Superbugs:

Multidrug resistance and reserve antibiotics

Jan Tkadlec

“It is time to close the book on infectious diseases and declare the war against pestilence won”.

William H. Stewart, the Surgeon General of the United States in 1969

Some quotations did not age well…

BACK TO THE FUTURE

CNN Health | Life, But Better | Fitness | Food | Sleep | Mindfulness | Relationships | Watch

Superbug crisis could get worse, killing nearly 40 million people by 2050, study estimates

By Jacqueline Howard, CNN

'It is a pandemic': UK's envoy on superbugs says scale of threat underestimated

Dame Sally Davies says action on deadly antibiotic-resistant infections must be prioritised

The Guardian Eur

Rise of drug-resistant superbugs could make Covid pandemic look 'minor', expert warns

Common infections will kill millions if drug resistance through misuse of antibiotics is not curbed, says England's ex-chief medical officer

Global burden of bacterial antimicrobial resistance 1990–2021: a systematic analysis with forecasts to 2050

*GBD 2021 Antimicrobial Resistance Collaborators**

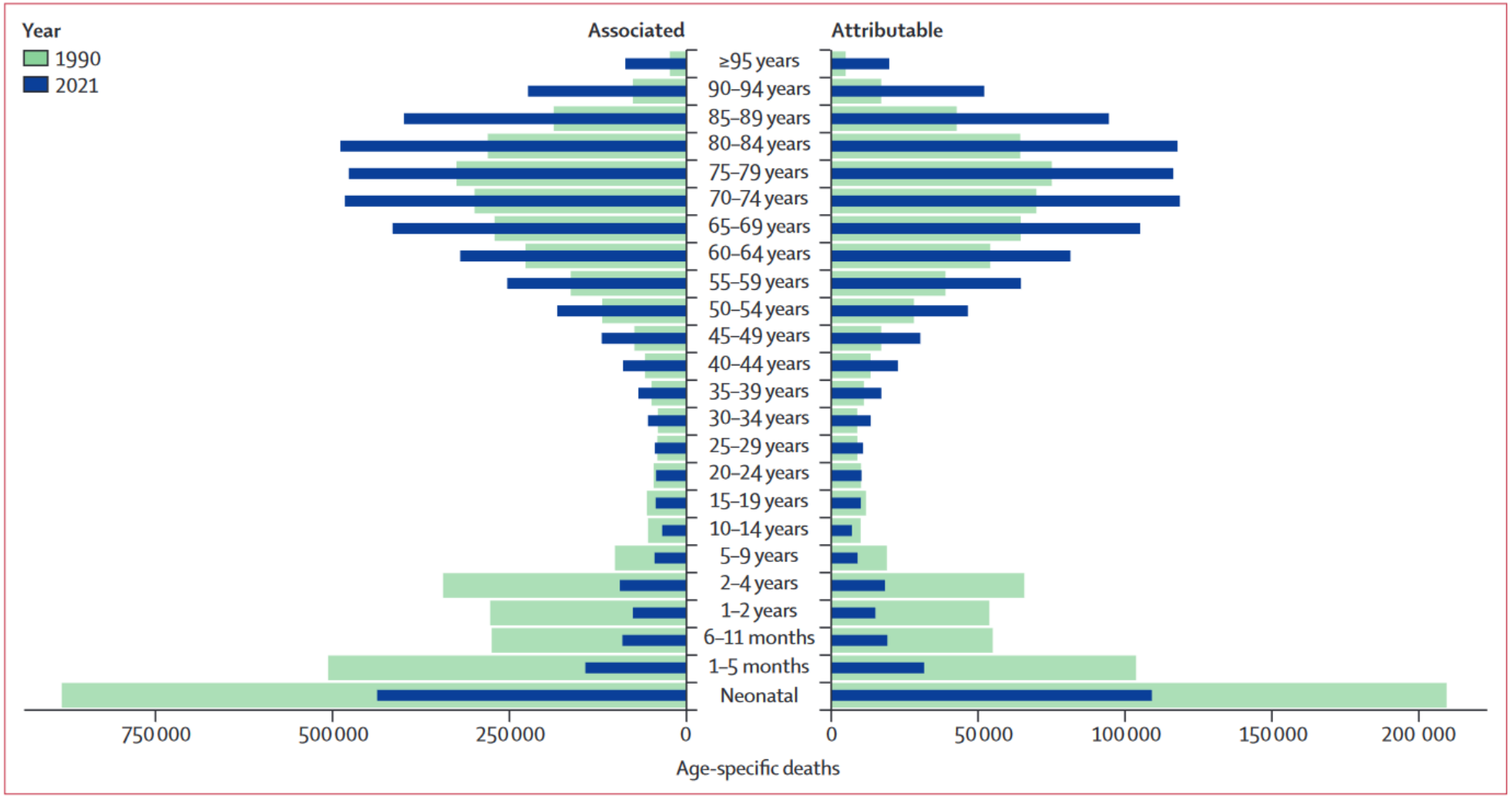

Figure 2: **Deaths attributable and associated with antimicrobial resistance, by detailed age group, for 1990 and 2021**
Counterfactuals have distinct x-axes.

Global burden of bacterial antimicrobial resistance 1990–2021: a systematic analysis with forecasts to 2050

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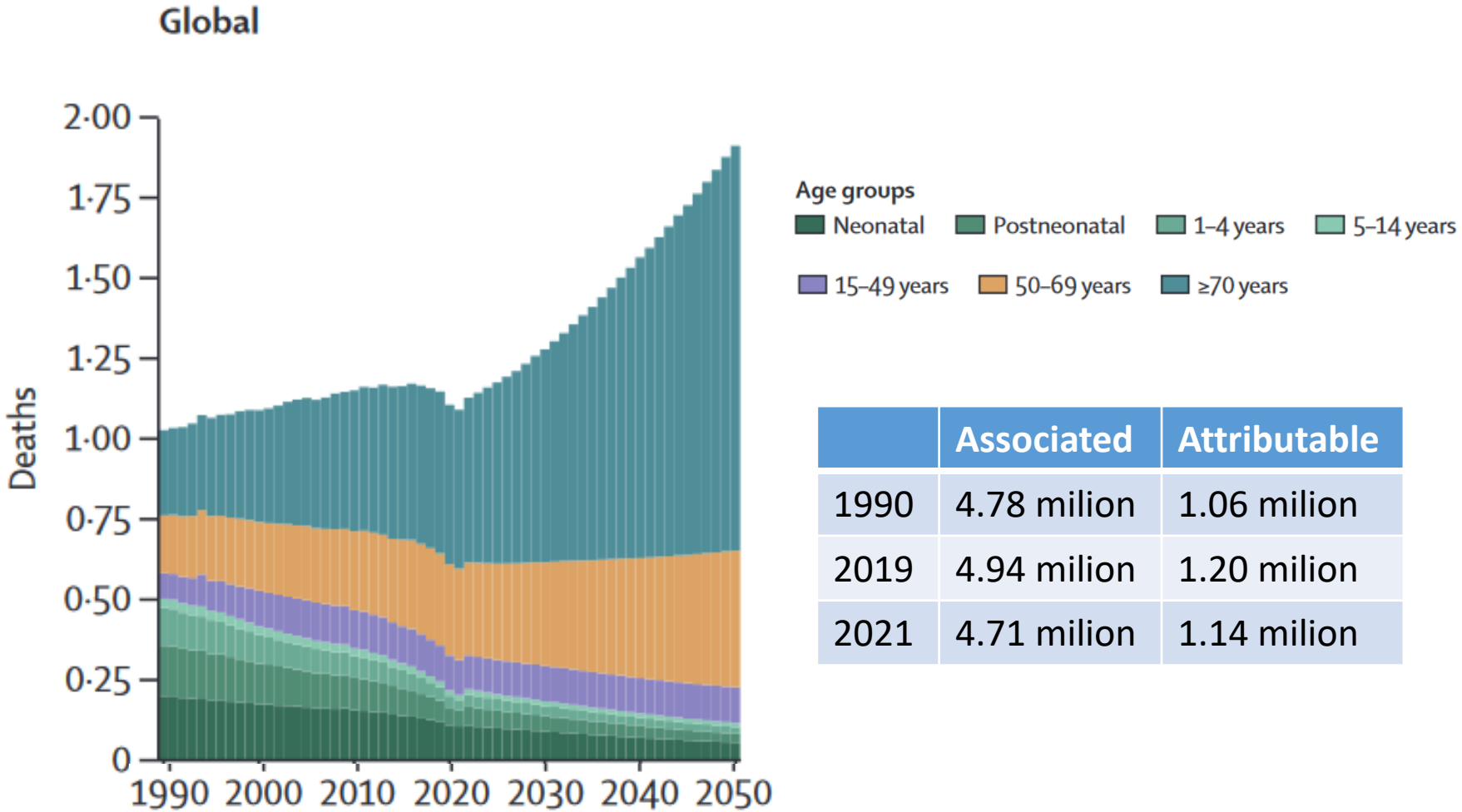


	Associated	Attributable
1990	4.78 milion	1.06 milion
2019	4.94 milion	1.20 milion
2021	4.71 milion	1.14 milion

Figure 7: Deaths attributable to AMR by age group and location in the reference scenario, 2022–2050 Units are in millions.

Main threats

Superbug definition

Bacterium	MDR	XDR	PDR
Staphylococcus aureus	The isolate is non-susceptible to at least 1 agent in ≥3 antimicrobial categories listed in Table 1[a]	The isolate is non-susceptible to at least 1 agent in all but 2 or fewer antimicrobial categories in Table 1.	Non-susceptibility to all agents in all antimicrobial categories for each bacterium in Tables 1–5
Enterococcus spp.	The isolate is non-susceptible to at least 1 agent in ≥3 antimicrobial categories listed in Table 2	The isolate is non-susceptible to at least 1 agent in all but 2 or fewer antimicrobial categories in Table 2.	
Enterobacteriaceae	The isolate is non-susceptible to at least 1 agent in ≥3 antimicrobial categories listed in Table 3	The isolate is non-susceptible to at least 1 agent in all but 2 or fewer antimicrobial categories in Table 3.	
Pseudomonas aeruginosa	The isolate is non-susceptible to at least 1 agent in ≥3 antimicrobial categories listed in Table 4	The isolate is non-susceptible to at least 1 agent in all but 2 or fewer antimicrobial categories in Table 4.	
Acinetobacter spp.	The isolate is non-susceptible to at least 1 agent in ≥3 antimicrobial categories listed in Table 5	The isolate is non-susceptible to at least 1 agent in all but 2 or fewer antimicrobial categories in Table 5.	

[a]All MRSA isolates are defined as MDR because resistance to oxacillin or cefoxitin predicts non-susceptibility to all categories of β-lactam antimicrobials listed in this document, with the exception of the anti-MRSA cephalosporins (i.e. all categories of penicillins, cephalosporins, β-lactamase inhibitors and carbapenems currently approved up until 25 January 2011).

MDR - Multidrug resistant
XDR - Extensive drug resistant
PDR - Pandrug resistant

Source: Magiorakos et al 2012

Antimicrobial category	Antimicrobial agent	Results of antimicrobial susceptibility testing (S or NS)
Aminoglycosides	Gentamicin	
Ansamycins	Rifampin/rifampicin	
Anti-MRSA cephalosporins	Ceftaroline	
Anti-staphylococcal β-lactams (or cephamycins)	Oxacillin (or cefoxitin)[a]	
Fluoroquinolones	Ciprofloxacin	
	Moxifloxacin	
Folate pathway inhibitors	Trimethoprim-sulphamethoxazole	
Fucidanes	Fusidic acid	
Glycopeptides	Vancomycin	
	Teicoplanin	
	Telavancin	
Glycylcyclines	Tigecycline	
Lincosamides	Clindamycin	
Lipopeptides	Daptomycin	
Macrolides	Erythromycin	
Oxazolidinones	Linezolid	
Phenicols	Chloramphenicol	
Phosphonic acids	Fosfomycin	
Streptogramins	Quinupristin-dalfopristin	
Tetracyclines	Tetracycline	
	Doxycycline	
	Minocycline	

World Health Organization

WHO PRIORITY PATHOGENS LIST FOR R&D OF NEW ANTIBIOTICS

Priority 1: CRITICAL#

Acinetobacter baumannii, carbapenem-resistant

Pseudomonas aeruginosa, carbapenem-resistant

Enterobacteriaceae*, carbapenem-resistant, 3rd generation cephalosporin-resistant

Priority 2: HIGH

Enterococcus faecium, vancomycin-resistant

Staphylococcus aureus, methicillin-resistant, vancomycin intermediate and resistant

Helicobacter pylori, clarithromycin-resistant

Campylobacter, fluoroquinolone-resistant

Salmonella spp., fluoroquinolone-resistant

Neisseria gonorrhoeae, 3rd generation cephalosporin-resistant, fluoroquinolone-resistant

Priority 3: MEDIUM

Streptococcus pneumoniae, penicillin-non-susceptible

Haemophilus influenzae, ampicillin-resistant

Shigella spp., fluoroquinolone-resistant

CDC
CENTERS FOR DISEASE CONTROL AND PREVENTION

Urgent Threats

- Carbapenem-resistant *Acinetobacter*
- *Candida auris (C. auris)*
- *Clostridioides difficile (C. difficile)*
- Carbapenem-resistant Enterobacteriaceae (CRE)
- Drug-resistant *Neisseria gonorrhoeae (N. gonorrhoeae)*

