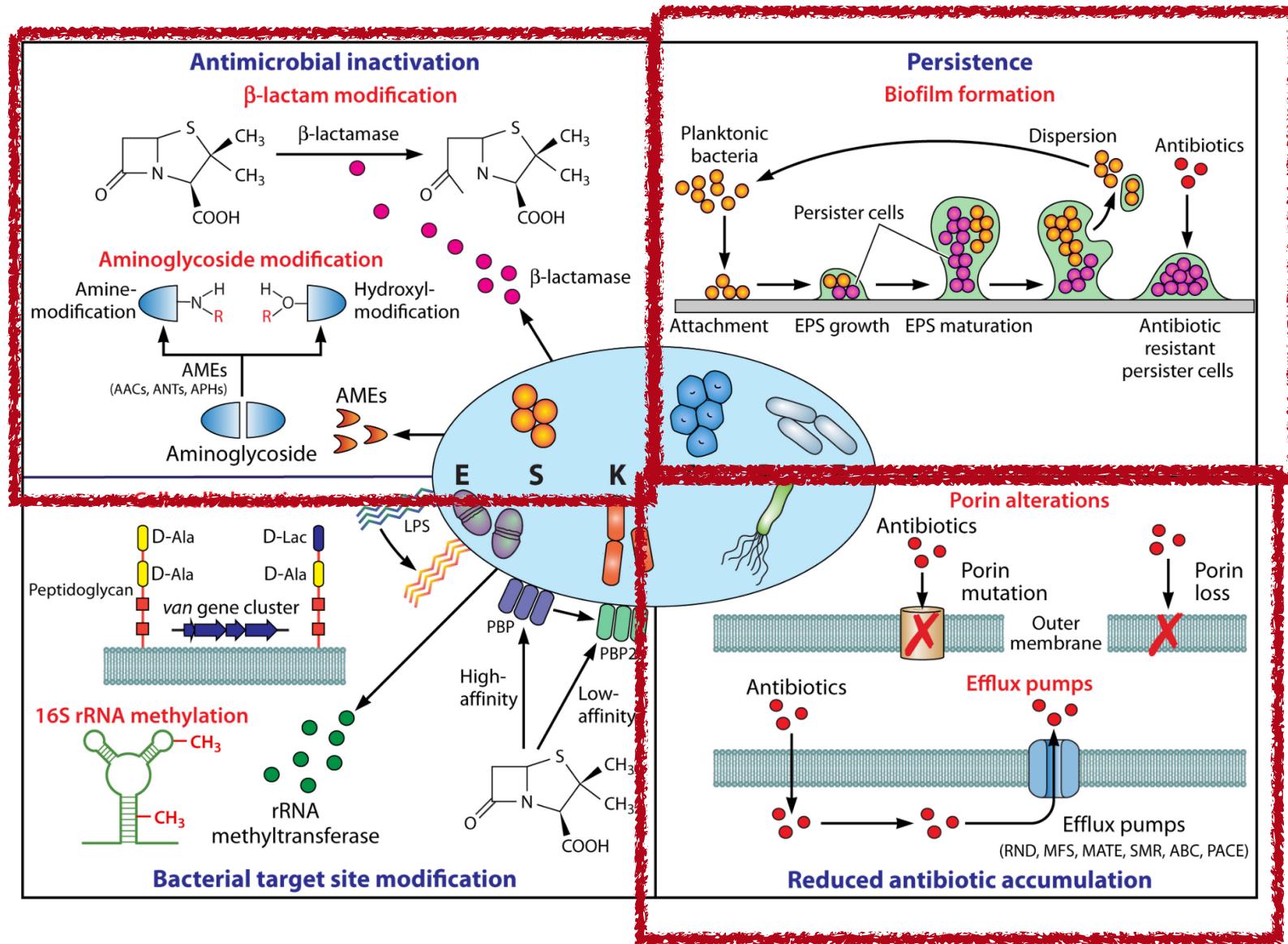
Know your  $\beta$ -lactamases!

