Multi-drug resistant bacteria & reserve antibiotics

Jan Tkadlec

Topics

- What is the problem with antimicrobial resistance
- Which bacteria are main threads
- Antibiotic stewardship
  - Monitoring resistant bacteria
  - Controling antibiotic usage

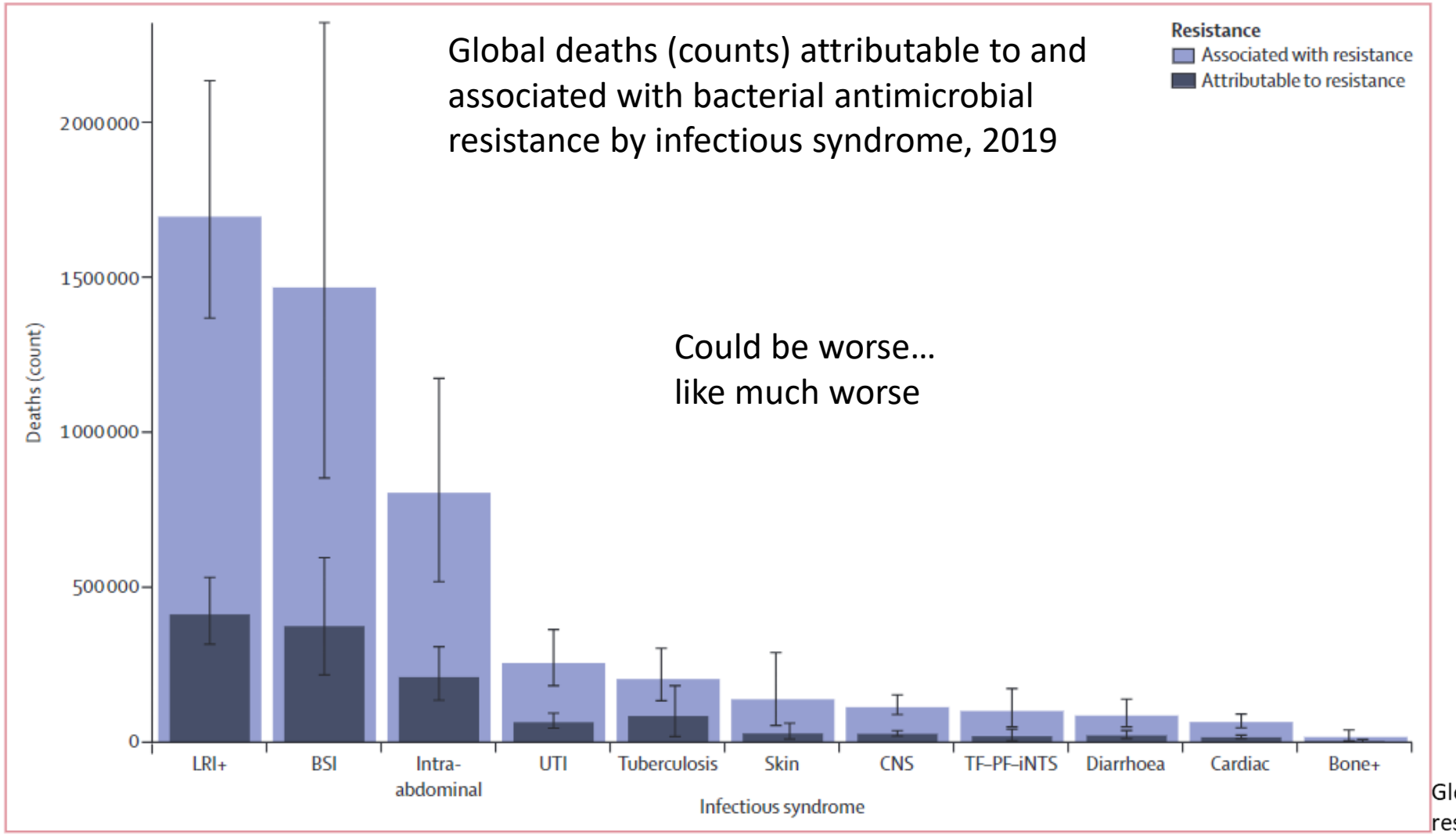
“It is time to close the book on infectious diseases and declare the war against pestilence won”.

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

Some quotations did not age well…

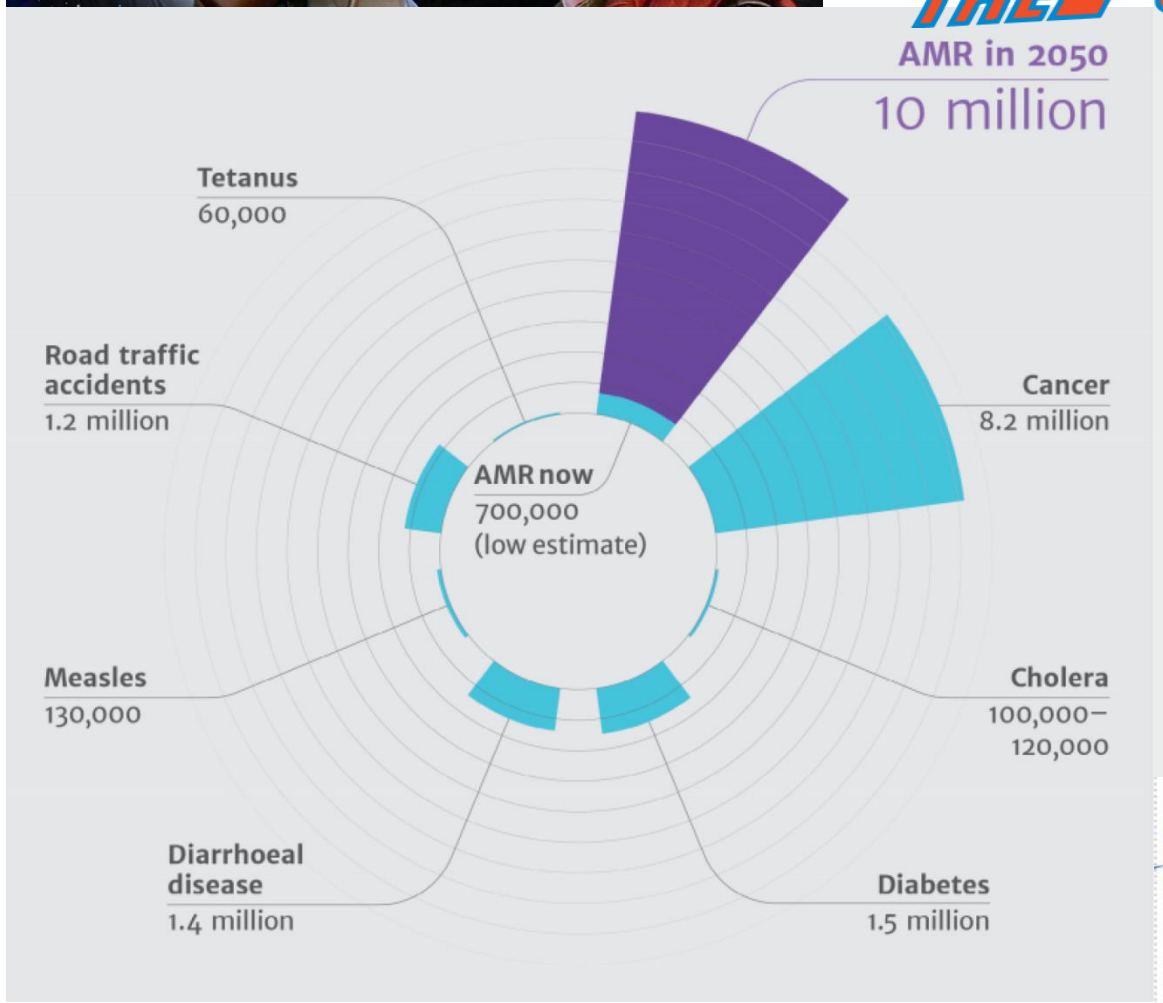
Global burden of antimicrobial resistance 2019

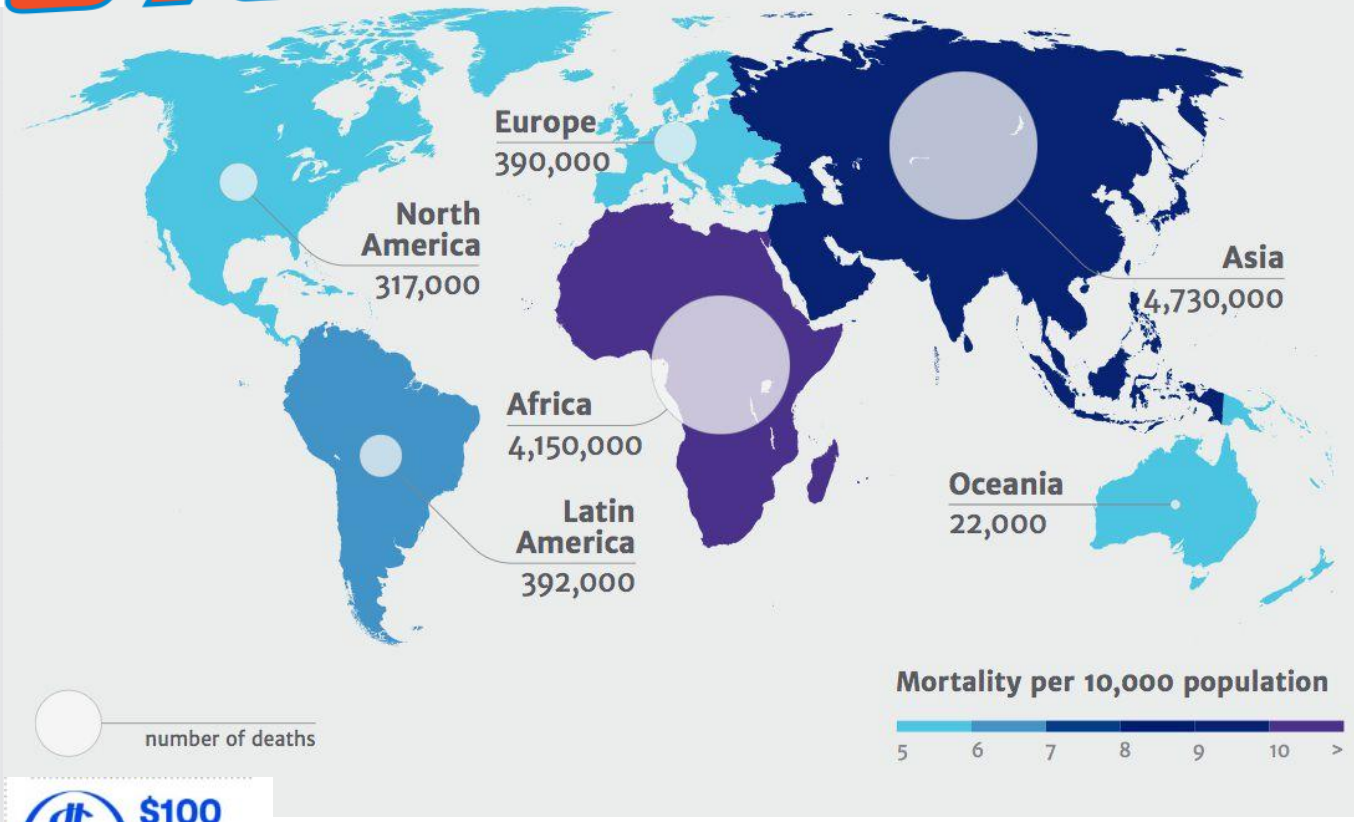
2019: 1.27 million deaths attributable to resistance



Global burden of antimicrobial resistance in 2019; Lancet 2022

BACK TO THE FUTURE





O´Neil et al 2015: Review on Antimicrobial Resistance

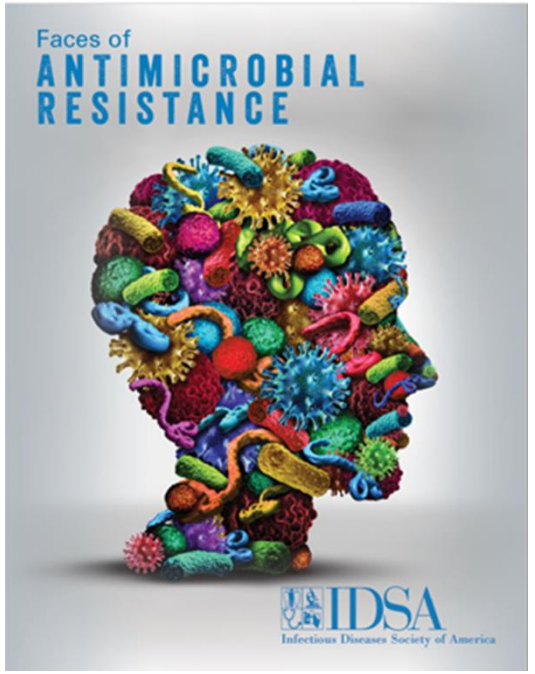
Not only the old and sick…

David
19 years old, hit by a train while volunteering in India
Repatriated to the US, wounds infected with a mixture of multidrug-resistant bacteria, (*P. aeruginosa, Klebsiella pneumoniae, Morganella morgani, Enterococcus sp*), including NDM-1 producers
Repeated surgical and antibiotic treatment lasting almost a year

Meredith
- 19 years old, treated with AML
- After a successful bone marrow transplant, she dies of a multidrug-resistant infection *Pseudomonas aeruginosa*

Rebeca
17 years old, student, competitive swimmer
Seemingly common cold leads to severe MRSA pneumonia > ECMO
After 4 months in the hospital, she dies.