Serious Threats

- Drug-resistant *Campylobacter*
- Drug-resistant *Candida*
- Extended-spectrum beta-lactamase (ESBL)-producing Enterobacteriaceae
- Vancomycin-resistant *Enterococci* (VRE)
- Multidrug-resistant *Pseudomonas aeruginosa (P. aeruginosa)*
- Drug-resistant nontyphoidal *Salmonella*
- Drug-resistant *Salmonella* serotype Typhi
- Drug-resistant *Shigella*
- Methicillin-resistant *Staphylococcus aureus* (MRSA)
- Drug-resistant *Streptococcus pneumoniae (S. pneumoniae)*
- Drug-resistant Tuberculosis (TB)

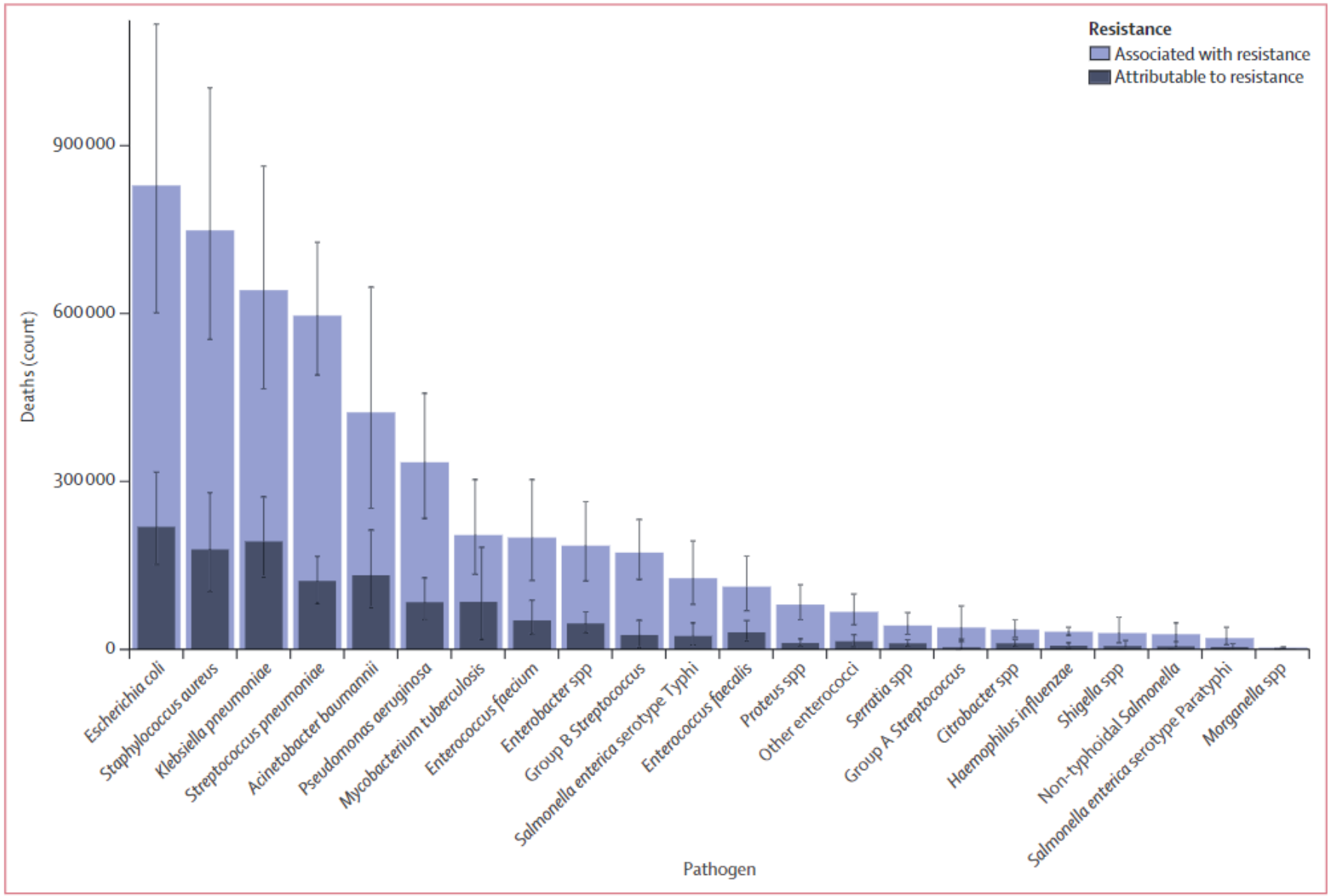
Concerning Threats

- Erythromycin-resistant group A *Streptococcus*
- Clindamycin-resistant group B *Streptococcus*

Watch List

- Azole-resistant *Aspergillus fumigatus (A. fumigatus)*
- Drug-resistant *Mycoplasma genitalium (M. genitalium)*
- Drug-resistant *Bordetella pertussis (B. pertussis)*

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

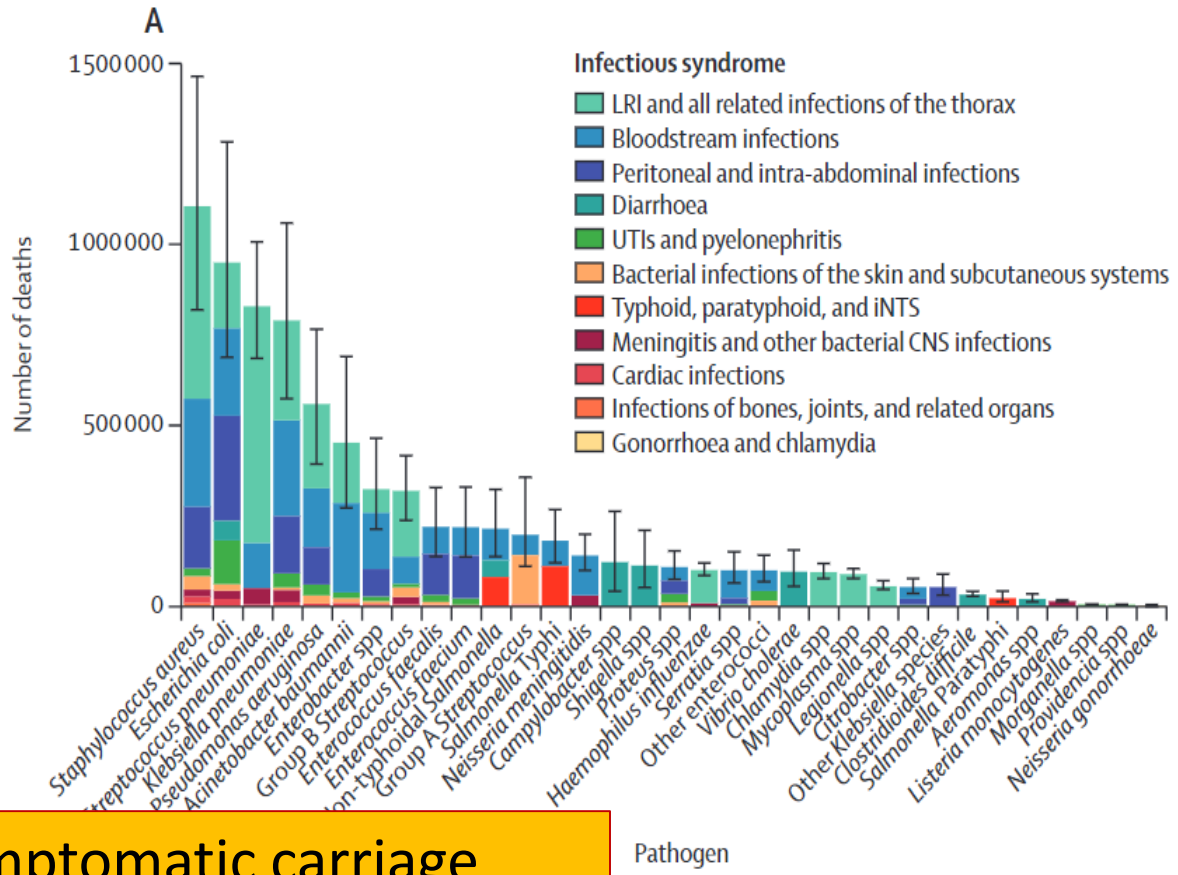


Global burden of antimicrobial resistance in 2019; Lancet 2022

Most common causative agents of bacterial infections.

Only 33 species of bacteria cause >50% of deaths from bacterial infections (7.7/13.7 million deaths/year)

(note: study does not include TB≈1.6 million deaths in 2021)
(note 2: there are more than 30,000 bacterial species known)



Top:
Staphylococcus aureus
Escherichia coli
Streptococcus pneumoniae
Klebsiella pneumoniae
Pseudomonas aeruginosa

Commonly asymptomatic carriage

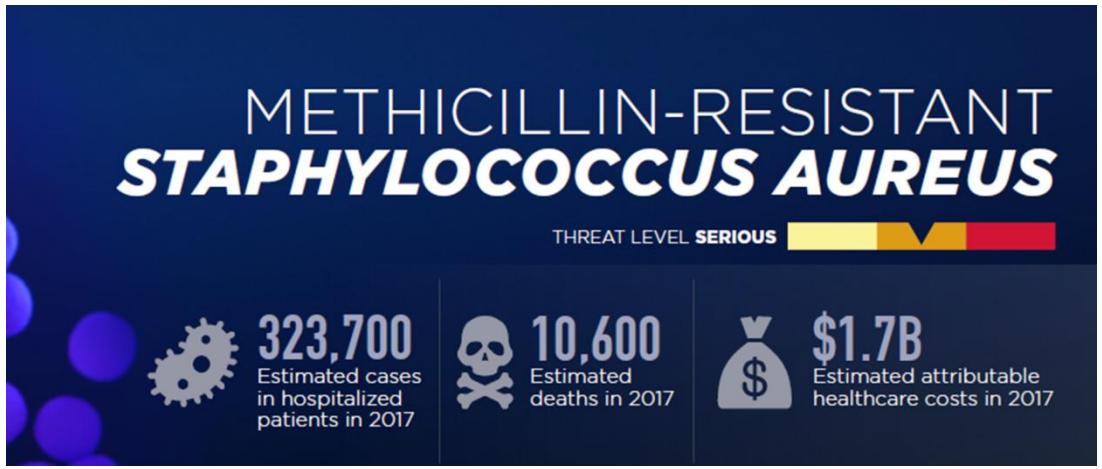
Often endogenous origin of infection

Tendency to accumulate antimicrobial resistance

No vaccine (almost)

Lancet 2022; 400: 2221–48

What is a bigger threat?



Vs.

How the level of threat is measured:

- Clinical impact (severity, mortality)
- Economic impact (when available)
- Incidence
- 10-year projection of incidence
- Transmissibility (how easily a germ spreads or causes infections)
- **Availability of effective antibiotics**
- Barriers to prevention
- Situation in other countries

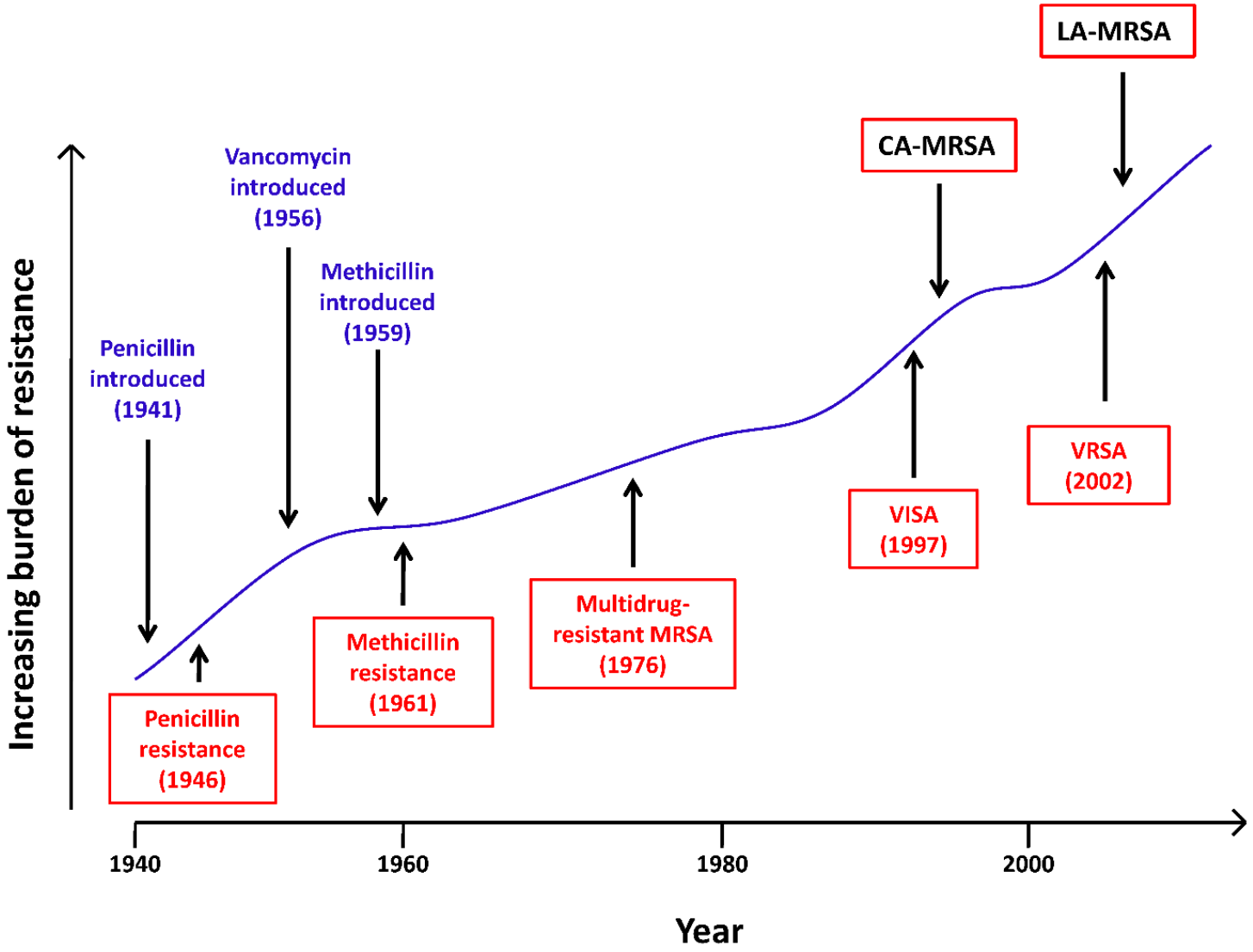
Source: CDC. Antibiotic Resistance Threats in the United States, 2019.