# Carbapenem-resistant *Pseudomonas*



# **Pseudomonas aeruginosa**





# Case

- 45 year old male with newly diagnosed acute myeloid leukemia admitted for induction chemotherapy with fludarabine, cytarabine and idarubicin.
- 7 days after completion of chemotherapy, while neutropenic, he develops fever 39°C, evidence of sepsis
- Complains of pain under his right toe
- Started on piperacillin-tazobactam
- Within 48 hours, blood cultures are positive for *P. aeruginosa*, skin lesion on toe rapidly develops into blisters
- Antibiogram reveals isolate sensitive only to amikacin, colistin and ceftolozane/tazobactam
- Patient is started on ceftolozane/tazobactam, colistin and amikacin

- **Pseudomonas aeruginosa ST175 and ST23**

- VIM-1 carbapenemase and OXA-488
- ExoU or ExoS exotoxins
- **Ceftolozane/tazobactam, ceftazidime-avibactam, imipenem-cilastatin-relebactam, cefiderocol, colistin**



Rapidly progressing necrotizing fasciitis from washing feet in bidet

Coppola PE et al. Microorganisms 2020; 8.

Tamma PD, et al. Clin Infect Dis 2021; 72:e169–e183.

Paul M, et al. Clin Microbiol Infect 2021;

Patient required right leg amputation but survived the infection

# **Pseudomonas aeruginosa ST175 and ST23 spread in the hematology ward in Bologna**

Strain (Source)	Sample	CAZ	FEP	IPM	MEM	MIC ( $\mu\text{g/mL}$ )			CST	GEN	AMK
						TZP	CAZ/AVI	C/T			
B062 (Case #3)	Blood	32	>8	<1	1	>16	4	<1	0.5	>4	16
BO48 (Case #4)	Blood	16	>8	>8	16	>16	4	<1	0.5	>4	16
BO68 (Case #6)	Blood	32	>8	>8	8	>16	4	<1	0.5	>4	<8
BO93 (bidet filter)	Bidet filter	32	>8	8	16	>16	>8	>16	0.5	>4	>16
BO94 (bidet)	Bidet water	32	>8	>8	16	>16	>8	>16	0.5	>4	>16

Caz, ceftazidime; FEP, cefepime; IPM, imipenem; MEM, meropenem; TZP, piperacillin-tazobactam; CAZ/AVI, ceftazidime/avibactam; C/T, ceftolozane/tazobactam; CST, colistin; GEN, gentamicin; AMK, amikacin.

*Susceptibility can vary widely from center to center or from patient to patient-  
Pay attention to MICs*

# **Recommended treatment for carbapenem-resistant *Pseudomonas aeruginosa***

**Table 4. Recommended Antibiotic Treatment Options for Difficult-to-Treat *Pseudomonas aeruginosa*, Assuming In Vitro Susceptibility to Agents in Table**

Source of Infection	Preferred Treatment	Alternative Treatment if First-line Options not Available or Tolerated
Cystitis	Ceftolozane-tazobactam, ceftazidime-avibactam, imipenem-relebactam, cefiderocol, or a single dose of an aminoglycoside	Colistin
Pyelonephritis or complicated urinary tract infection <sup>a</sup>	Ceftolozane-tazobactam, ceftazidime-avibactam, imipenem-cilastatin-relebactam, and cefiderocol	Once-daily aminoglycosides
Infections outside of the urinary tract	Ceftolozane-tazobactam, ceftazidime-avibactam, or imipenem-cilastatin-relebactam	Cefiderocol Aminoglycoside monotherapy: limited to uncomplicated bloodstream infections with complete source control <sup>b</sup>

<sup>a</sup>A complicated urinary tract infection (UTI) is defined as a UTI that occurs in association with a structural or functional abnormality of the genitourinary tract, or any UTI in a male patient.

<sup>b</sup>Uncomplicated bloodstream infections include a bloodstream infection that is due to a urinary source or a catheter-related bloodstream infection with removal of the infected vascular catheter.

# **Summary**

## **Can we ESKAPE resistance?**

- **High index of suspicion:**
  - Previous healthcare exposures, patient history
  - Previous antibiotic therapy(ies)
  - Critically-ill
  - Failure of first/second line antibiotics
- **Growing number of new antibiotics active against ESKAPE pathogens, but drugs have specific niches**
  - Knowledge of local epidemiology
  - Communication with clinical microbiology laboratory, molecular test confirmation

Questions?

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