Simon
- A healthy 1.5 year old boy
- Died within 24 hours of infection caused by community-acquired MRSA after unsuccessful treatment with broad-spectrum antibiotics



Main threats

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)

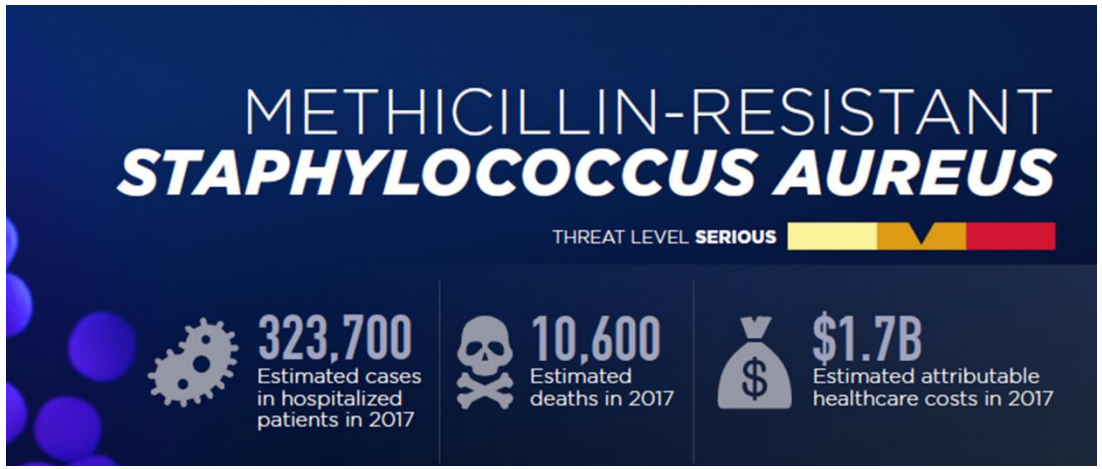
Concerning Threats

- 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)*

What is a bigger threat?



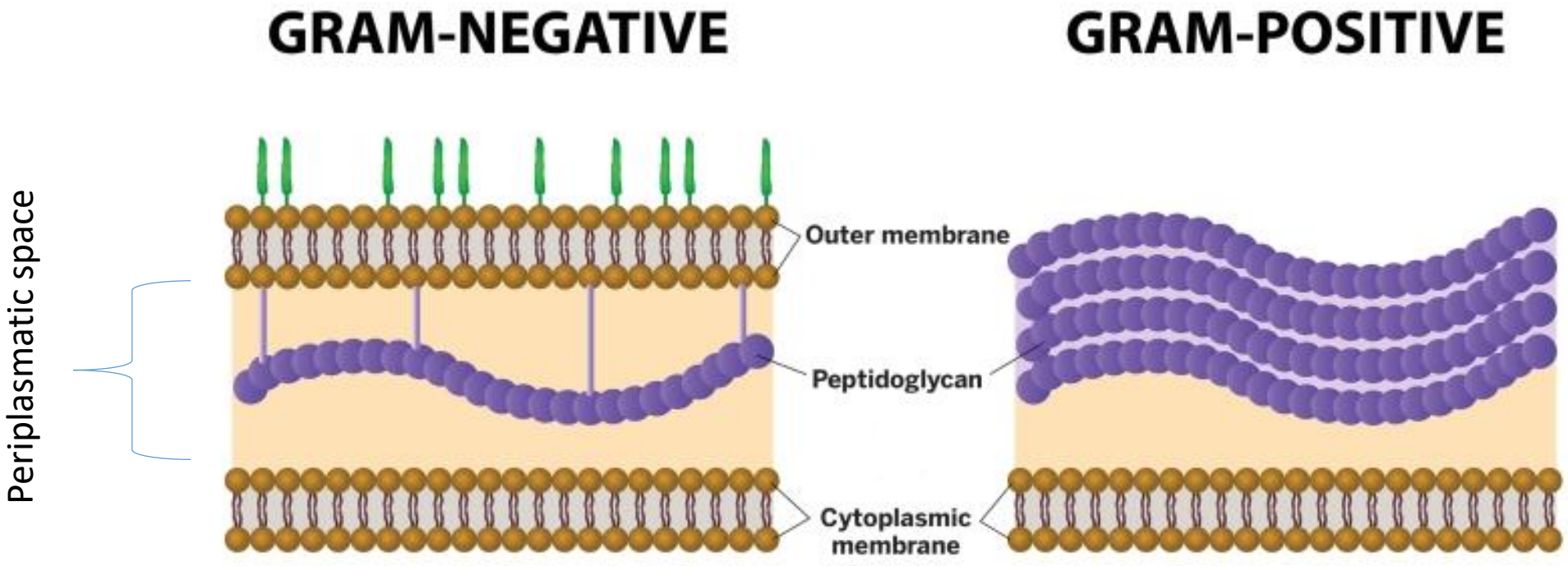
Vs.

How the level of threat is measured:

- Clinical impact (severity, mortality)
- Economic impact (when available)
- Incidence
- 10-year projection of incidence (new infections over the next 10 years)
- 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.

Key differences between



e.g. *E. coli*

Bound to **moisture** – intestinal/soil/wastewater bacteria

Spreads by aerosol, faecal/oral transmission

Chemical/biochemical resistance

Advantage of outer membrane

- Limited antibiotic penetration
- Efflux pumps
- ATB lysing enzymes in periplasm

Extensive horizontal gene transfer

e.g. S. aureus

Physically resistant

- to drying, heat, high salt concentration, disinfection
- Spread by contaminated surfaces or direct contact

Colonised persons

Clonal spread

Frequent resistance by change in target site modification – methicillin, vancomycin, macrolides

Multidrug resistant bacteria

Multidrug resistant
Extensive drug resistant
Pandrug resistant

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).

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	

Source: Magiorakos et al 2012

Multidrug resistant bacteria

- *Escherichia coli*
- *Klebsiella pneumoniae*
- *Pseudomonas aeruginosa*
- *Acinetobacter* spp.
- *Streptococcus pneumoniae*
- *Staphylococcus aureus*
- *Enterococcus faecalis*
- Other gramnegative rods (*Enterobacter*, *Citrobacter*, *Serratia*,…)
- *Mycobacterium tuberculosis*

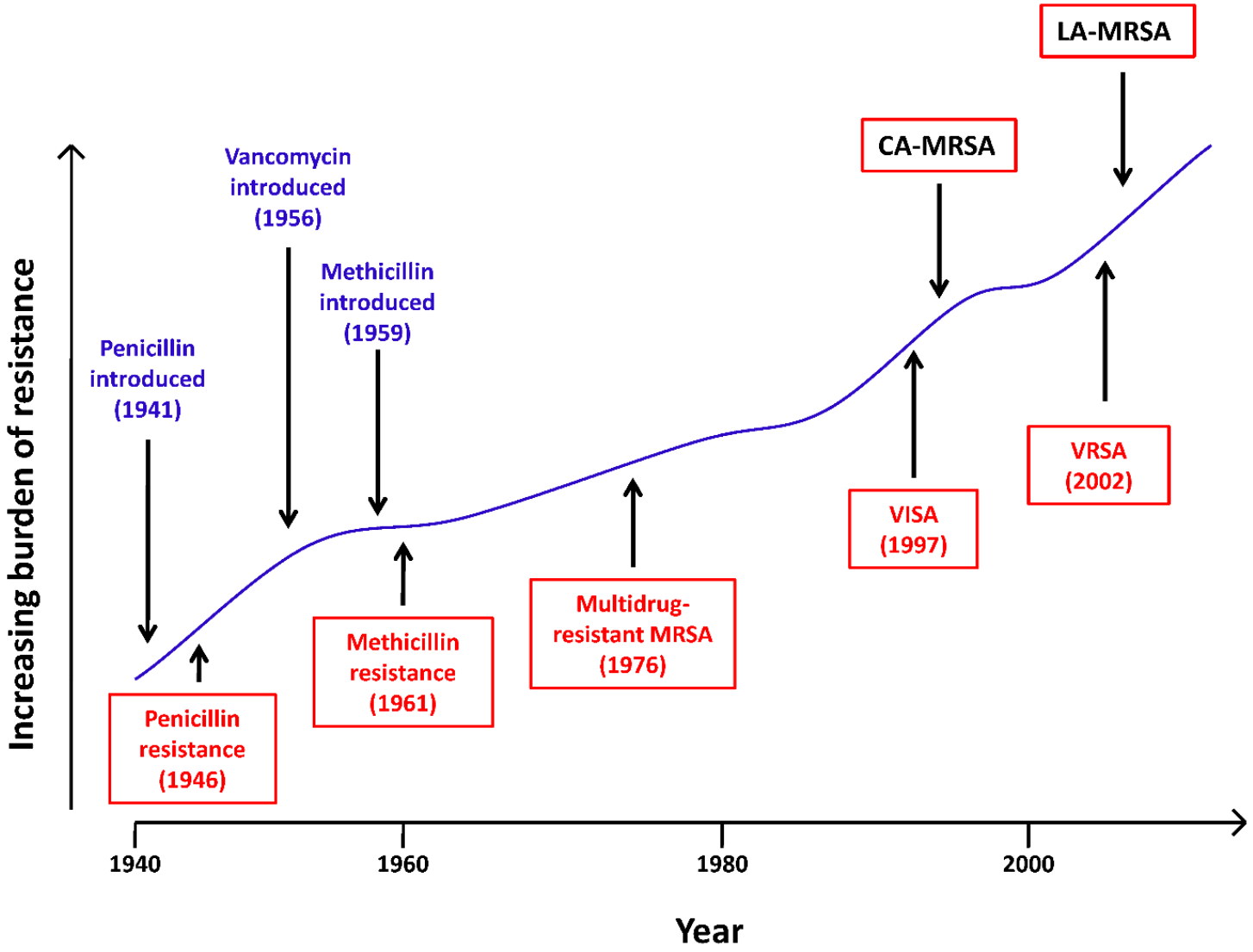
What they have in common?