Staphylococcus aureus

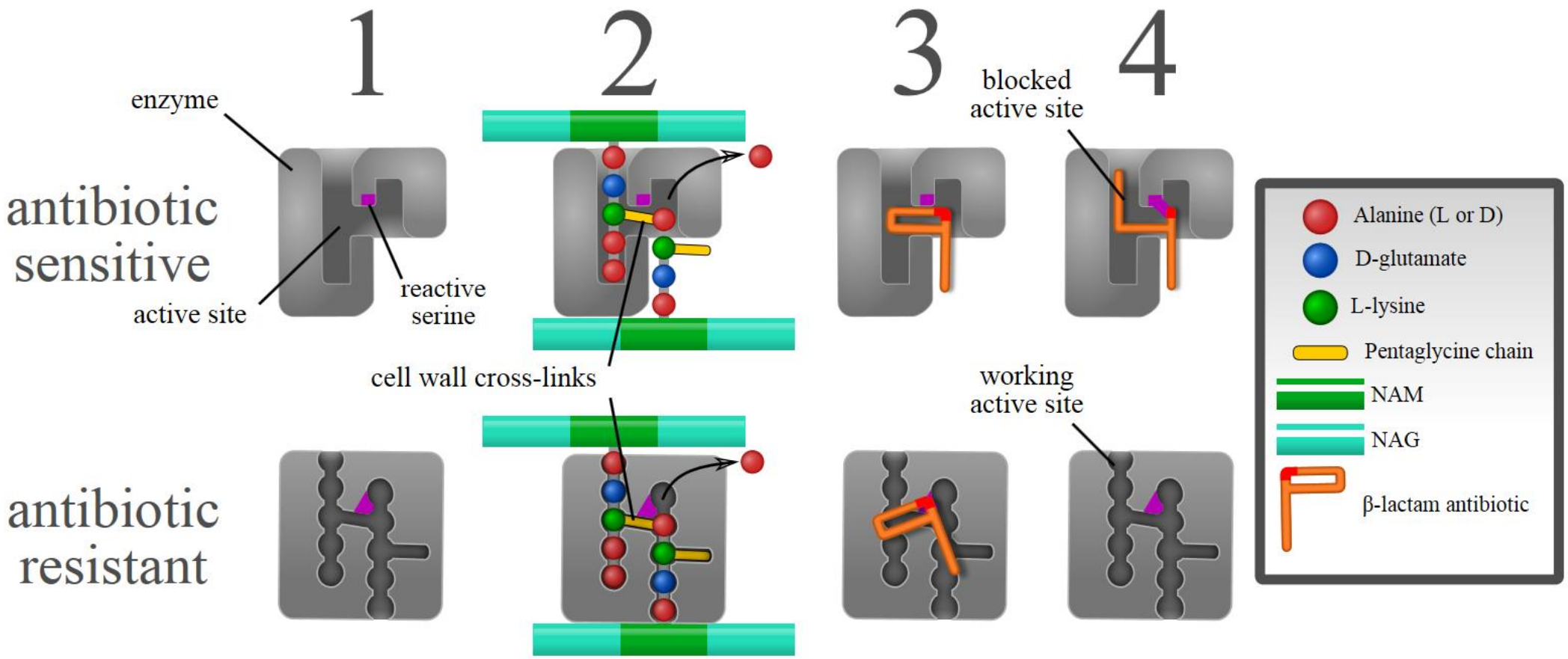
S. aureus – the first superbug

- 1940s – pandemic penicilin resistant-*S. aureus* – enzym penicillinase
- Introduction of methicillin (1959)
  - Semisynthetic derivate of penicillin
  - Resistant to penicillinase
- MRSA (methicillin-resistant *S. aureus*) 1961
  - Resistance to penicillin, methicillin (oxacillin) and cefalosporins
  - MDR: often resistant to fluoroquinolones, tetracyclines, macrolides and aminoglycosides
  - Susceptible to vancomycin, linezolid, daptomycin
  - Higher mortality and morbidity compare to MSSA

Gradual increase of resistence in *S. aureus*

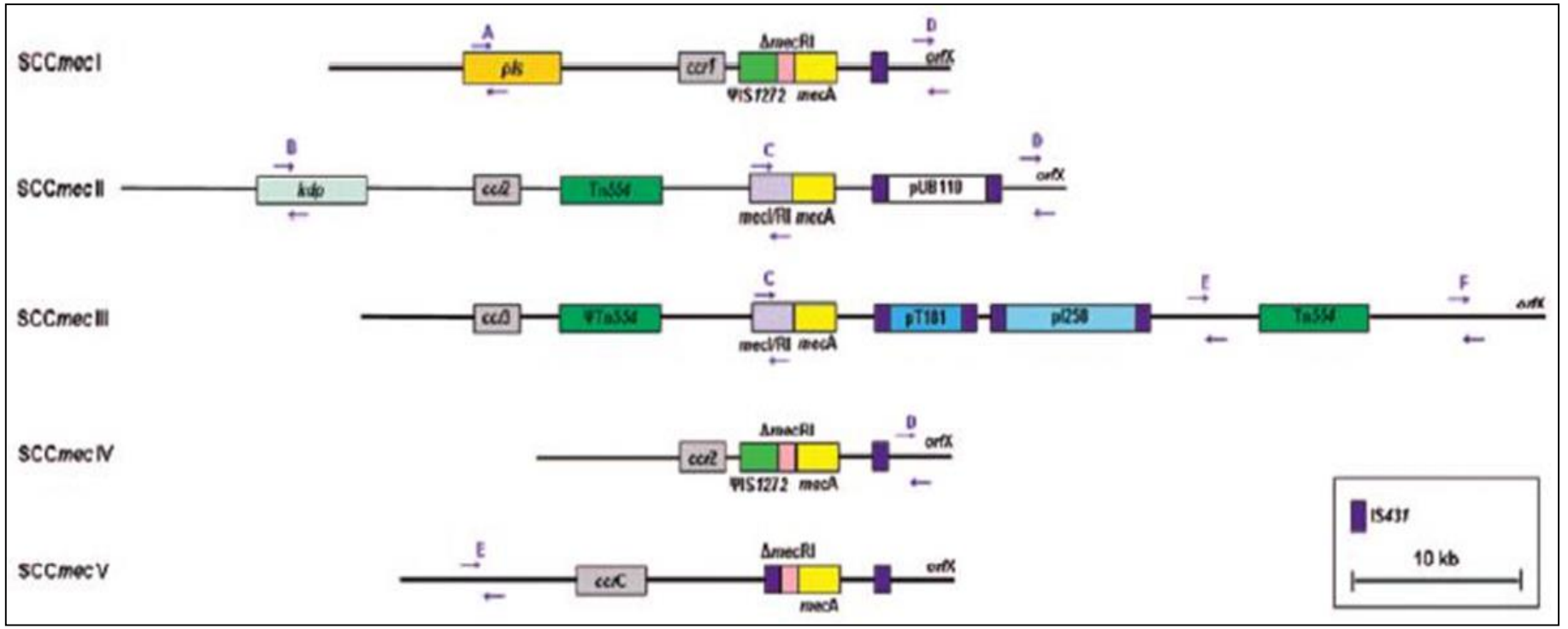


Mechanism of MRSA resistance

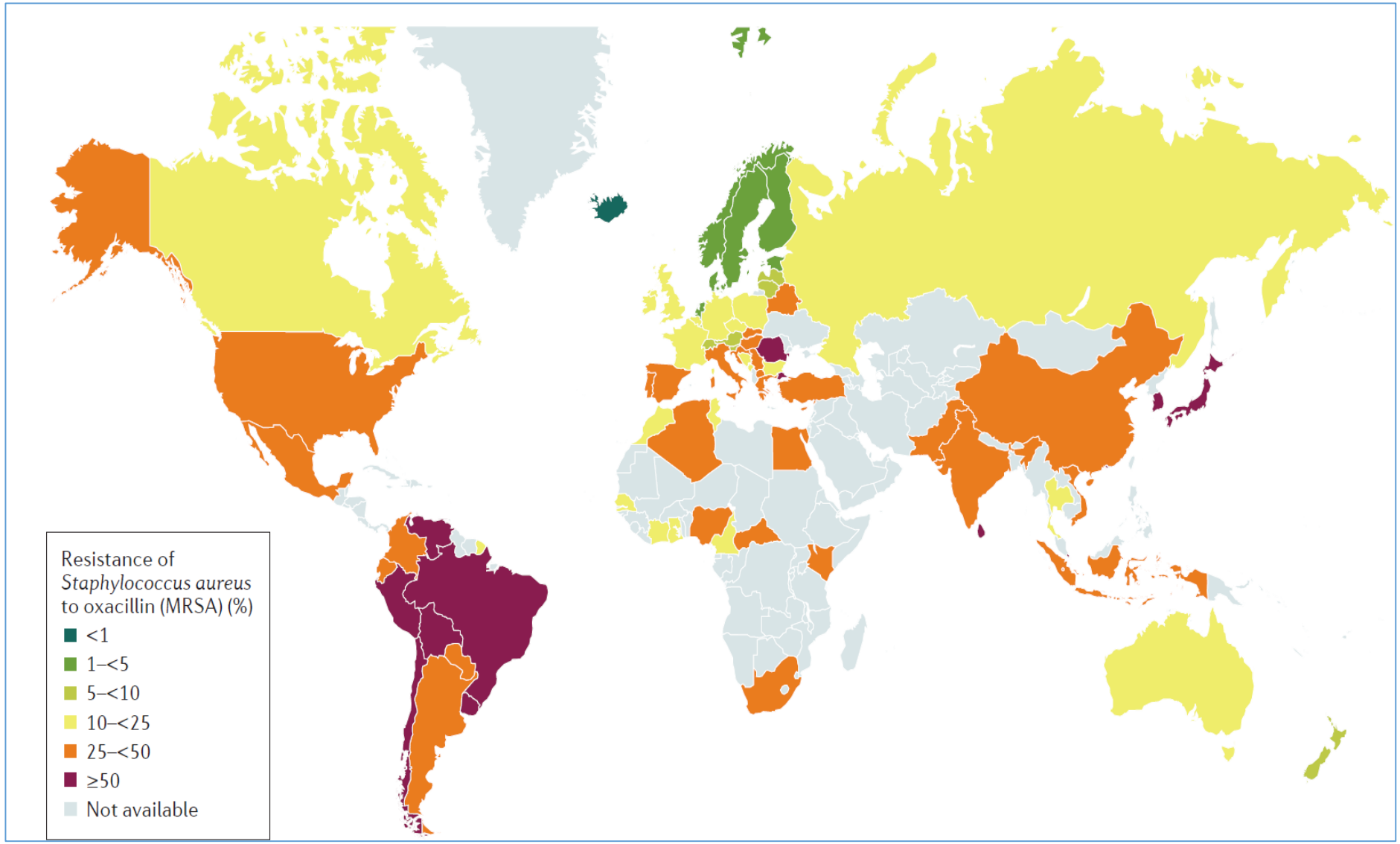


Genetic background for MRSA

- SCC*mec* cassette
  - Gene cassette (mobile genetic element)
  - Codes for PBP2a on the *mecA* gene (plus several other genes).
  - 7 types of varying size and composition (and sub-types)