- Human comensals
- Environmental bacteria

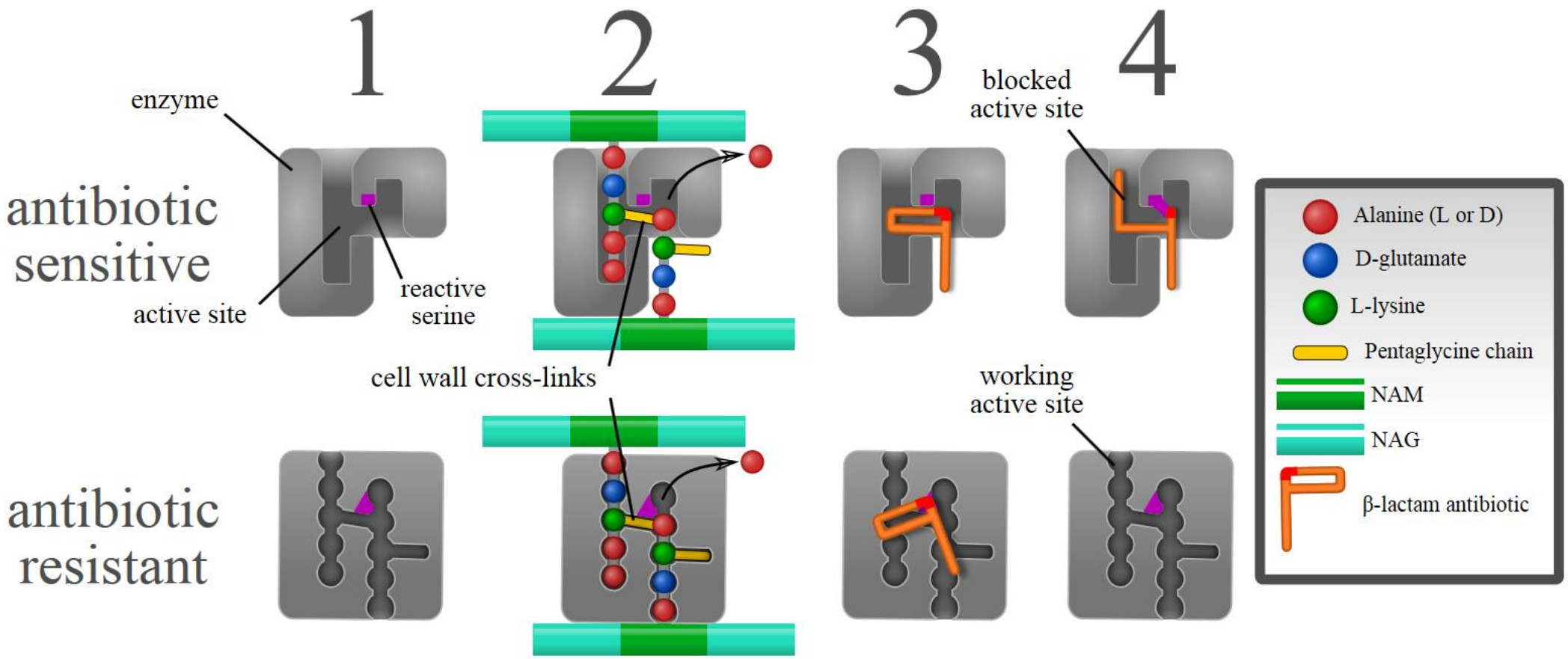
S. aureus – the first superbug

- 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*

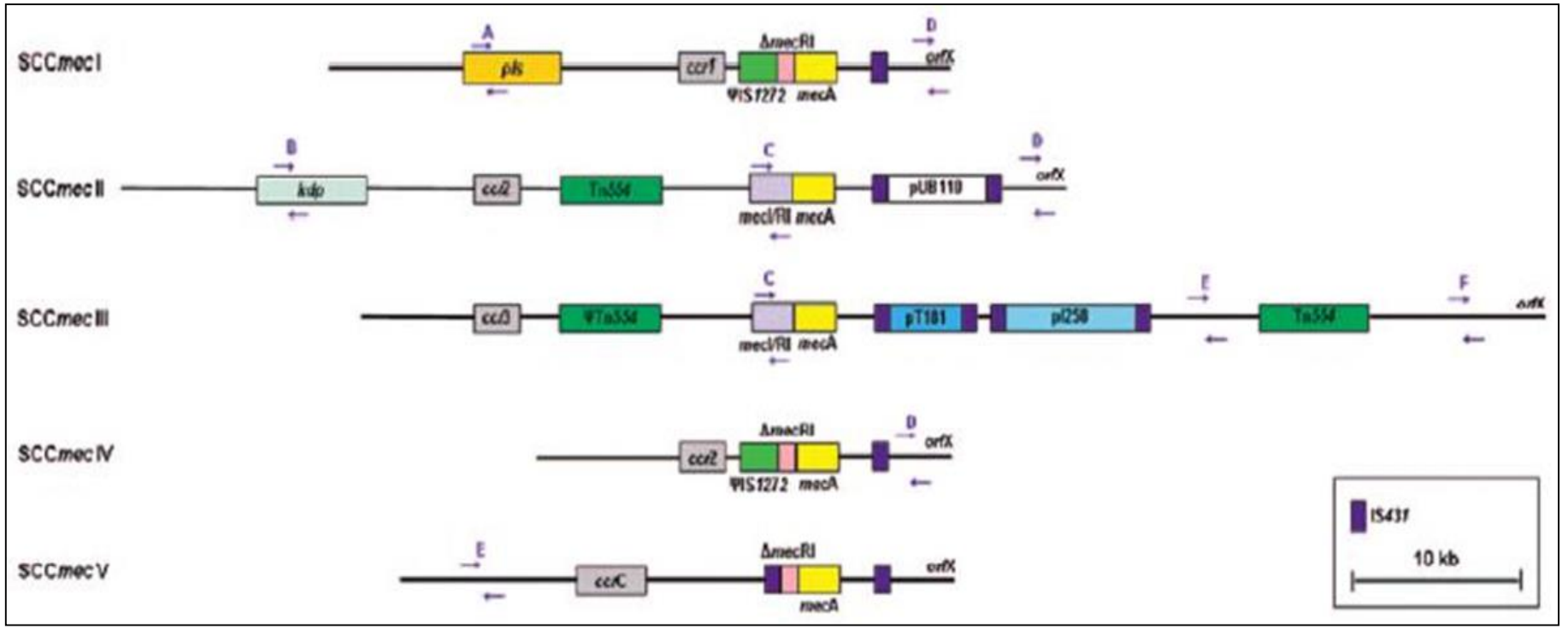


Mechanism of MRSA resistance

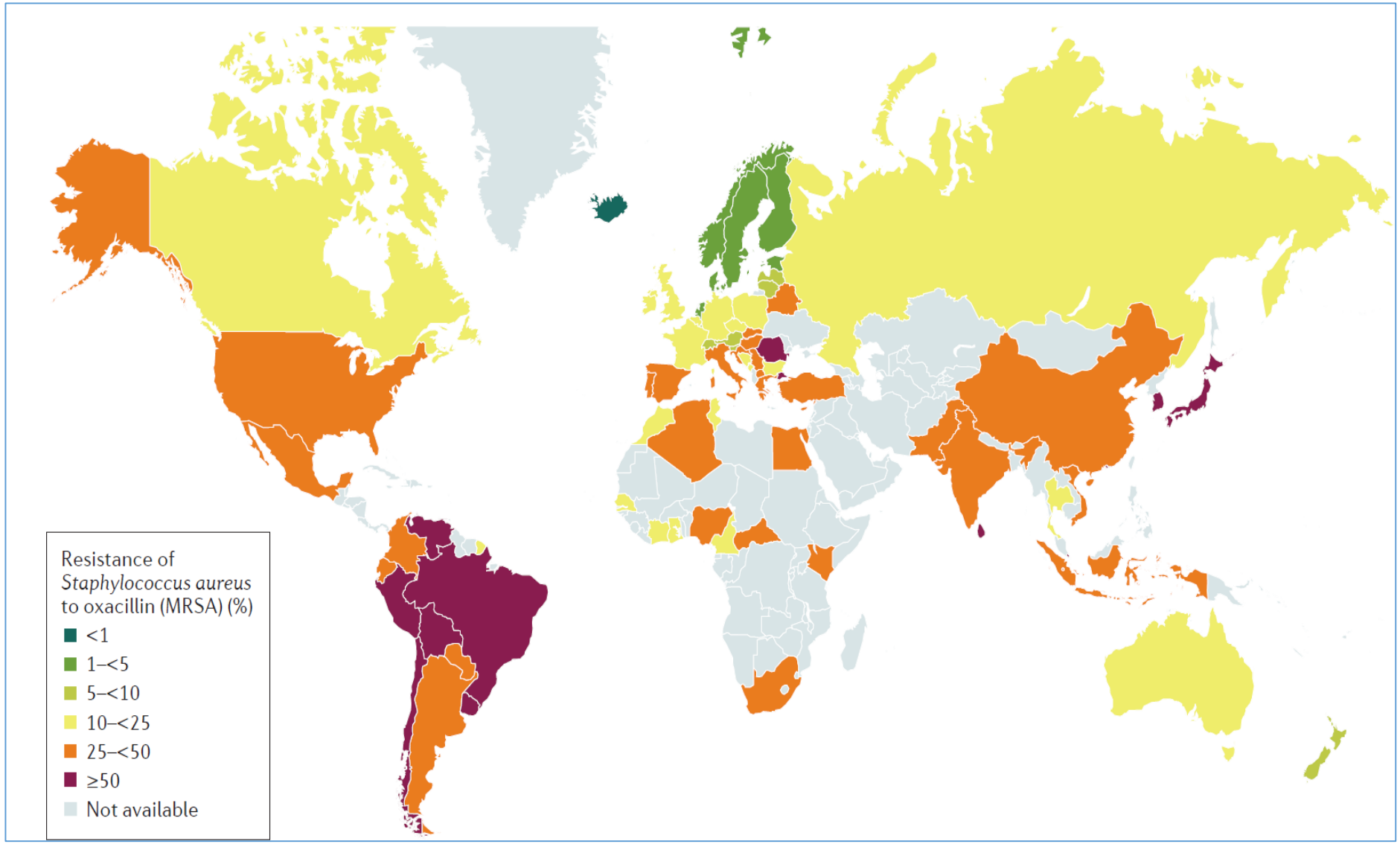


Genetic background for MRSA

- 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)

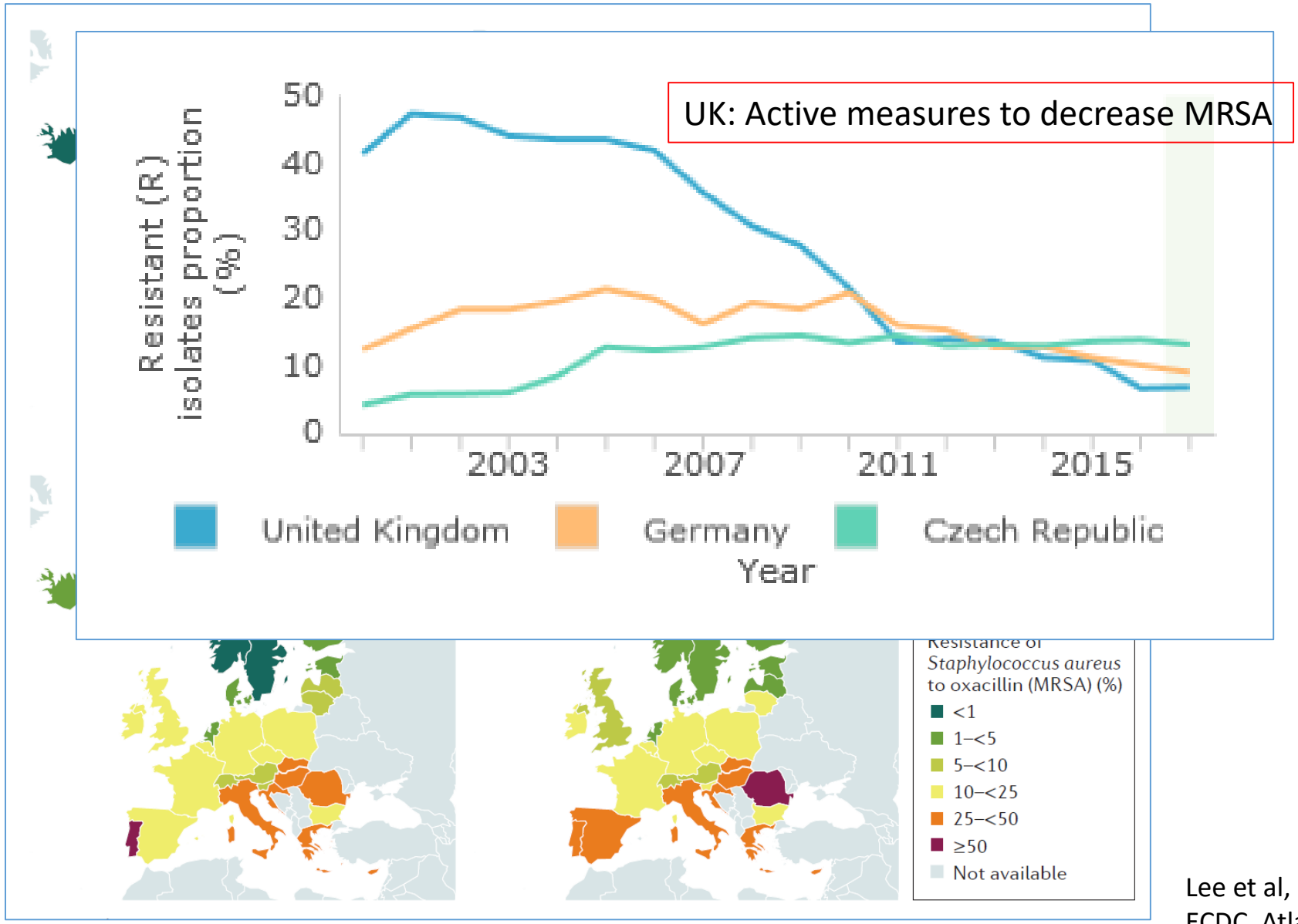


Global MRSA prevalence (%)



Lee et al 2018

Europe (invasive isolates)



Lee et al, 2018

ECDC, Atlas of antimicrobial resistance

Therapeutic options for MRSA (existing or near future)

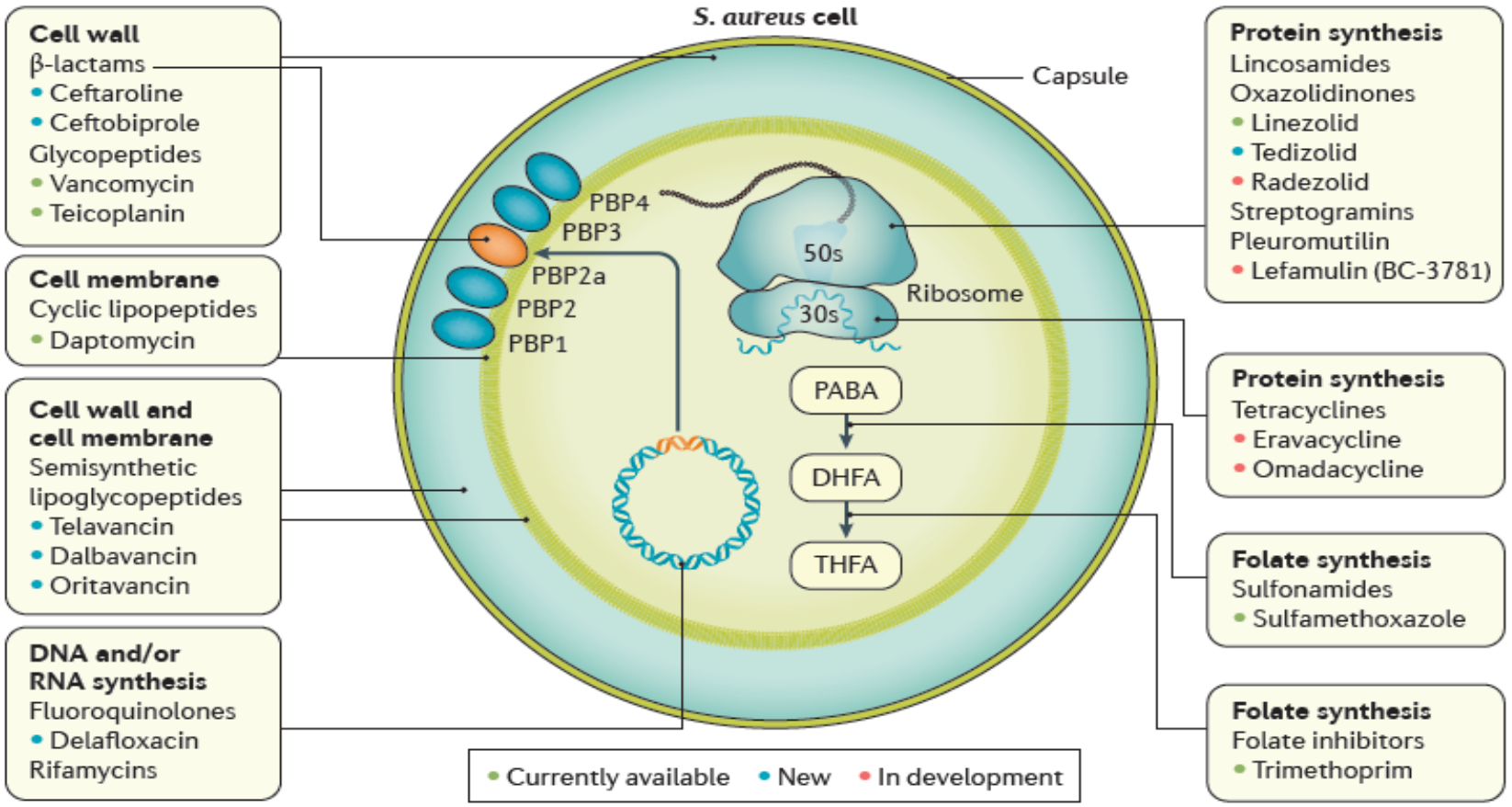
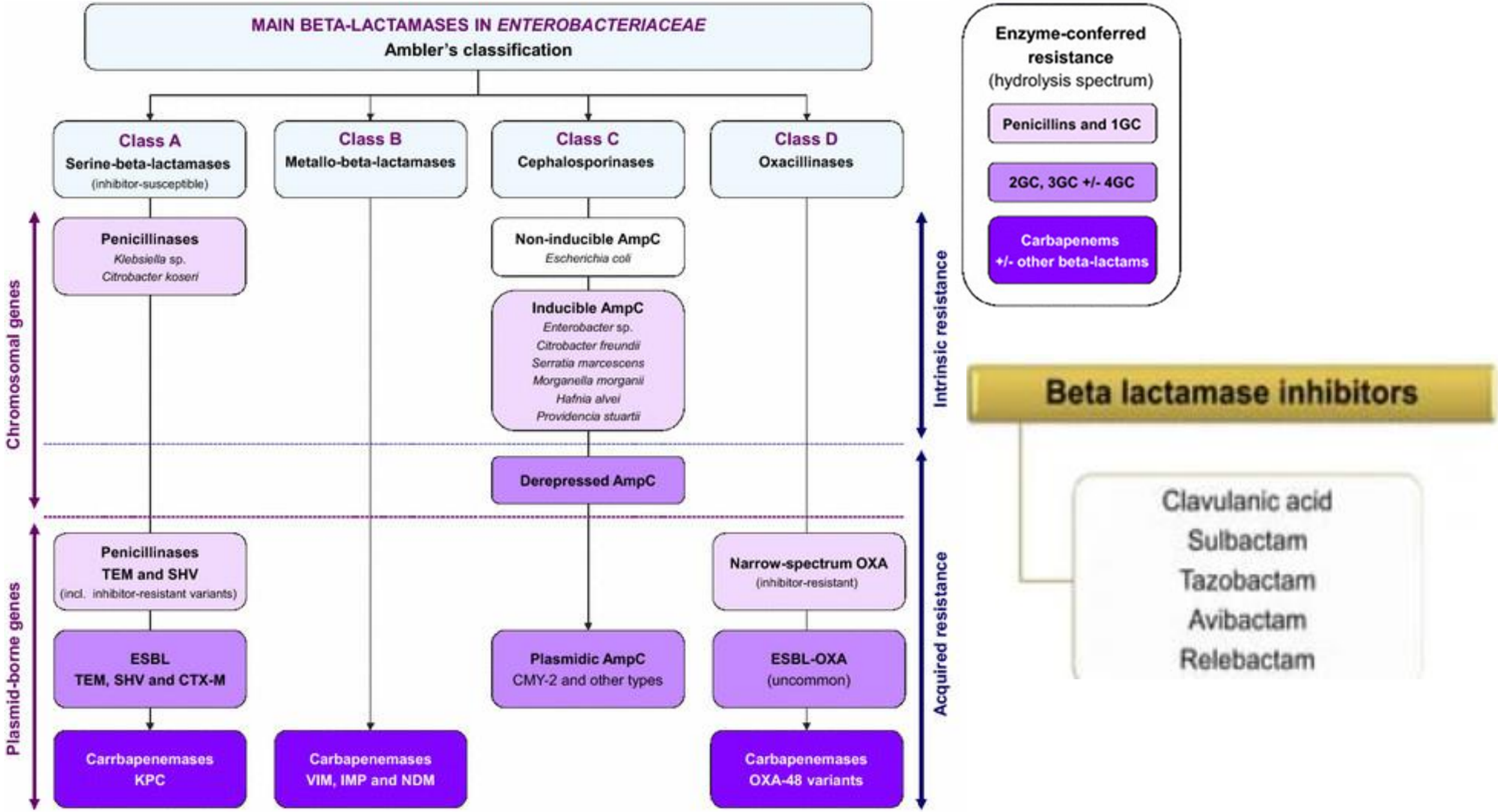


Figure 5 | **Bacterial targets of antibiotics active against MRSA.** Antibiotics have diverse mechanisms of action and target different bacterial structures or metabolic pathways. Existing antibiotic options are in green, new antibiotics approved and on the market are in blue and antibiotics in the pipeline 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