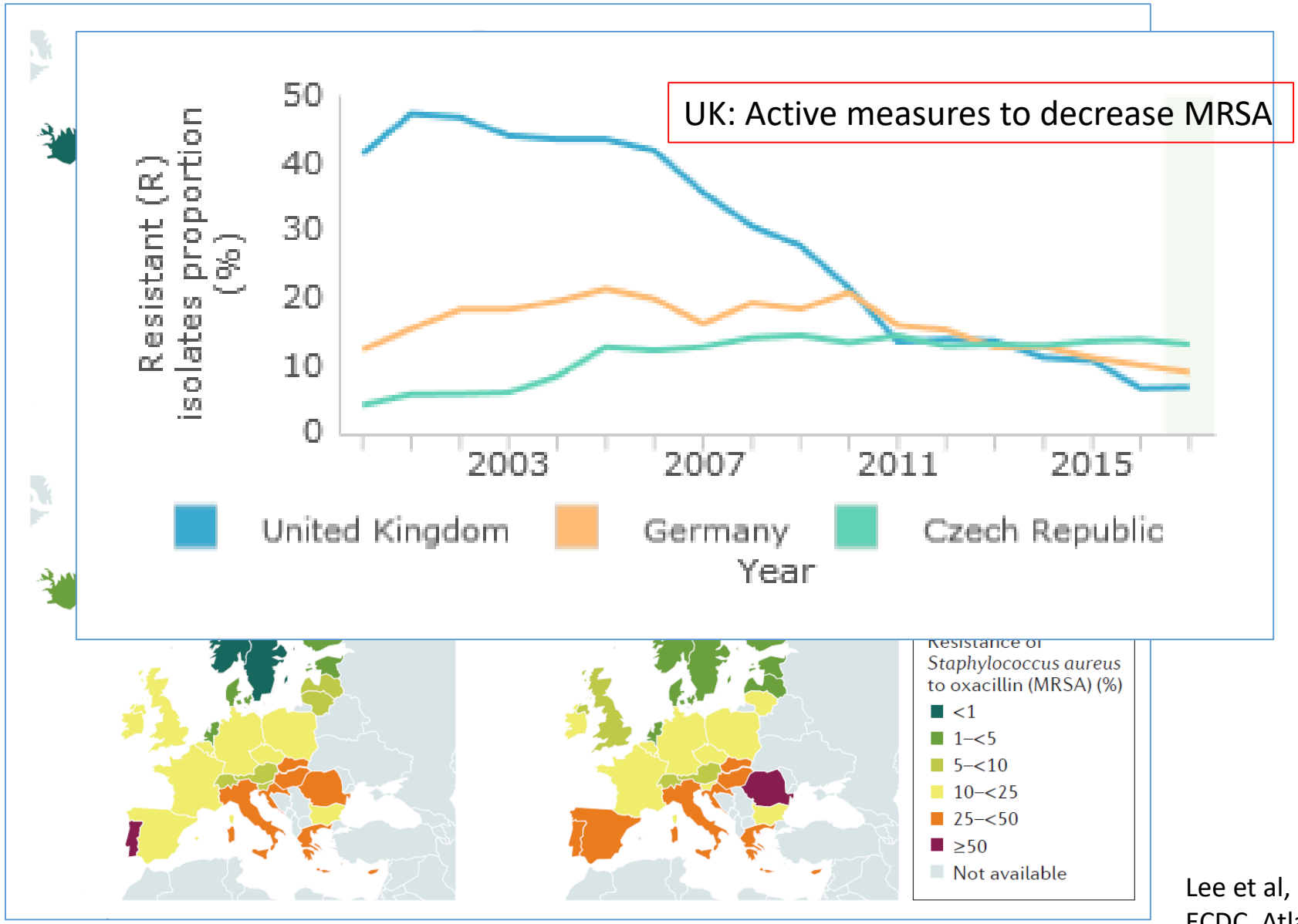


Global MRSA prevalence (%)



Lee et al 2018

Europe (invasive isolates)



Lee et al, 2018

ECDC, Atlas of antimicrobial resistance

Therapeutic options for MRSA (existing or near future)

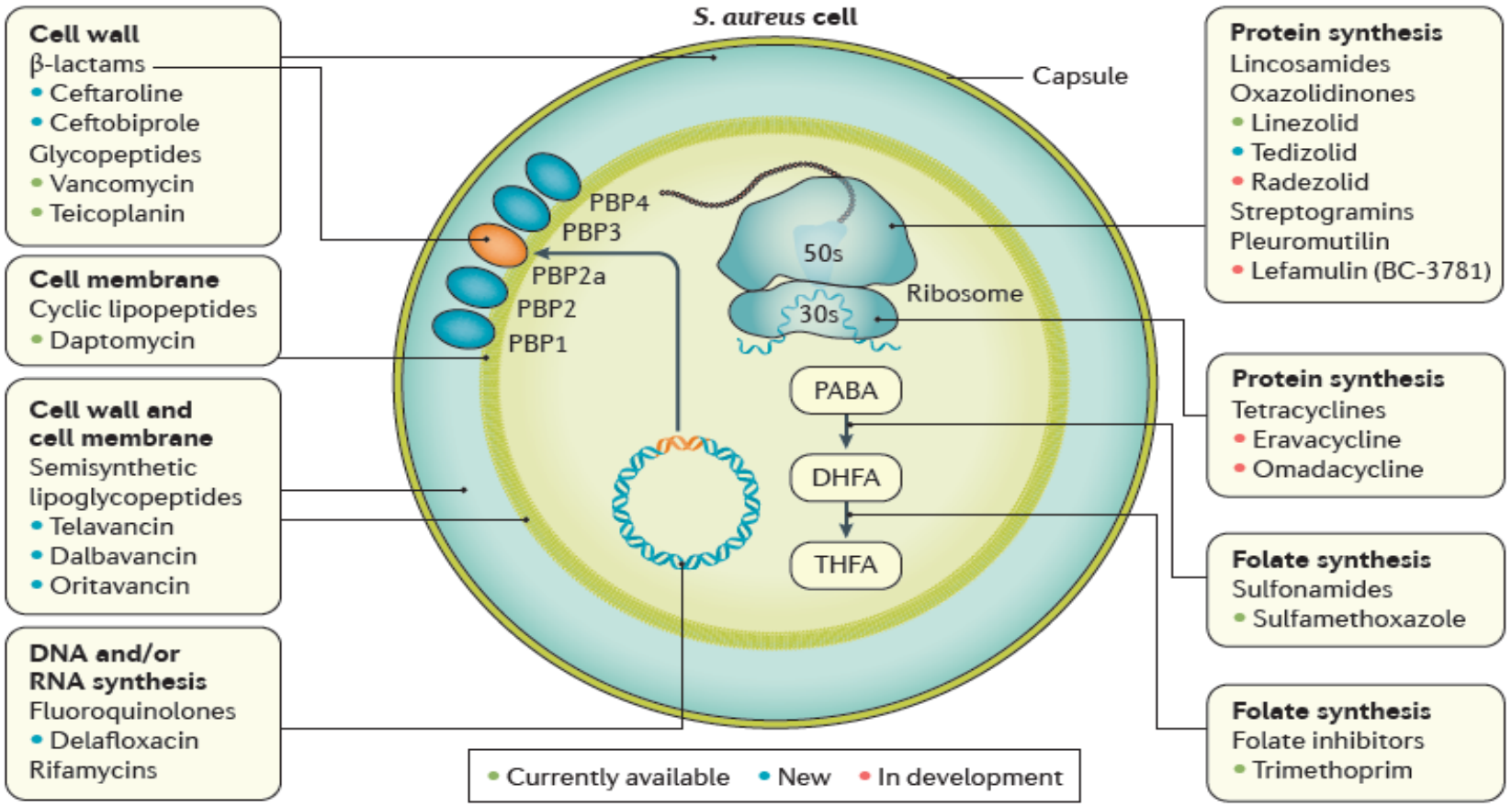
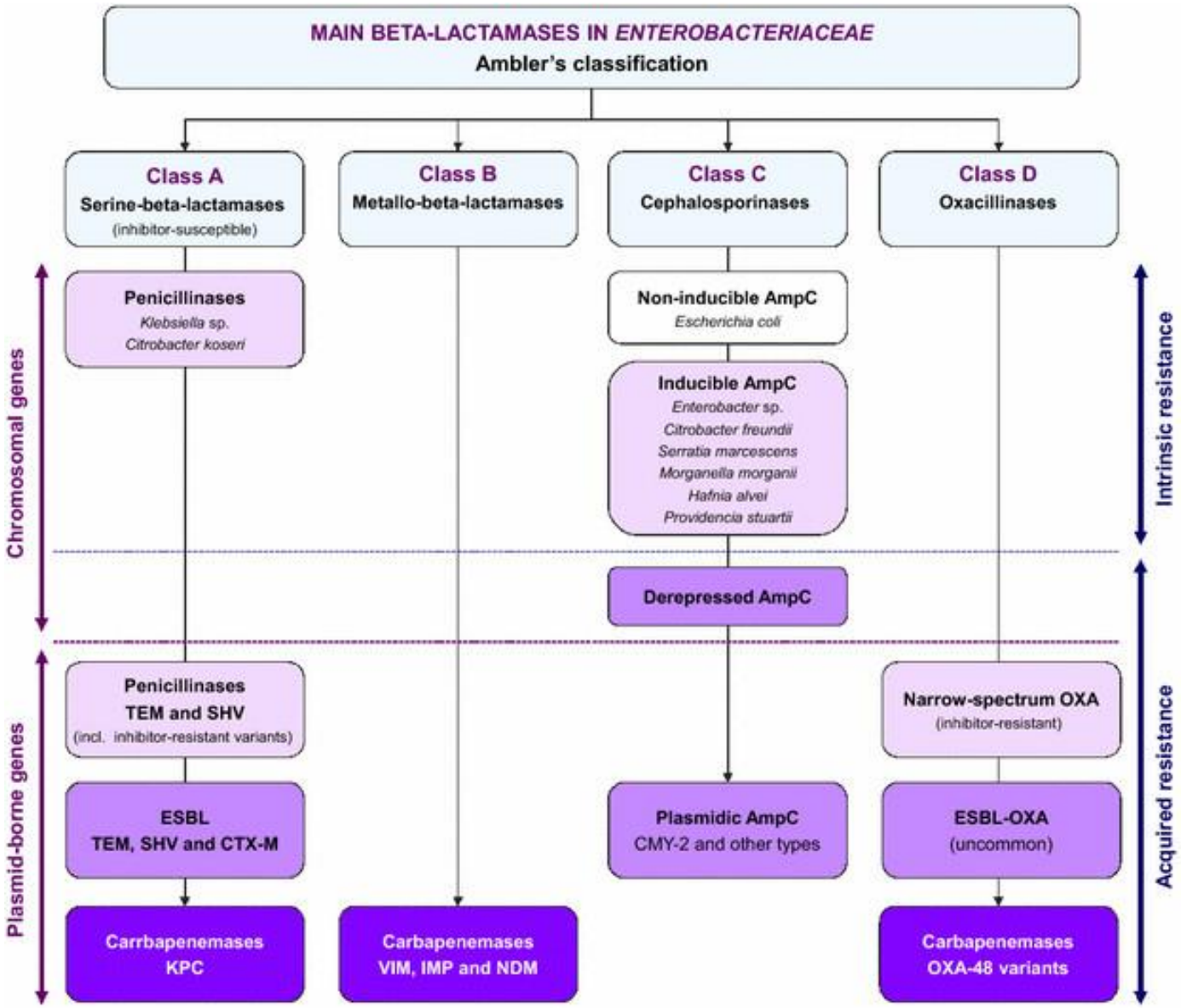


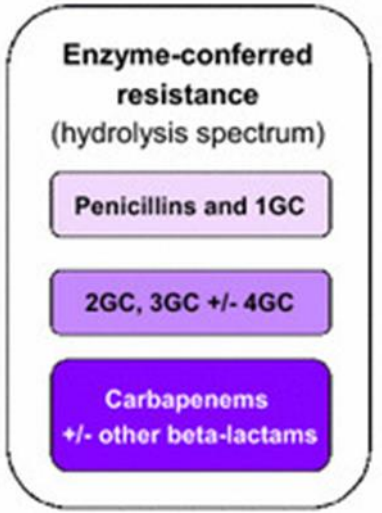
Figure 5 | **Bacterial targets of antibiotics active against MRSA.** Antibiotics have diverse mechanisms of action and target different bacterial structures or metabolic pathways. Existing antibiotic options are in green, new antibiotics approved and on the market are in blue and antibiotics in the pipeline are in orange. DHFA, dihydrofolic acid; PABA, para-aminobenzoic acid; PBP, penicillin-binding protein; *S. aureus*, *Staphylococcus aureus*; THFA, tetrahydrofolic acid. Figure adapted from REF.[229], Macmillan Publishers Limited.

Lee et al, 2018

Enterobacteriaceae

Betalactamases in gramnegative bacteria

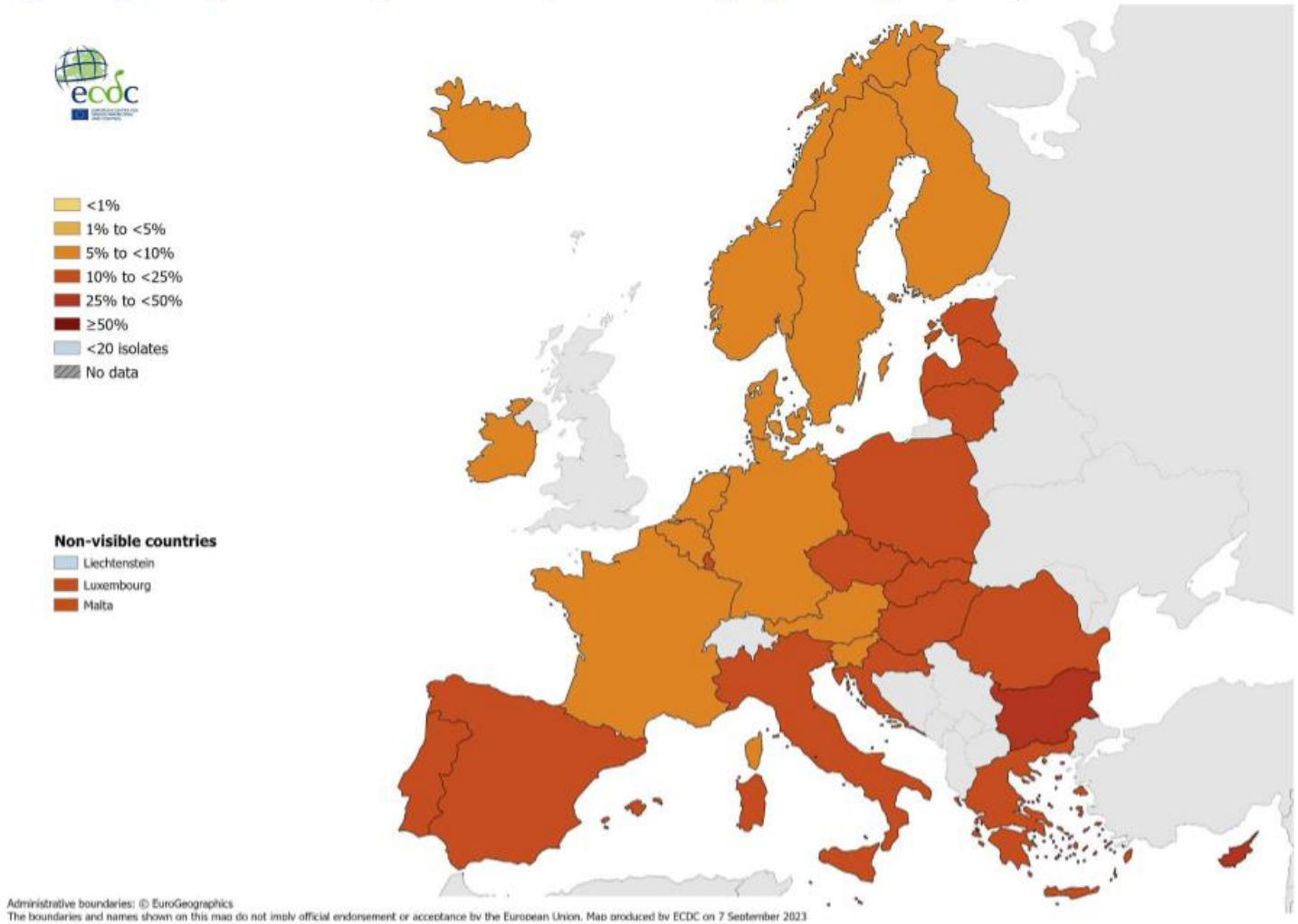




Extended spectrum betalactamase producing bacteria (ESBL)

- *E. coli, K. pneumoniae*
- TEM, SHV, CTX, OXA enzymes
- These enzymes are sensitive to betalactamase inhibitors
- Resistance to penicillins and first to third generation cefalosporins
- Plasmid mediated
- Often resistant to quinolones, trimetoprim, azteonam
- Sensitive to amikacin, carbapenems, colistin

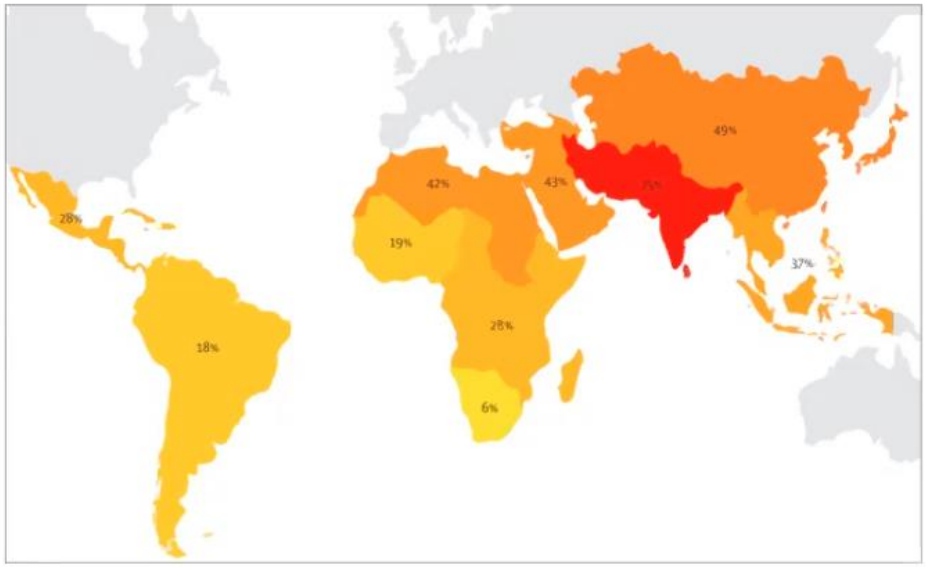
Figure 2. ***Escherichia coli*****. Percentage of invasive isolates resistant to third-generation cephalosporins (cefotaxime/ceftriaxone/ceftazidime), by country, EU/EEA, 2022**

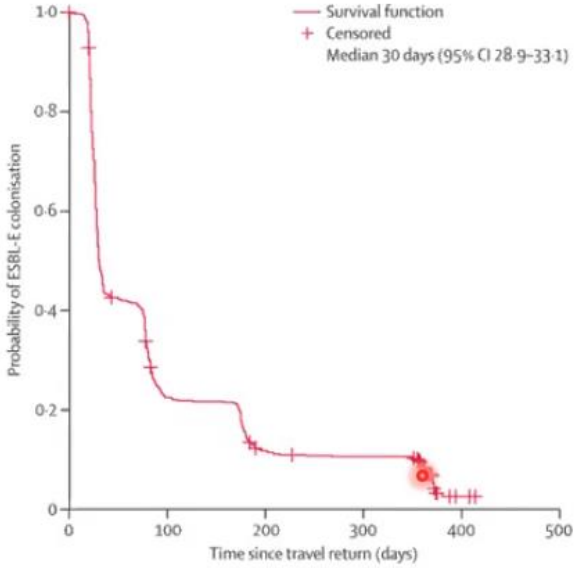


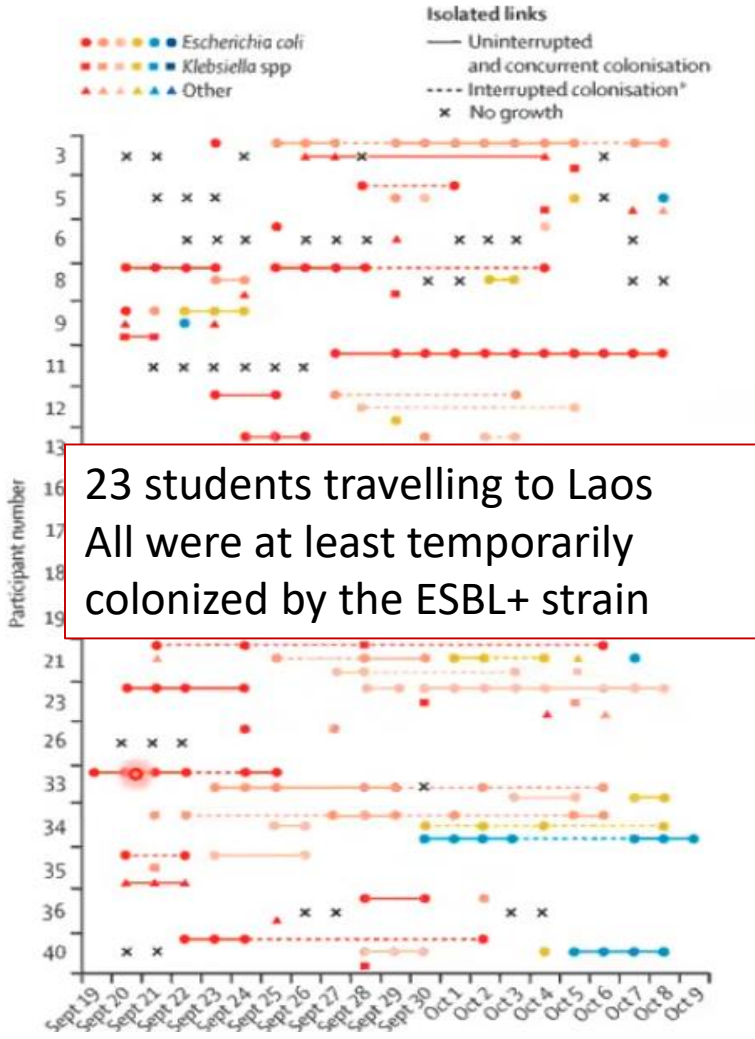
Most common MDR in Europe

ECDC: EARSNET report 2022

Travellers in danger to aquire MDR *E. coli*







23 students travelling to Laos
All were at least temporarily colonized by the ESBL+ strain

Large numbers of returning tourists is colonized by ESBL clones
The original strain of *E. coli* is completely replaced
Colonisation can persist for several months

Arcilla et al, Lancet ID 2017

Bevan et al, MBio 2018

MDR *E. coli* colonisation dynamic

Kantele et al. Lancet Microbe 2021

Carbapenem-resistant Enterobacteriaceae (CPE)

- ***Enterobacteriaceae*** – *Klebsiella pneumoniae, E. coli, Serratia marcescens, Enterobacter, Citrobacter…*
- But also *Pseudomonas aeruginosa* and *Acinetobacter*
- Carbapenems (ertapenem, imipenem, meropenem)
  - For bacteria resistant to other beta-lactams (ESBLs) - the drugs for multidrug-resistant Enterobacteriaceae
- 2008 India: NDM-1 gene - bacteria resistant to everything except colistin and tigecycline
- Spread in hospitals
- Most serious problem today
- Treatment : cefalosporin/inhibitor, aztreonam, colistin, tigecyclin, cefiderocol

Carbapenemases

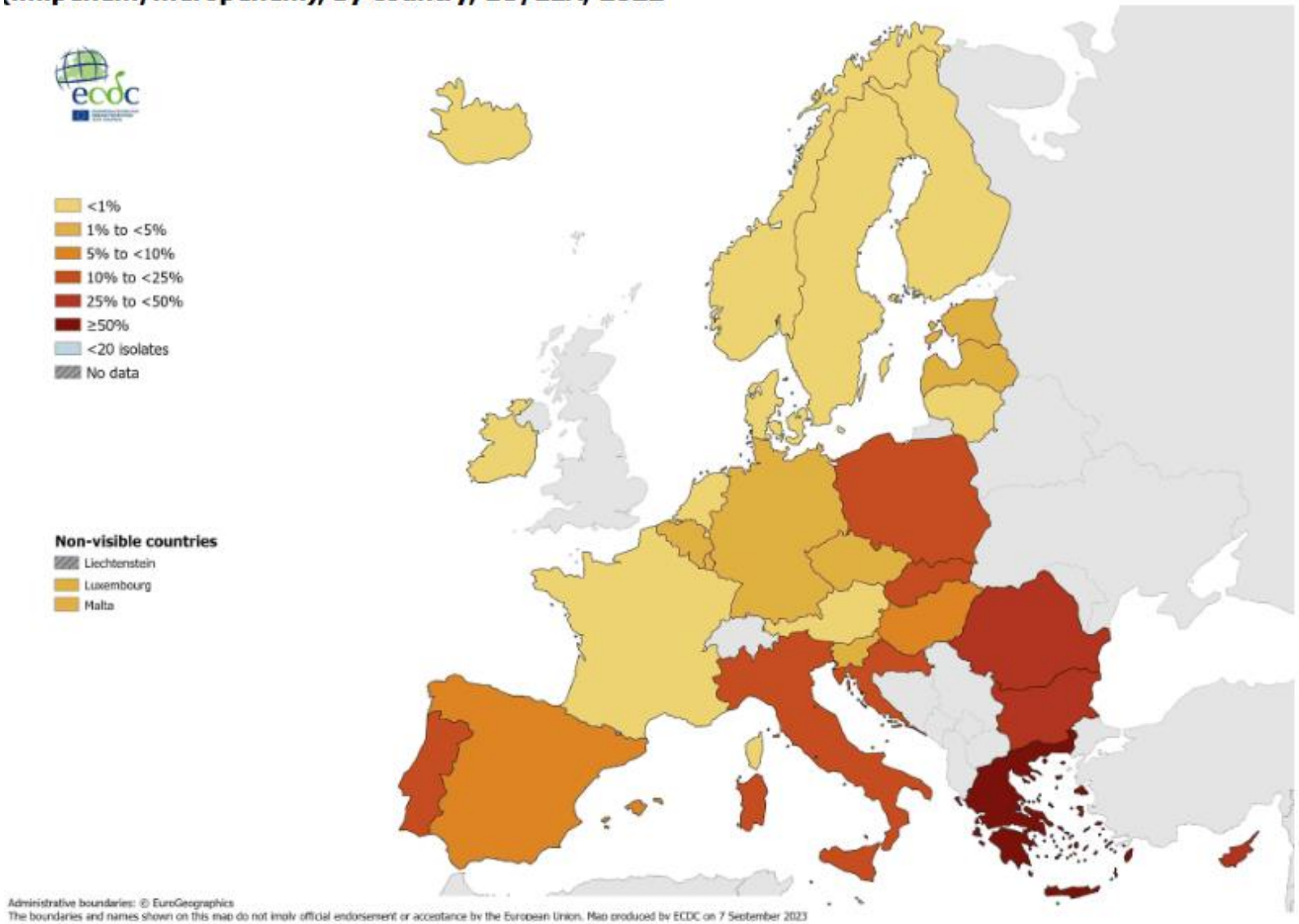
- Class A
  - KPC, GES, SME, IMI, NMC
  - Sensitive to inhbitors (clavulanic acid, tazobactam, relebactam, avibactam)
  - *Enterobacteriaceae, P. aeruginosa, Acinetobacter* sp
- Class B - metalobetalactamases
  - VIM, IMP, GIM, SIM, NDM,…
  - Resistant to inhibitors
  - *Enterobacteriaceae, P. aeruginosa, Acinetobacter* sp
- Class D - oxacillinases
  - OXA-48 - *K. pneumoniae, E. cloacae, E. coli*
  - OXA-23, OXA-58, OXA-40 - *Acinetobacter* sp
  - Resistant to inhibitors except avibactam/ (OxA-23,48)