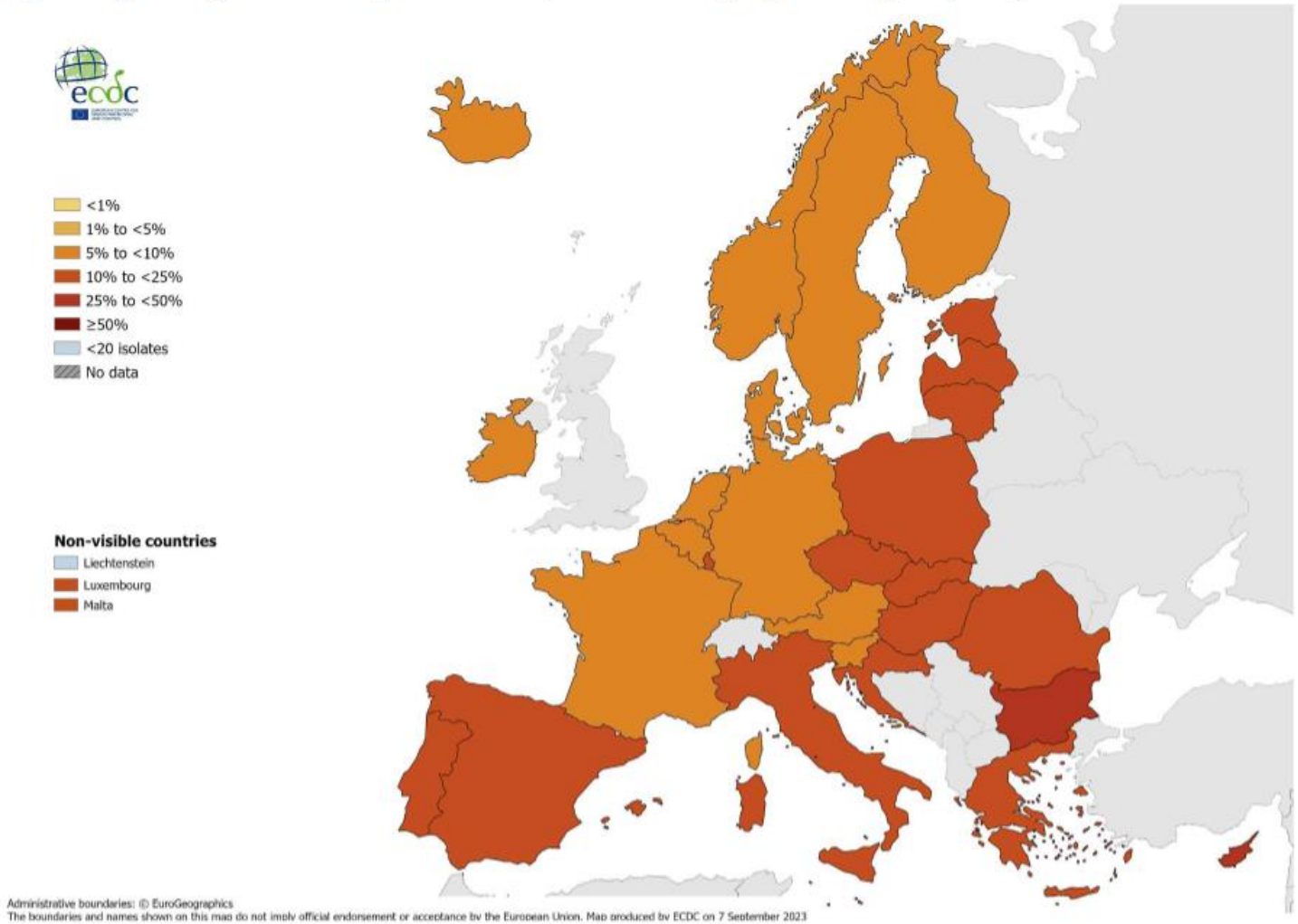
Betalactamases in gramnegative bacteria


MAIN BETA-LACTAMASES IN ENTEROBACTERIACEAE
Ambler's classification
Class A
Serine-beta-lactamases
(inhibitor-susceptible)
Class B
Metallo-beta-lactamases
Class C
Cephalosporinases
Class D
Oxacillinases
Penicillinases
Klebsiella sp.
Citrobacter koseri
Non-inducible AmpC
Escherichia coli
Inducible AmpC
Enterobacter sp.
Citrobacter freundii
Serratia marcescens
Morganella morganii
Hafnia alvei
Providencia stuartii
Derepressed AmpC
Penicillinases
TEM and SHV
(incl. inhibitor-resistant variants)
ESBL
TEM, SHV and CTX-M
Carrbapenemases
KPC
Carbapenemases
VIM, IMP and NDM
Plasmidic AmpC
CMY-2 and other types
Narrow-spectrum OXA
(inhibitor-resistant)
ESBL-OXA
(uncommon)
Carbapenemases
OXA-48 variants
Chromosomal genes
Plasmid-borne genes
Intrinsic resistance
Acquired resistance
Enzyme-conferred resistance
(hydrolysis spectrum)
Penicillins and 1GC
2GC, 3GC +/- 4GC
Carbapenems
+/- other beta-lactams
Beta lactamase inhibitors
Clavulanic acid
Sulbactam
Tazobactam
Avibactam
Relebactam

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

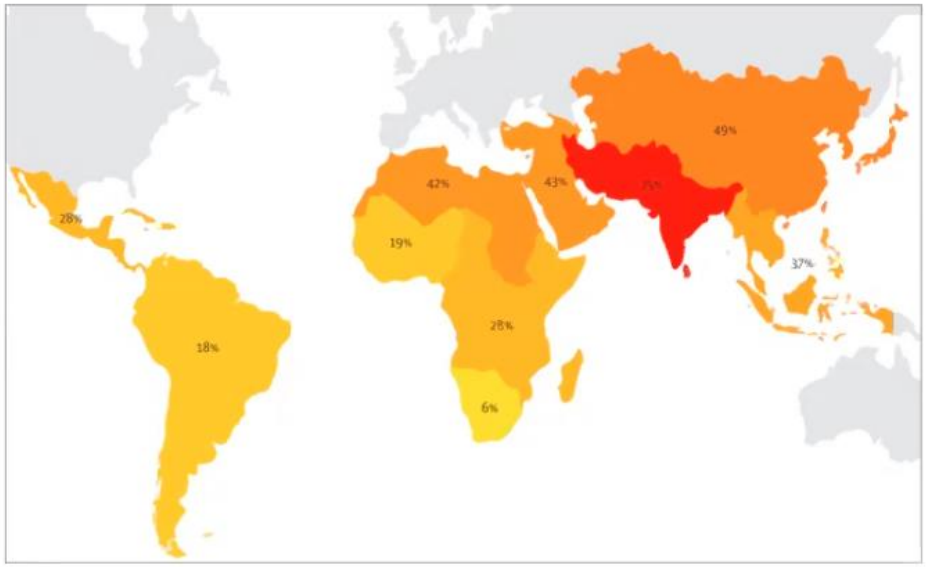
Figure 2. ***Escherichia coli*****. Percentage of invasive isolates resistant to third-generation cephalosporins (cefotaxime/ceftriaxone/ceftazidime), by country, EU/EEA, 2022**

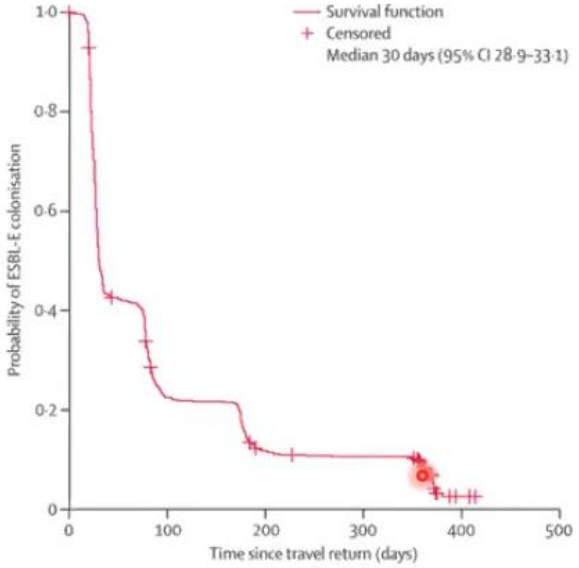


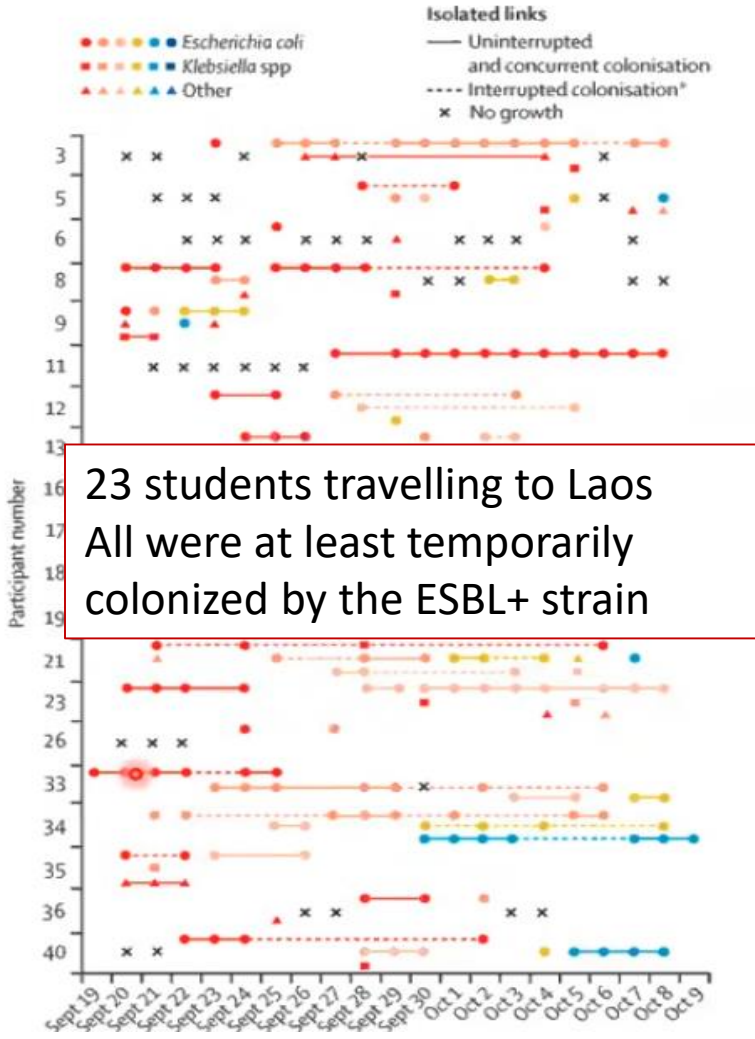
Most common MDR in Europe

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

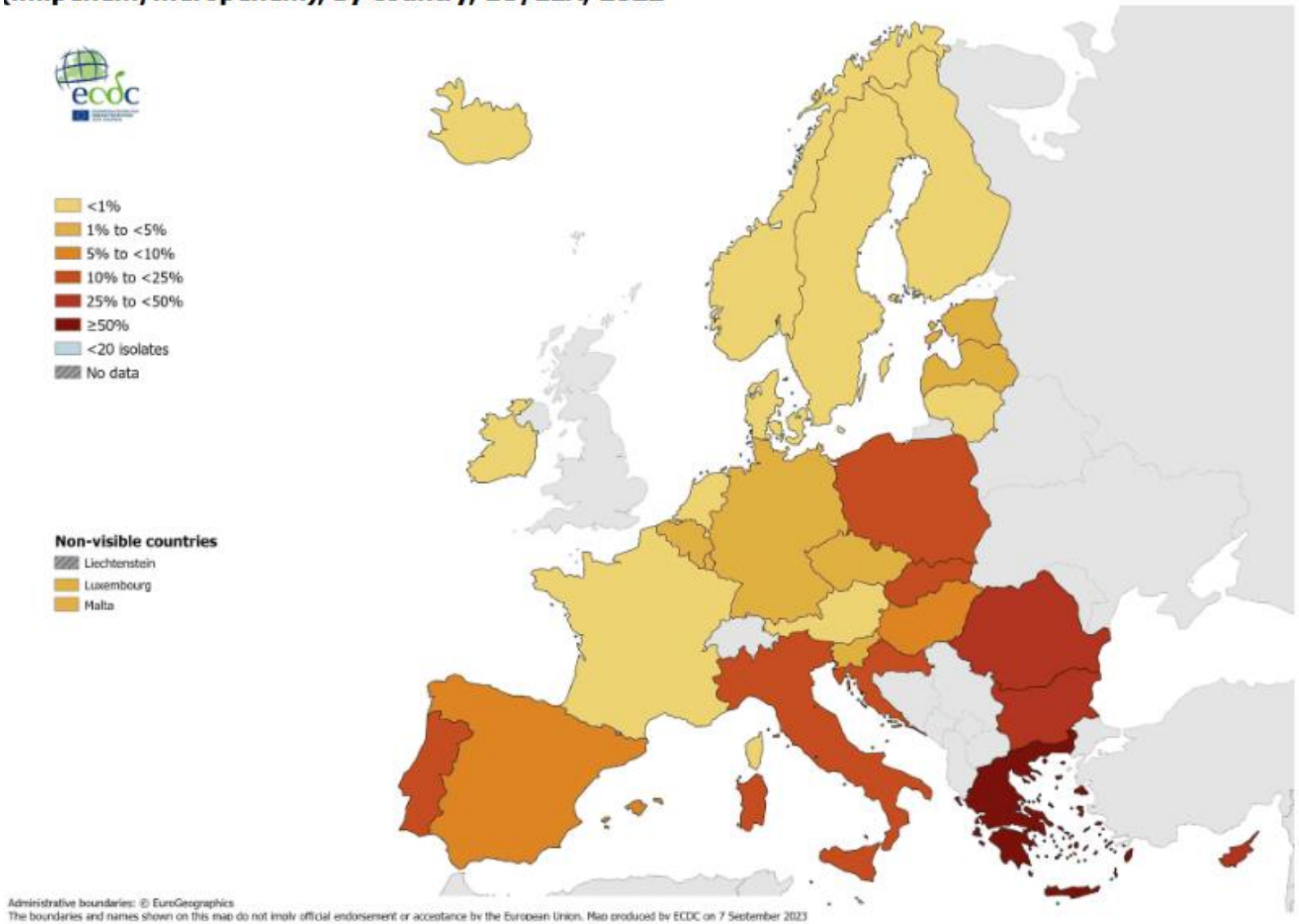
- Class A
  - KPC, GES, SME, IMI, NMC
  - Sensitive to inhbitors (clavulanic acid, tazobactam, relebactam, avibactam)
  - *Enterobacteriaceae, P. aeruginosa, Acinetobacter* sp
- Class B - metalobetalactamases
  - VIM, IMP, GIM, SIM, NDM,…
  - Resistant to inhibitors
  - *Enterobacteriaceae, P. aeruginosa, 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