Other non-enzymatic mechanisms

- PBP alteration – targett site modification
- Porins – limited intake
- Efflux pumps – pumping out

- *P. aeruginosa, Acinetobacter*

Figure 5. *Klebsiella pneumoniae*. Percentage of invasive isolates resistant to carbapenems (imipenem/meropenem), by country, EU/EEA, 2022



CPE:
High mortality, over 50% in sepsis
Klebsiella pneumoniae – main threat
Increasing trend
High potential for hospital spread

ECDC: EARSNET report 2022

Risk factors for CPE infection

Recent gastroenterology procedure

Recent intensive care admission

Recent prolonged hospitalisation

Overseas medical treatment

Inapropriate use of antimicrobials

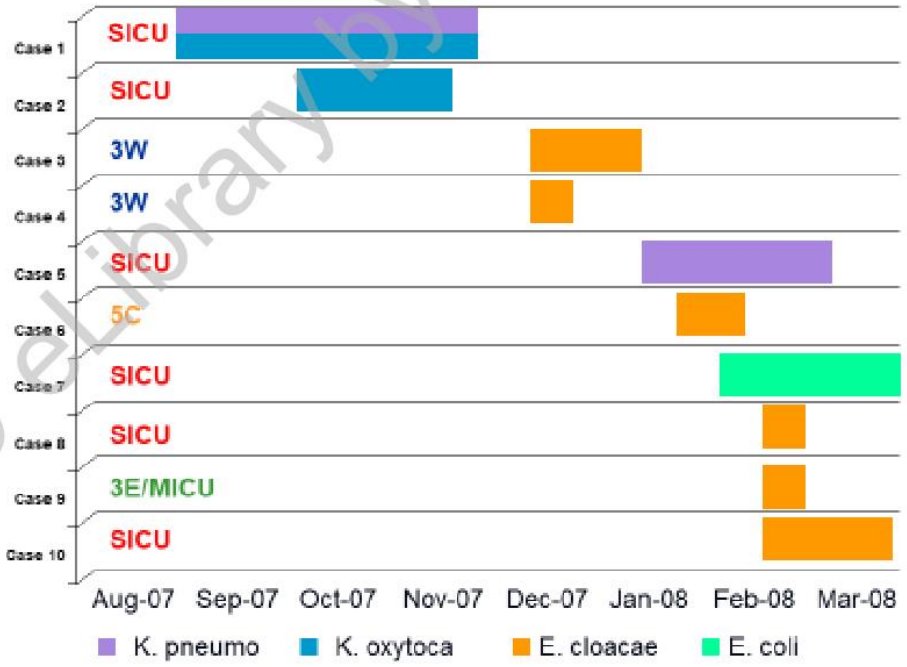
Weakened immunity

Indwelling medical device

Example of KPC outbreak

2007---Index case of KPC-producing *K. pneumoniae* and *K. oxytoca*

First six months:
Transmission not clear but there seemed to be a problem in the Surgical ICU



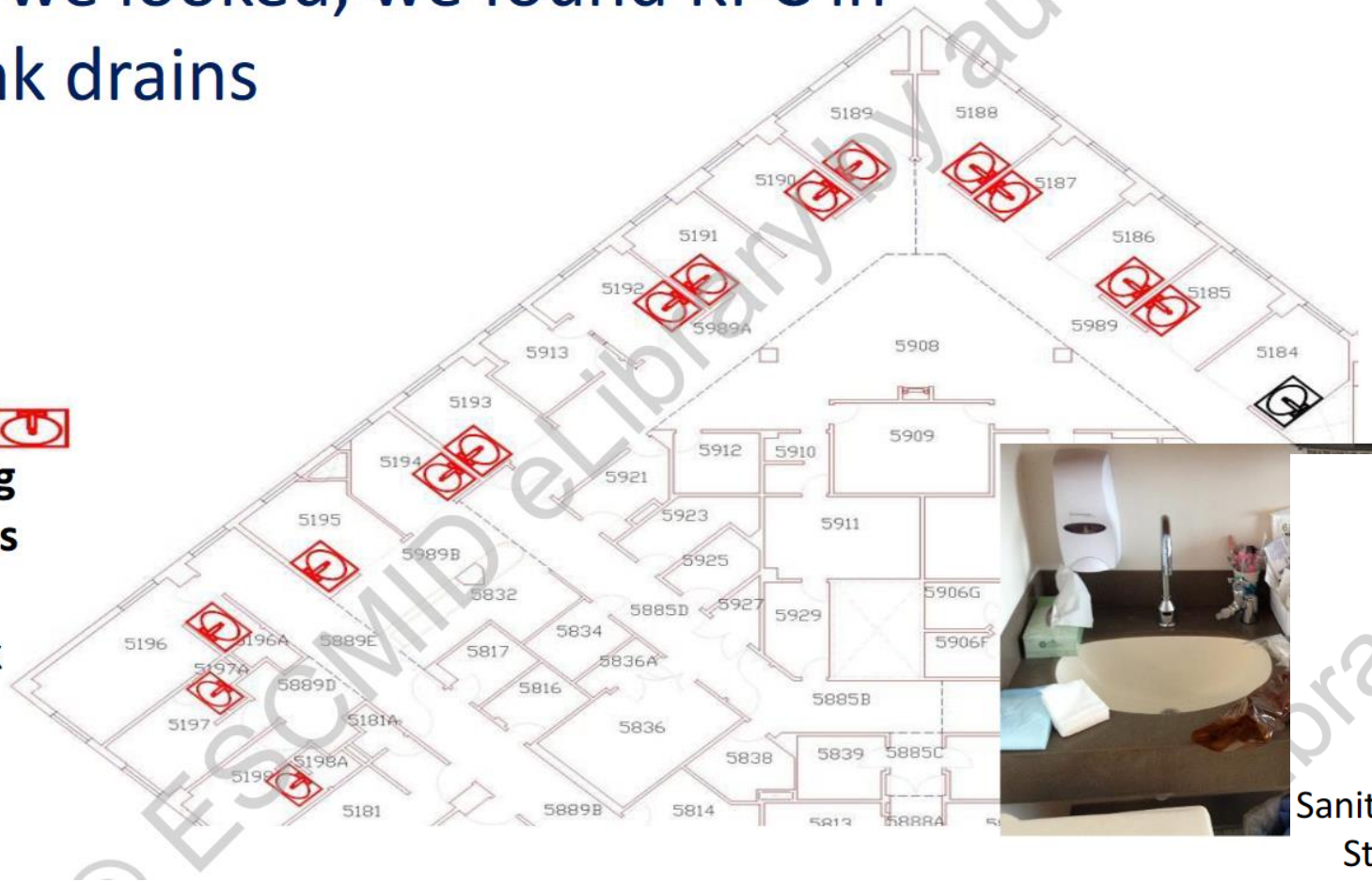
KPC = type of carbapenemase

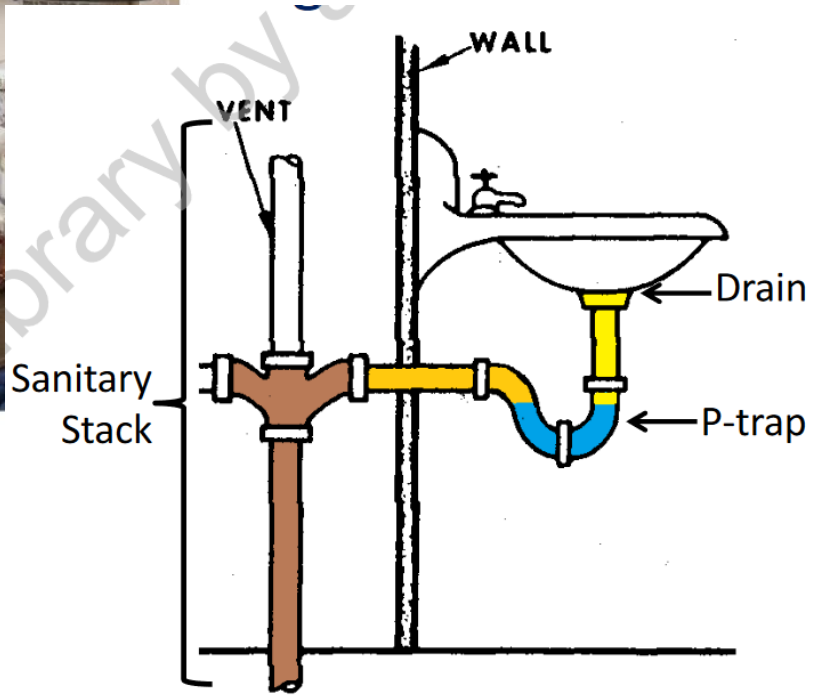
2009-2011: cca 281 isolates from 182 patien
Transpozon Tn4401 carrying *bla*$_{KPC}$
11 plasmids
Different species and genera

Amy Mathers IMMEM 2019

When we looked, we found KPC in the sink drains

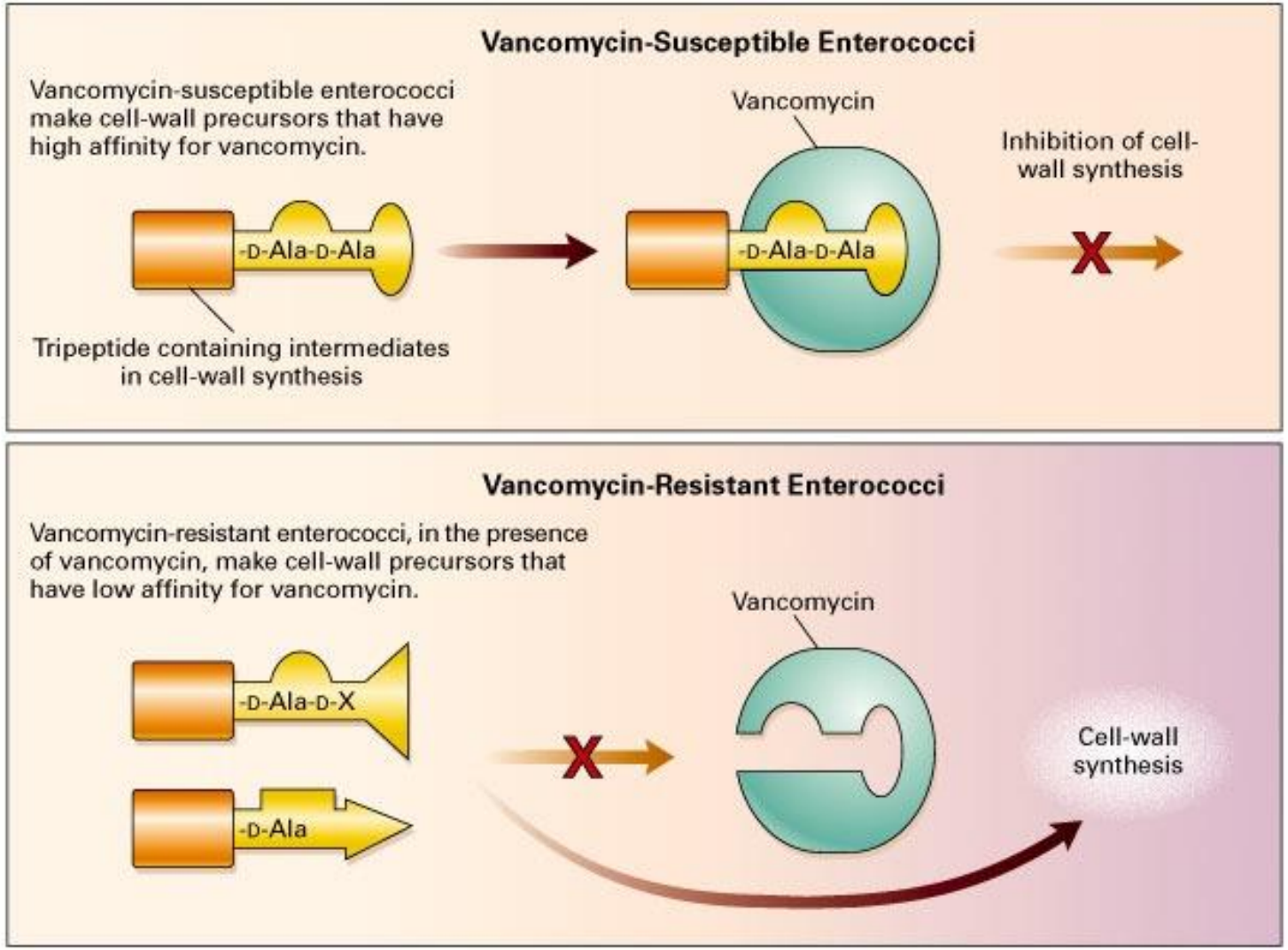
KPC-producing organisms isolated from sink