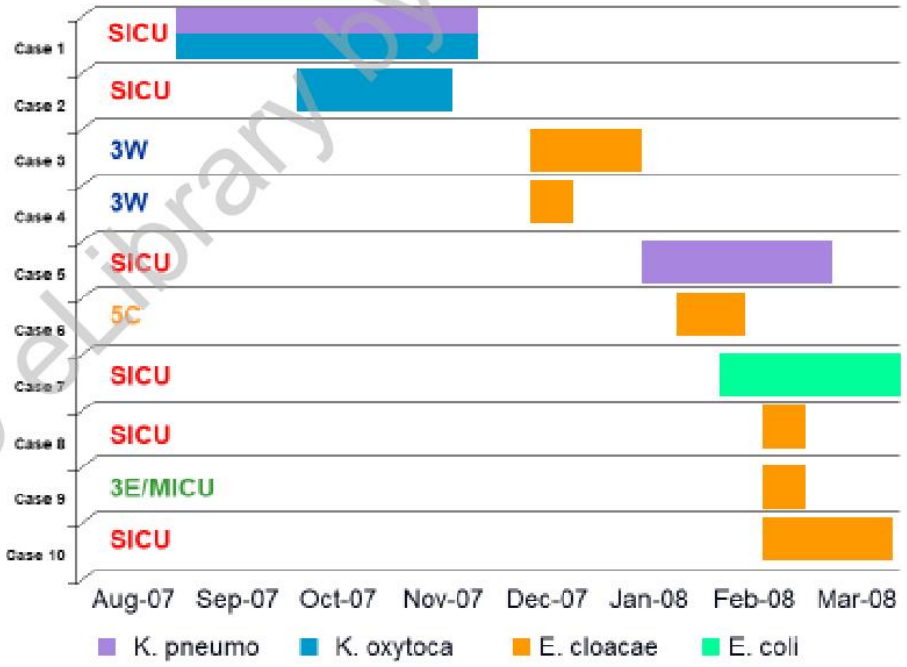
Weakened immunity

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



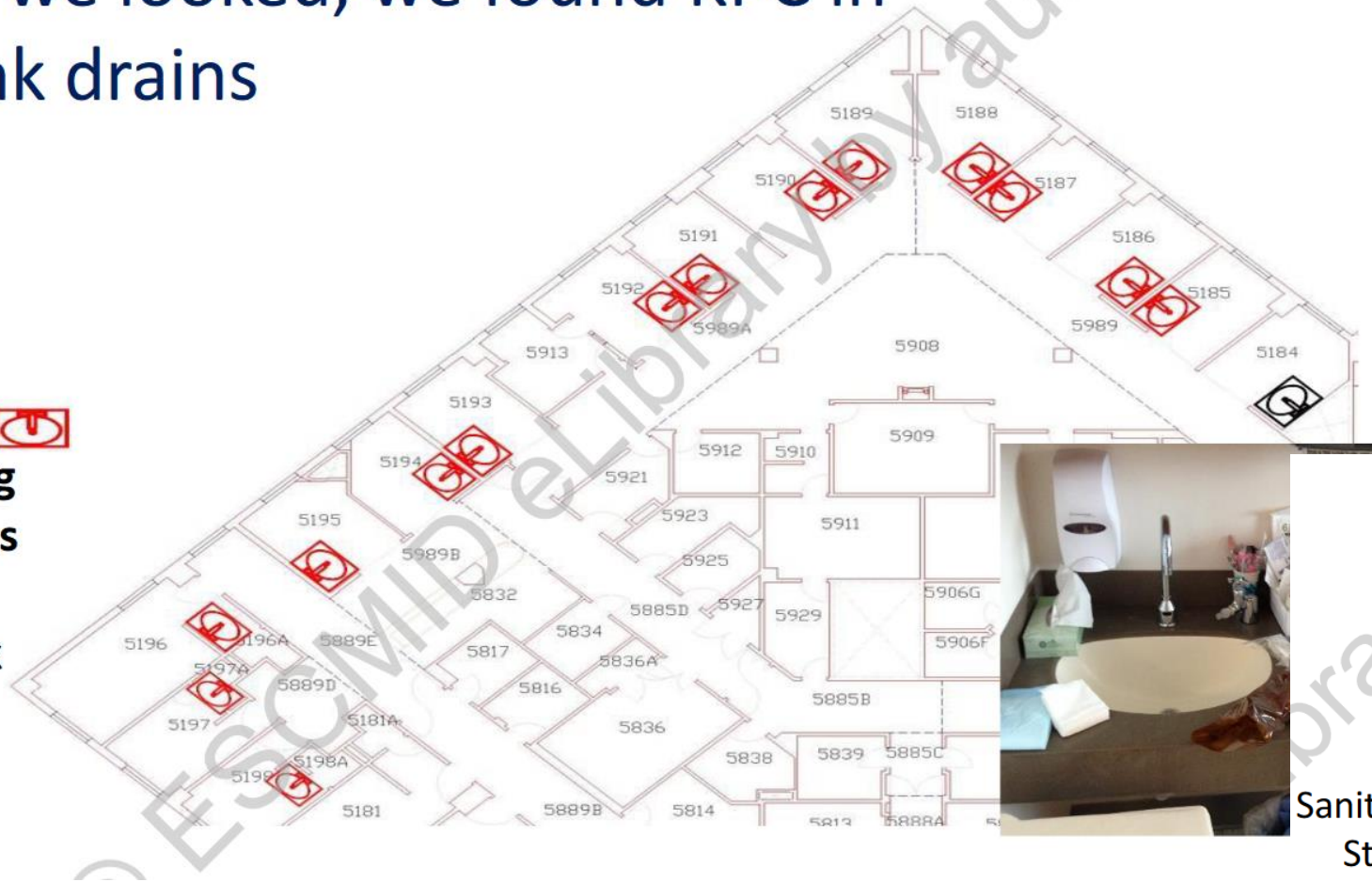
KPC = type of carbapenemase

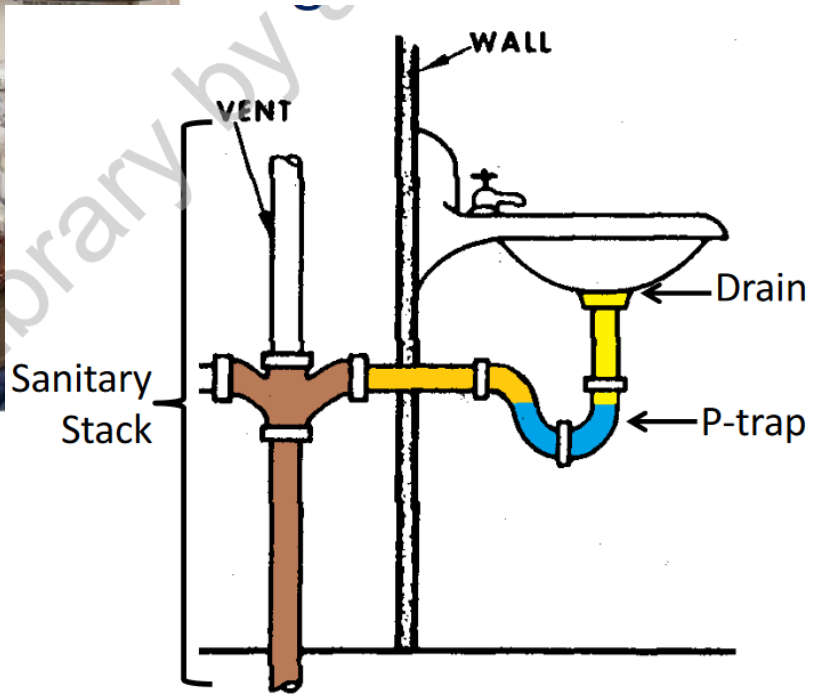
2009-2011: cca 281 isolates from 182 patien
Transpozon Tn4401 carrying *bla*$_{KPC}$
11 plasmids
Different species and genera

Amy Mathers IMMEM 2019

When we looked, we found KPC in the sink drains

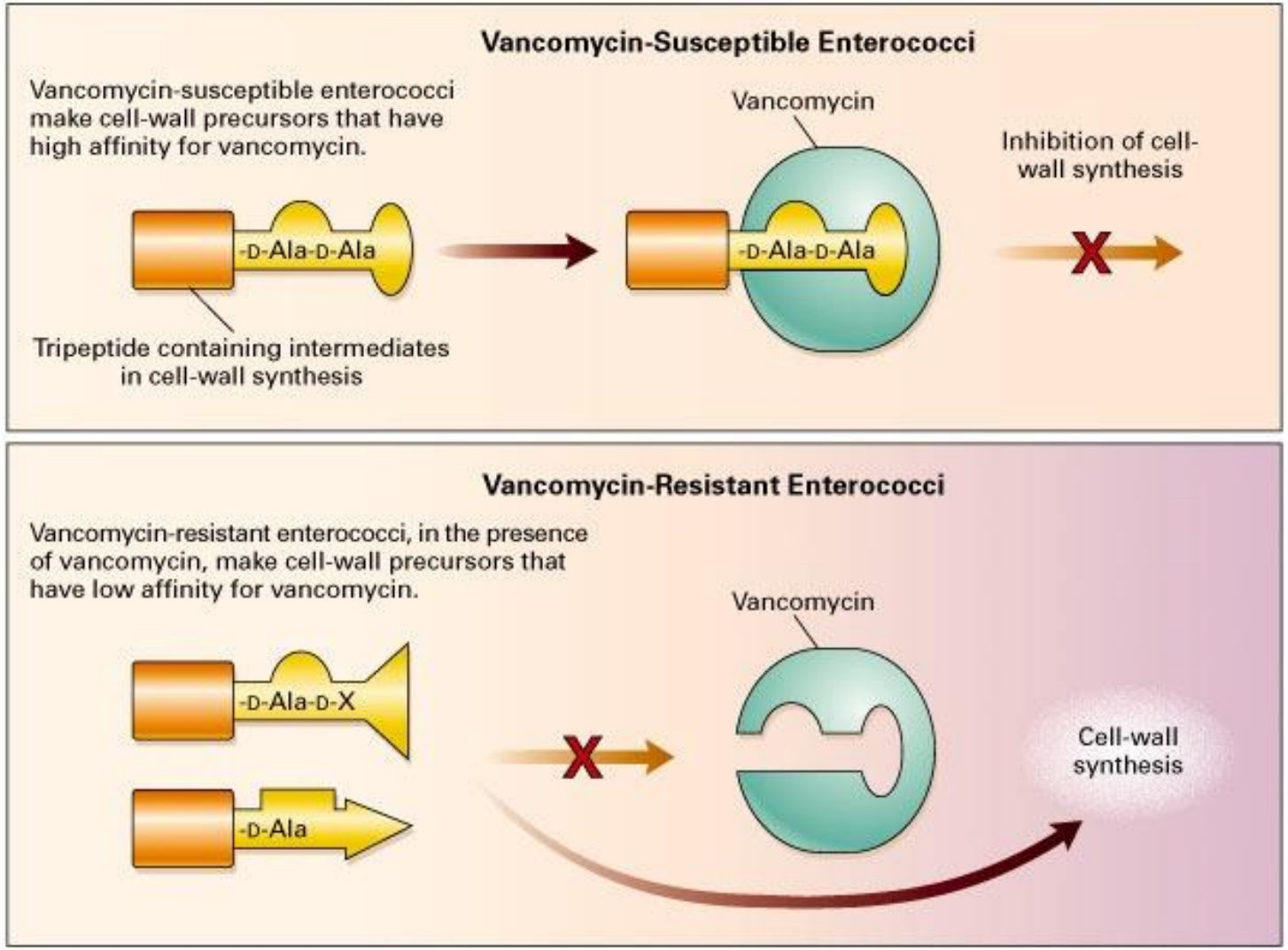
KPC-producing organisms isolated from sink