Enterobacteria could colonise pipes via biofilm formation

Vancomycin resistant enterococci (VRE)



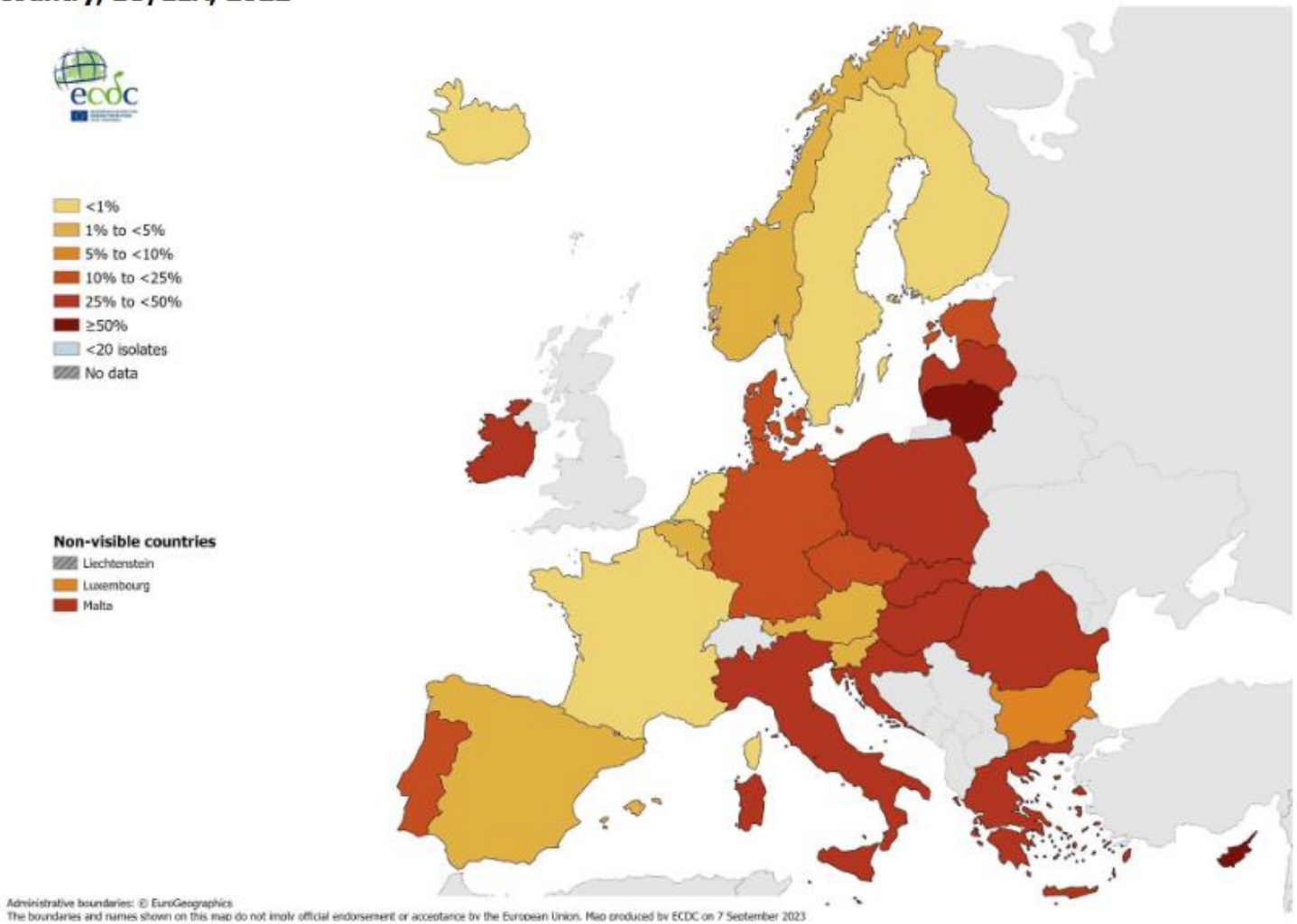
E. faecium
E. faecalis
GIT comensals

vanA or *vanB*
Plasmid mediated

UTI, Sepsis, endocarditis

Treatment: linezolid, daptomycin, tigecycline, chloramphenycol

Figure 10. ***Enterococcus faecium*****. Percentage of invasive isolates resistant to vancomycin, by country, EU/EEA, 2022**



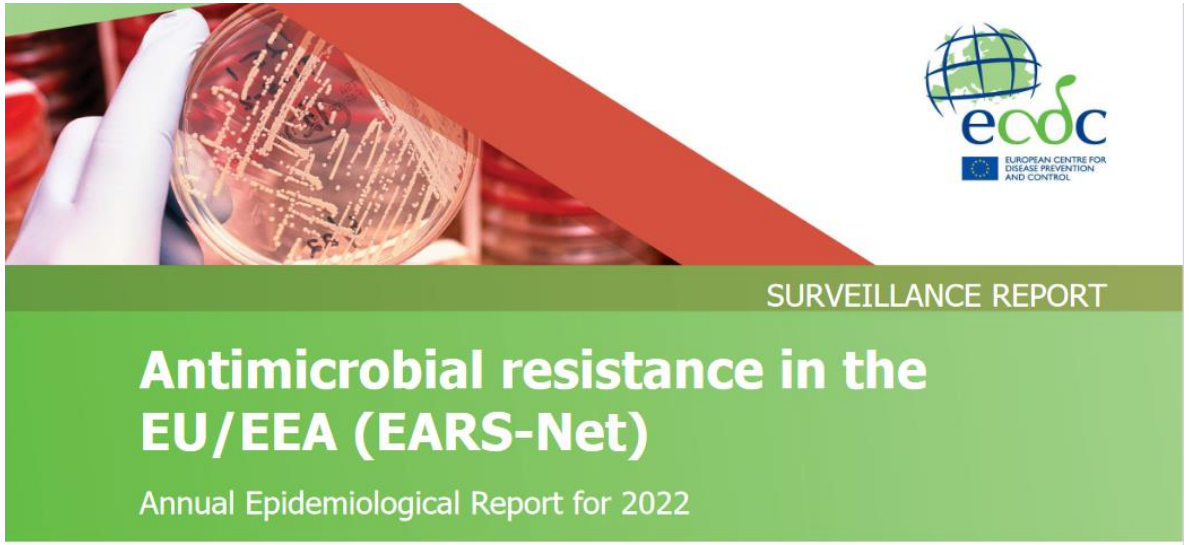
Increasing trend

ECDC: EARSNET report 2022

Surveillance of antimicrobial resistance

European Antimicrobial Resistance Surveillance Network (EARS-Net)

- Since 1998
- 30 participating countries in Europe
- invasive isolates
  - blood or cerebrospinal fluid samples
- Annual reports

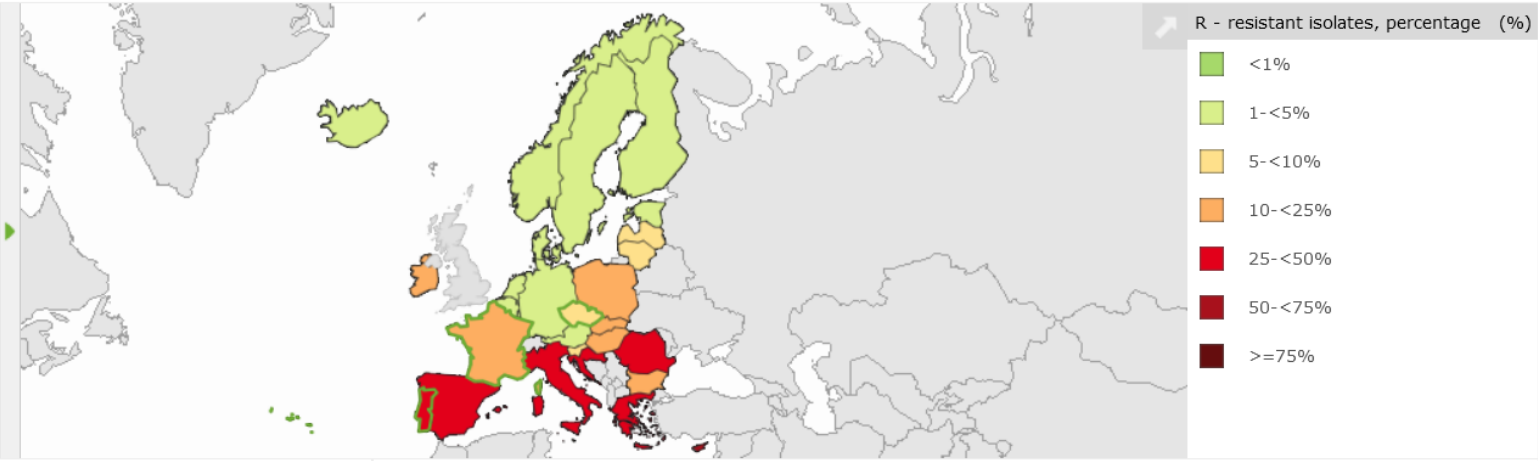


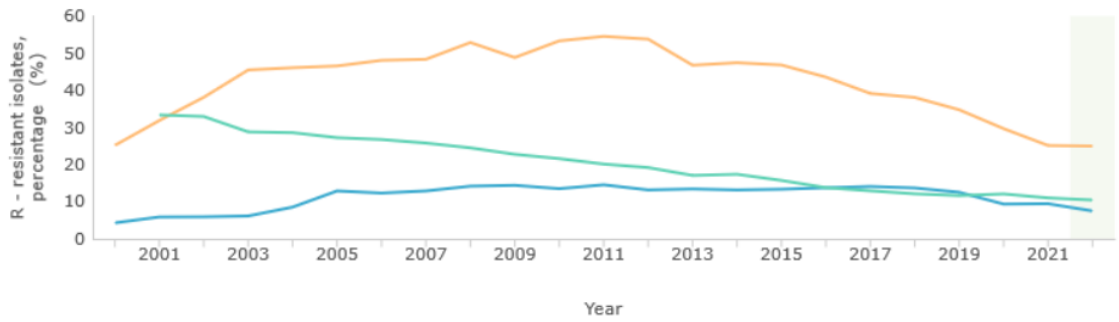
Monitored species:
Escherichia coli
Klebsiella pneumoniae
Pseudomonas aeruginosa
Acinetobacter species
Streptococcus pneumoniae
Staphylococcus aureus
Enterococcus faecalis
Enterococcus faecium

Surveillance Atlas of Infectious Diseases

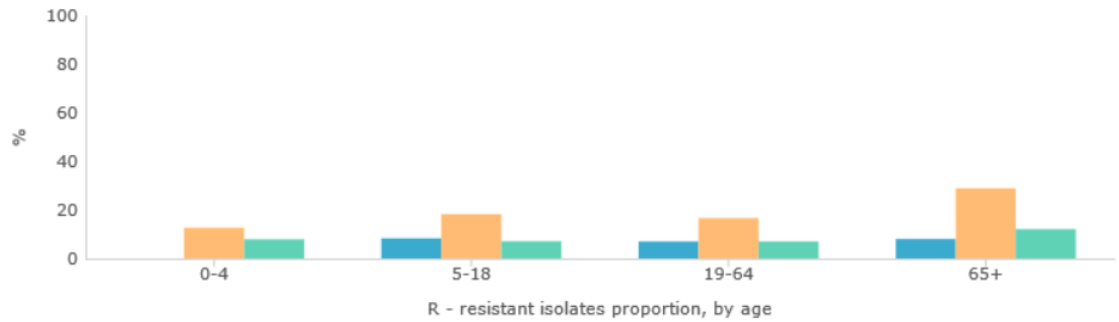
Antimicrobial resistance | Staphylococcus aureus | Meticillin (MRSA) | R - resistant isolates, percentage | 2022

Region	R - resistant isolates, percentage (%)
Austria	3.9
Belgium	4.2
Bulgaria	12.0
Croatia	31.1
Cyprus	50.8
Czechia	7.5
Denmark	1.9
Estonia	2.2
Finland	2.3
France	10.4
Germany	3.9





R - resistant isolates proportion, by age | Bar



Czechia Portugal France

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WHO

World Health Organization

Since 2015
132 participating countries

Reserve antibiotics

Classification of antibiotics – different types of therapy

Initial - therapy is started before pathogen identification, broad spectrum to cover all posible causes. E.g. Patient hospitalised with bacterial meningitidis or sepsis

Empirical – treatment without microbiological diagnostics, e.g. Streptococal tonsilitis

Targetted – known cause end its susceptibility

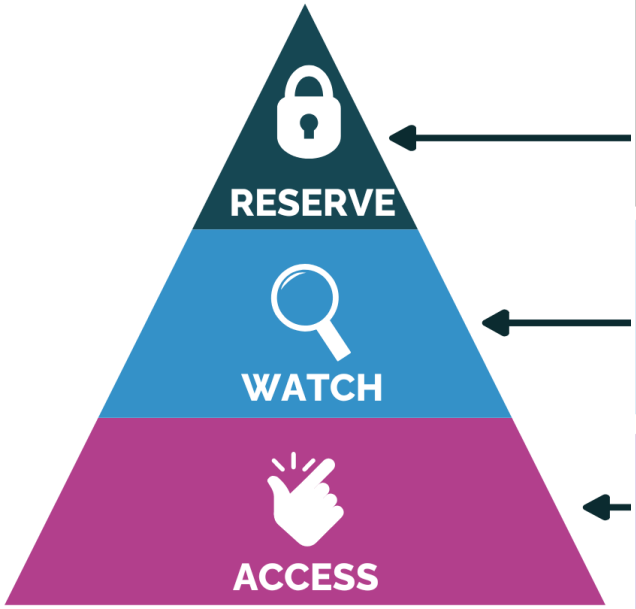
Deescalation – switch to targetted therapy after identification of cause

Prophylaxis – to prevent infection,e.g. surgical prophylaxis, imunokompromised patients

- Antimicrobials reserved for human medicine
- Antimicrobials reserved for serious infections

AWARE classification

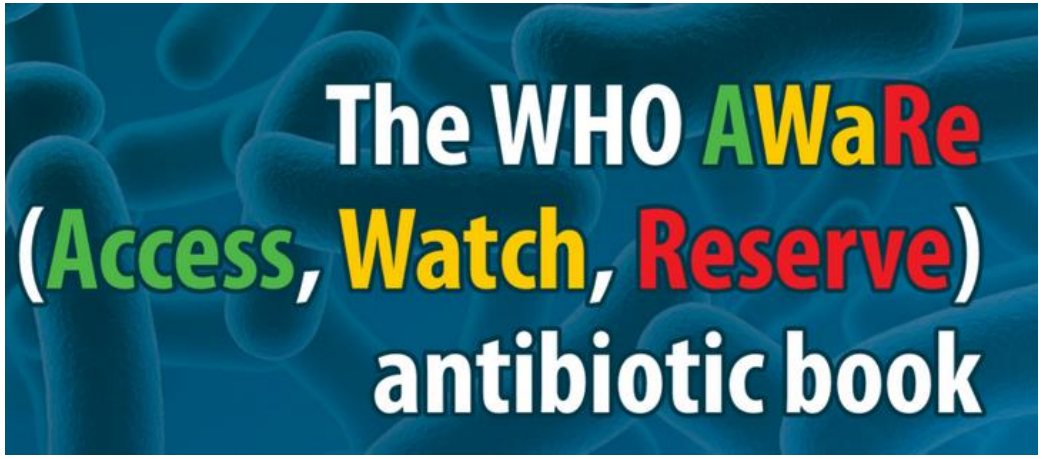
The AWaRe classification is intended as a tool for monitoring antibiotic consumption, defining targets and monitoring the effects of stewardship policies that aim to optimize antibiotic use and curb antimicrobial resistance.



Last line antibiotics to treat MDR bacteria
To be used after other options failed
For serious/complicated infections
New antibiotics

Critically important
High resistence potential,
Limited specific indication

First choice (empiric) for common infection by susceptible bacteria
Save, cheap, low resistence potential
Should be always awailable



Examples

Colistin, tigecycline, linezolid, Meropenem/vaborbactam, Daptomycin, Aztreonam, ceftarolin, cefiderocol

Azithromycin, Ciprofloxacin, 2nd to 4th gen cefalosporins, Erythromycin, fidaxomicin, Meropenem, rifampicin, vancomycin

Ampicillin, clindamycin, doxycyklin, oxacillin, nitrofurantoin, benzylpenicillin, first generation cefalosporins

Be AWARE yes, but….

CNN US World Politics Business Opinion Health Entertainment Style Travel Sports Video

A new season of infections is here, but the shortage of a common kids' antibiotic never ended

By Brenda Goodman, CNN

5 minute read · Published 6:47 AM EDT, Fri September 22, 2023

Unexpected demant - increase in respiratory infection i.e. streptococcal
Manufacturing issues – supply chain

Consequences – treatment by less optimal drugs – selection of resistance

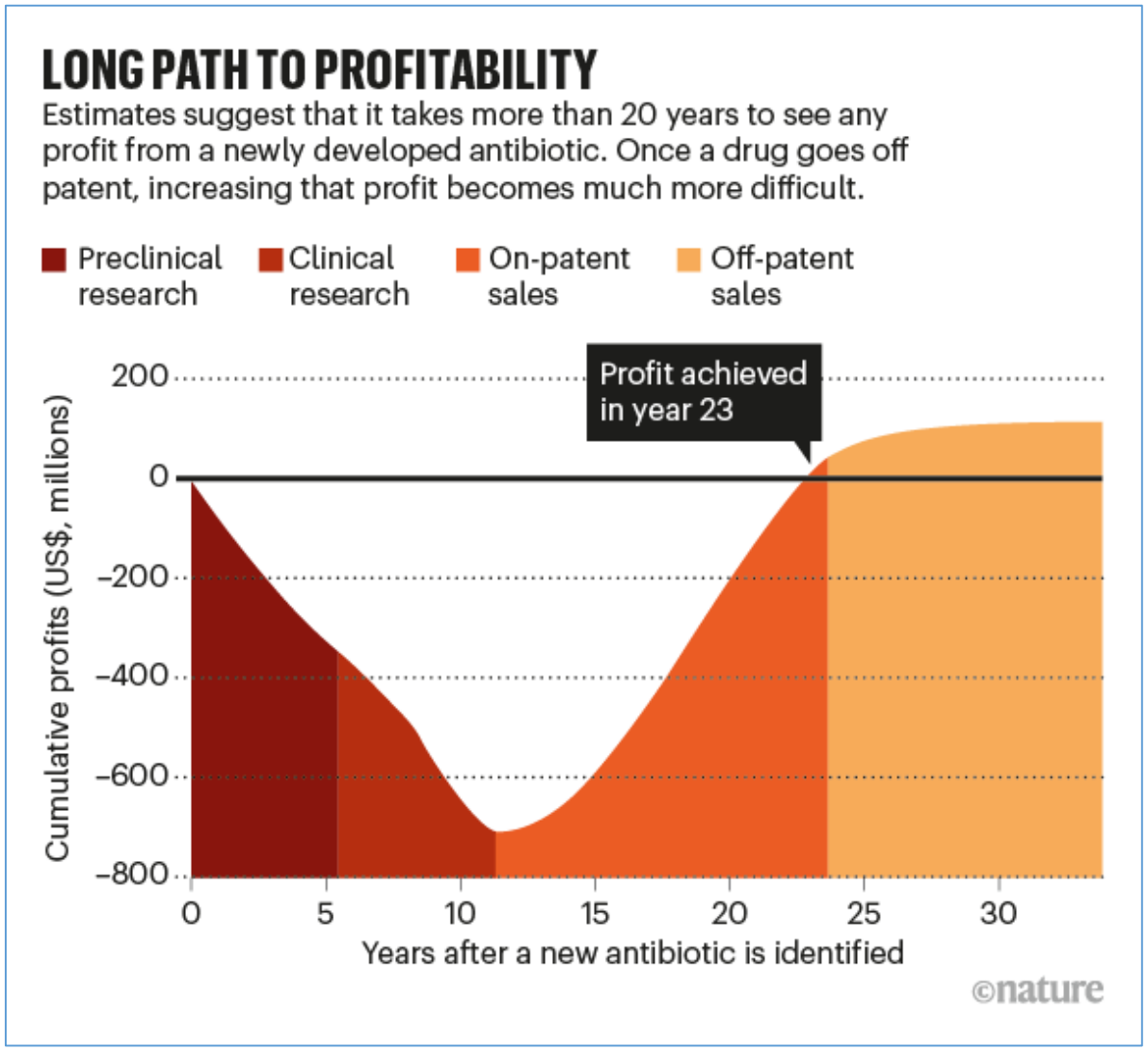
HEALTH, EUROPE

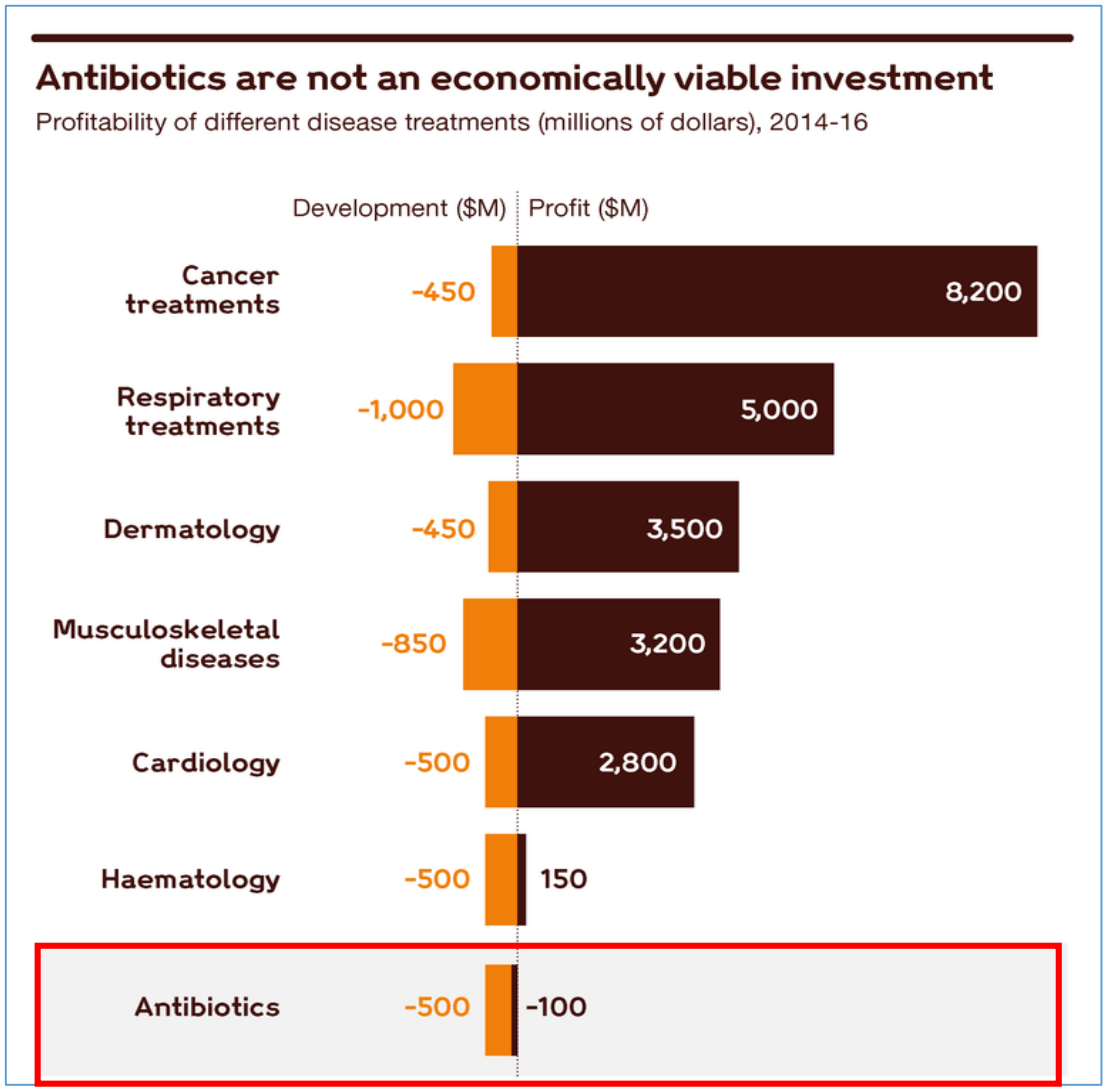
Antibiotics shortage crisis deepens in Germany

What happens now in Germany is tip of iceberg, says spokesman for German pediatricians association

Erbil Basay | 07.05.2023 - Update : 08.05.2023

Antibiotics – high risk business adventure





Thank you for your attention!