Enterobacteria could colonise pipes via biofilm formation

Vancomycin resistant enterococci (VRE)



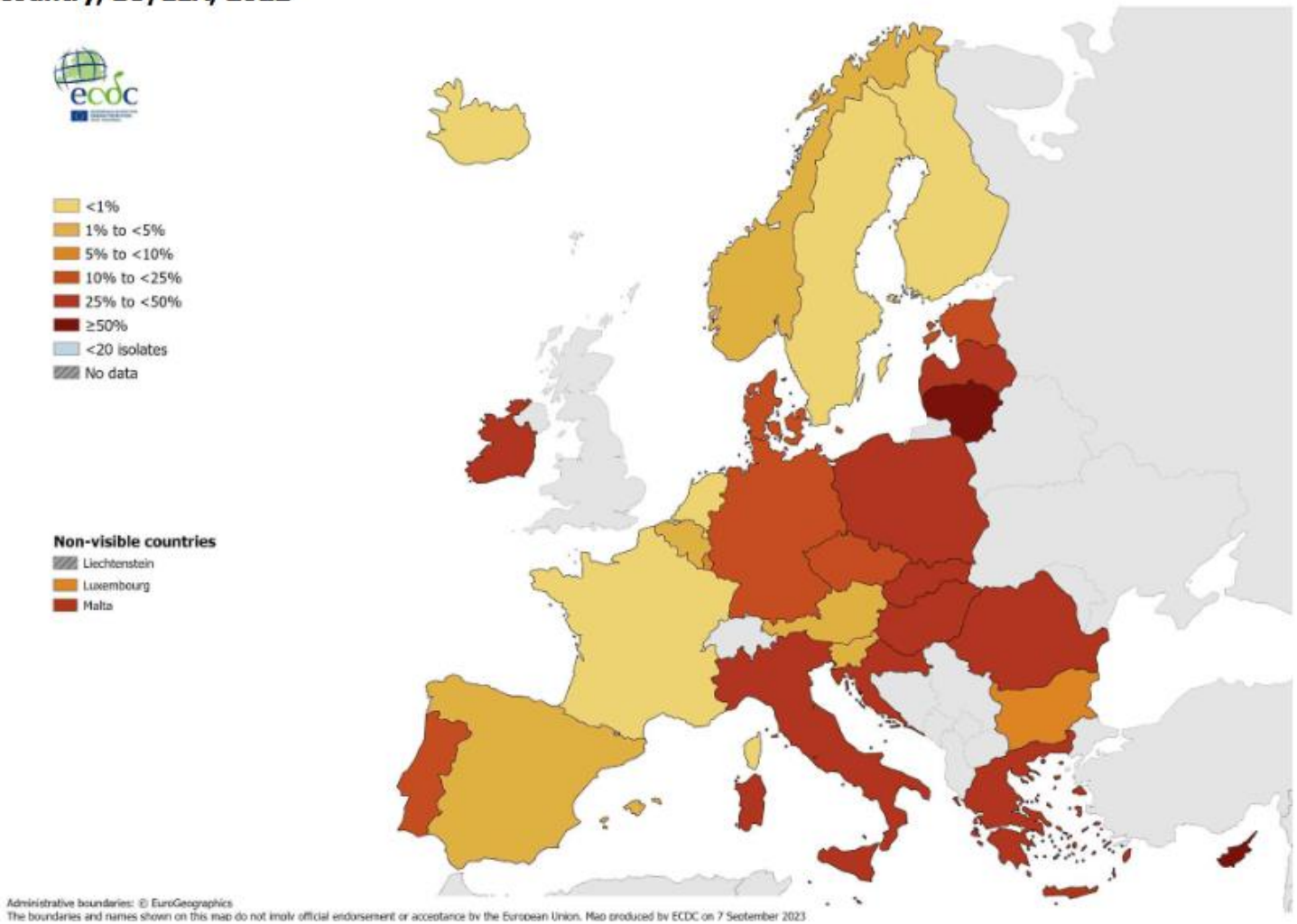
E. faecium
E. faecalis
GIT comensals

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

Antibiotic stewardship

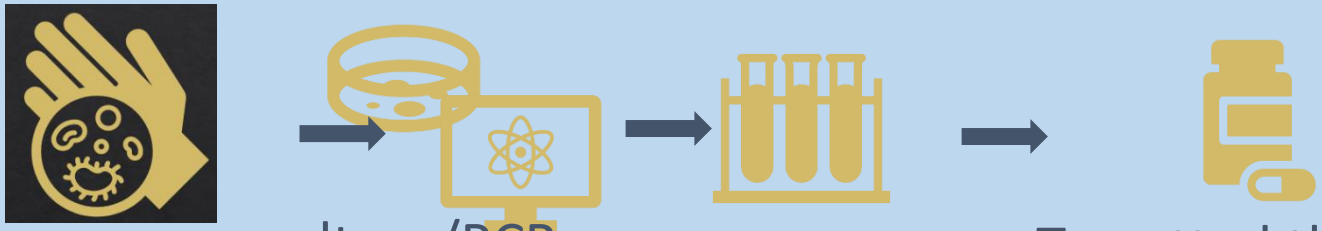
- the effort to keep antibiotics effective
- Key elements:
  - Controling the level of AMR (**surveillance**, infection prevention and control, education)
  - Controling antibiotic prescription and usage

Monitoring of resistant bacteria, because…

Surveillance of antimicrobial resistance

Clinical issue - infections

- **The problem is a patient with an infection**

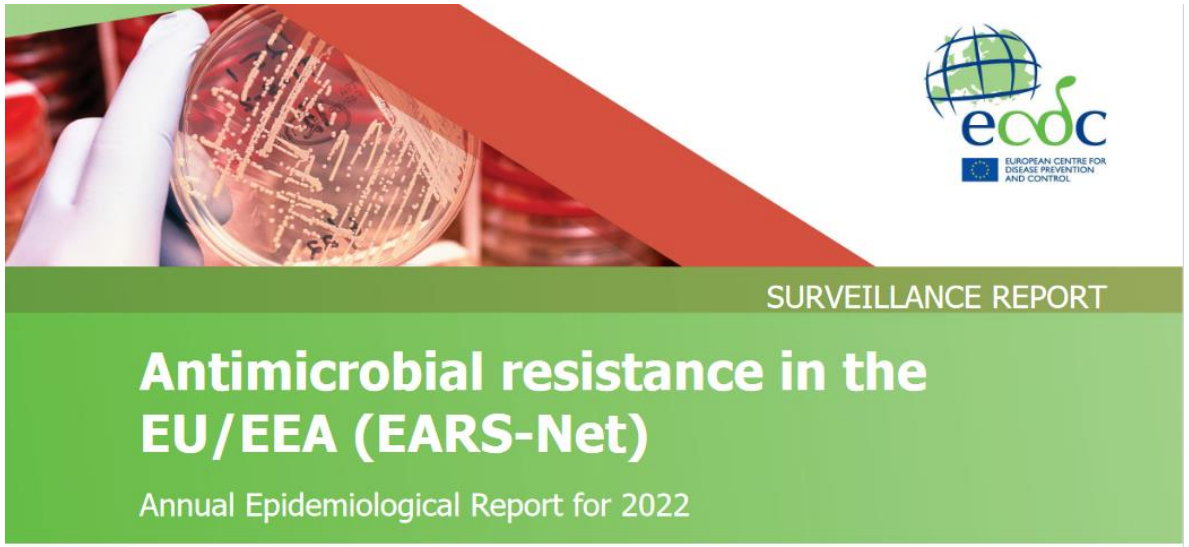


- Monitoring prevalence of resistant strains (e.g. MRSA in BSI)
- Important for initial/empirical therapy
- Observing the trends, identifying problem
- Local/national/international/global AMR surveillance
  - EARS-NET, GLASS

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



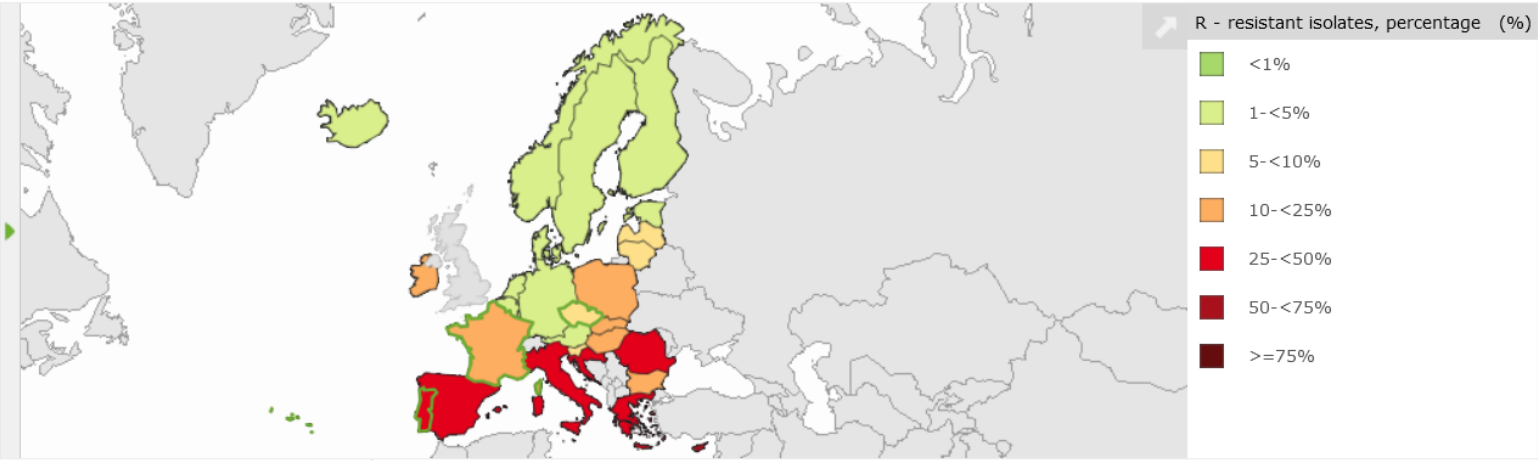
Key facts 2022

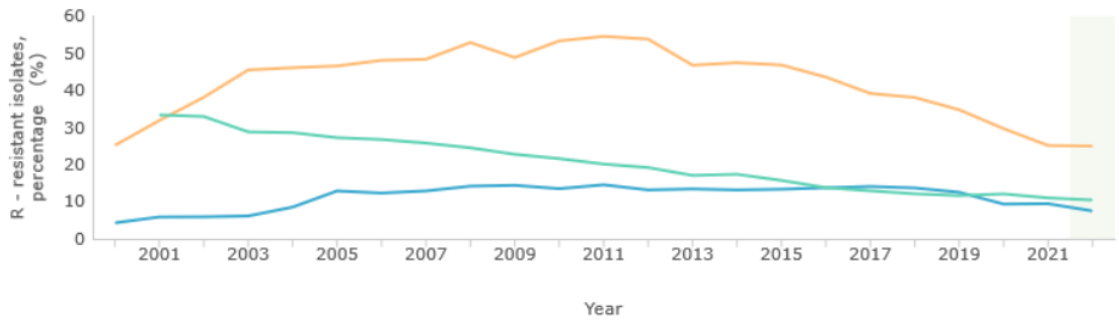
- incidence of bloodstream infections with both MRSA and third- generation cephalosporin-resistant *E. coli* showed a favourable decreasing trend between 2019 and 2022,
- the EU incidence of carbapenem-resistant *K. pneumoniae* increased by almost 50%
- continuous increase in carbapenem-resistant *K. pneumoniae* (10.9% in 2022) and vancomycin-resistant *E. faecium* (17.6% in 2022).
- decreases in the EU/EEA population-weighted mean AMR percentages for *Acinetobacter* spp. compared to 2021,
- increasing trend for the EU/EEA population-weighted mean percentage of macrolide resistance and penicillin non-wild-type, including combined resistance in *S. pneumoniae* during the period 2018-2022.

Surveillance Atlas of Infectious Diseases

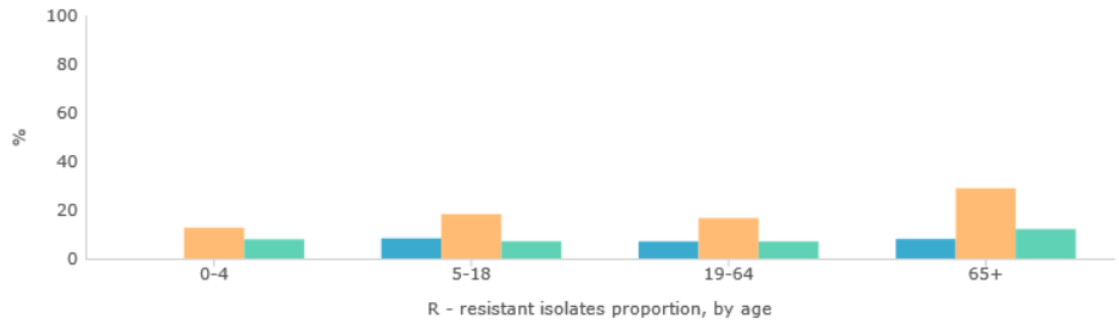
Antimicrobial resistance | Staphylococcus aureus | Meticillin (MRSA) | R - resistant isolates, percentage | 2022

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

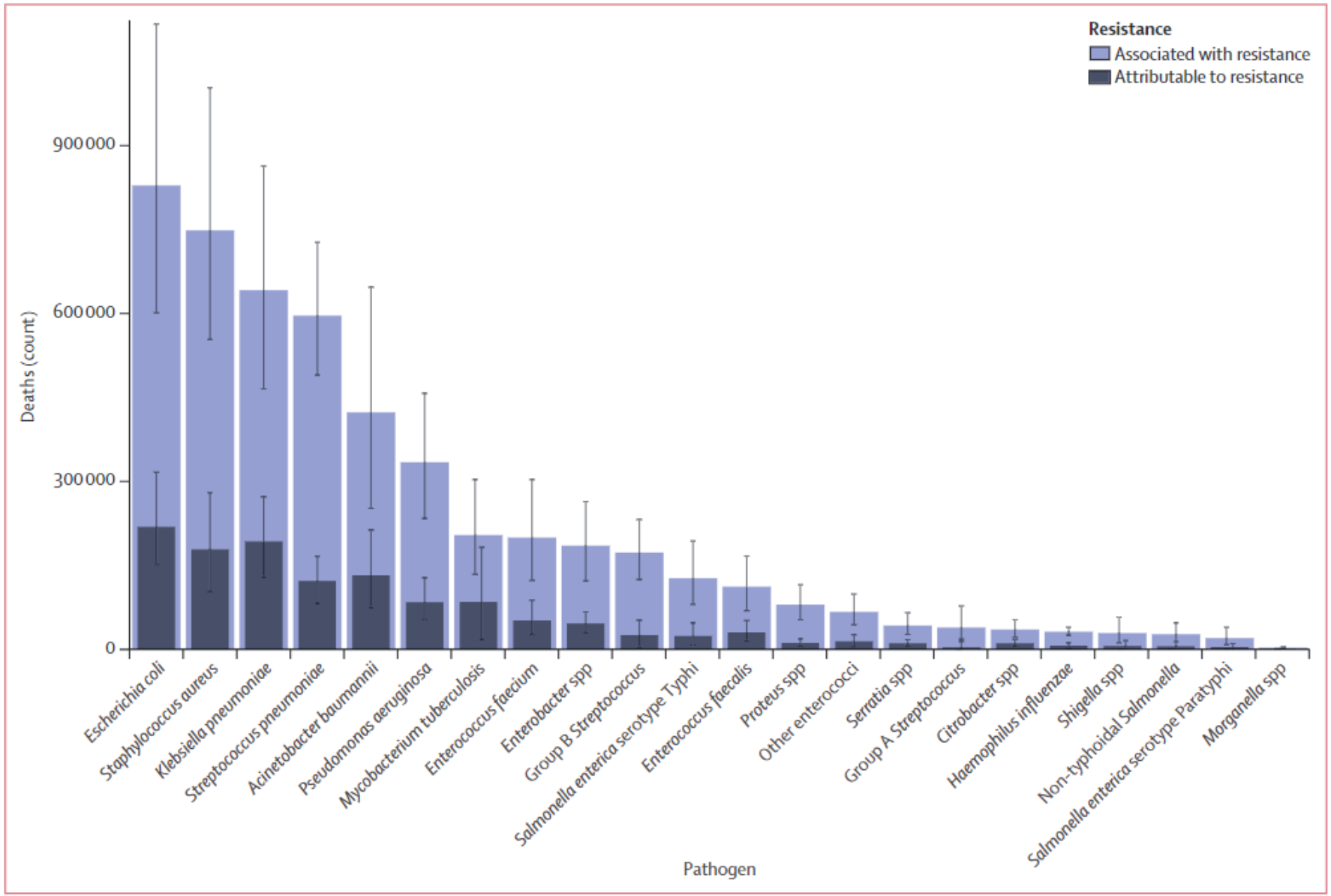
Manage cookies

WHO

World Health Organization

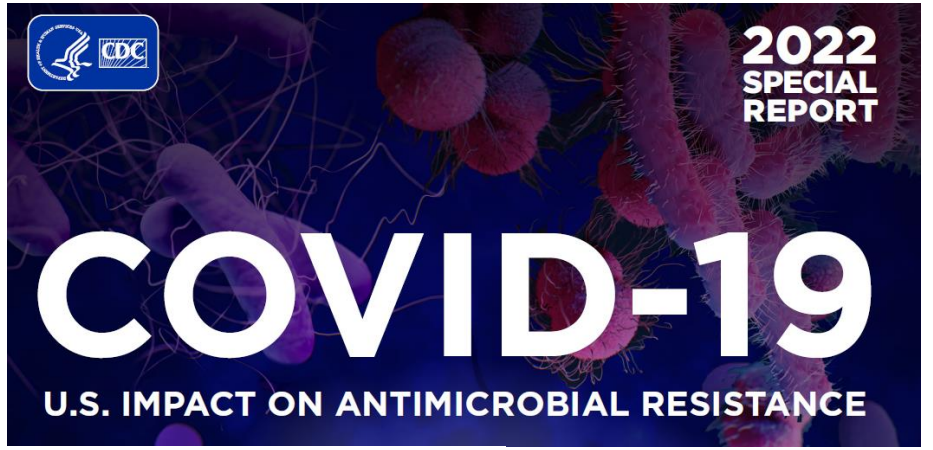
Since 2015
132 participating countries

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



Global burden of antimicrobial resistance in 2019; Lancet 2022

Efect of COVID

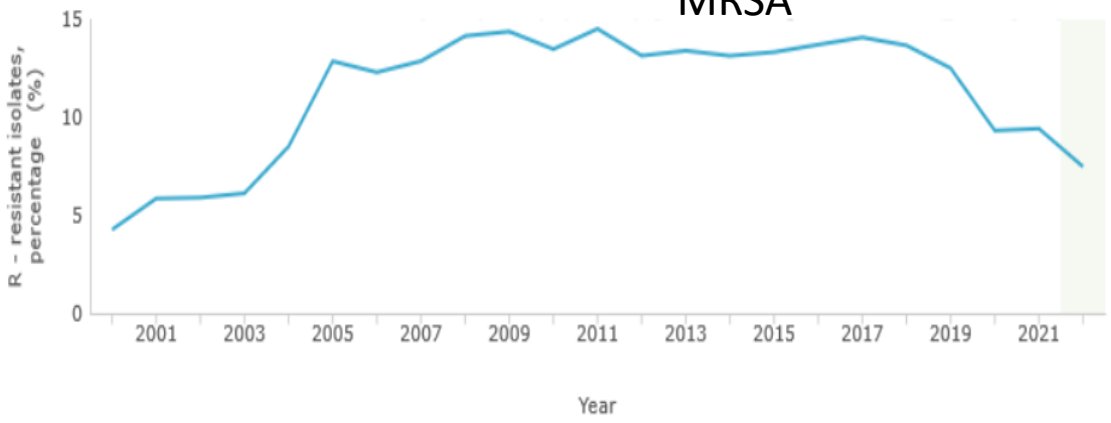


Available data show an alarming increase in resistant infections starting during hospitalization, growing at least 15% from 2019 to 2020.

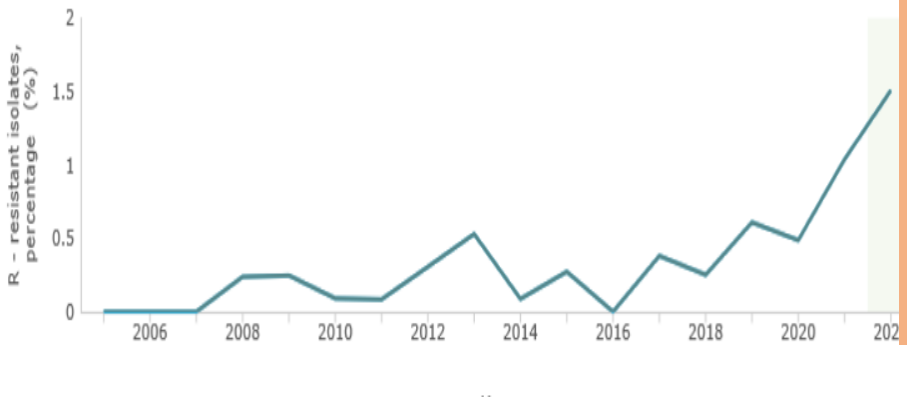
- Carbapenem-resistant *Acinetobacter* (↑78%)
- Antifungal-resistant *Candida auris* (↑60%)*
- Carbapenem-resistant Enterobacterales (↑35%)
- Antifungal-resistant *Candida* (↑26%)
- ESBL-producing Enterobacterales (↑32%)
- Vancomycin-resistant Enterococcus (↑14%)
- Multidrug-resistant *P. aeruginosa* (↑32%)
- Methicillin-resistant *Staphylococcus aureus* (↑13%)

Czech Republic:

MRSA



Carbapenem resistant *K. pneumoniae*



Various factors:

- Increase general hygiene
- Lower intake of non-covid patients
- High workload and antibiotic usage on covid units

Surveillance of antimicrobial resistance

Epidemiological issue - colonisation

- **Main epidemiological problem is the colonized (healthy) patient**

- infections are a tip of the iceberg, regarding the presence of resistant bacteria
- **Localy used to preventing spread of resistance**
- Cost-effectiveness – it is cheaper to prevent spread of MDR (decolonisation, isolation) than to treat infection

Screening for MDR colonisation

Resistance based

- Resistance to reserve antibiotics - colistin, carbapenems, ESBL, MRSA

Risk groups of patients

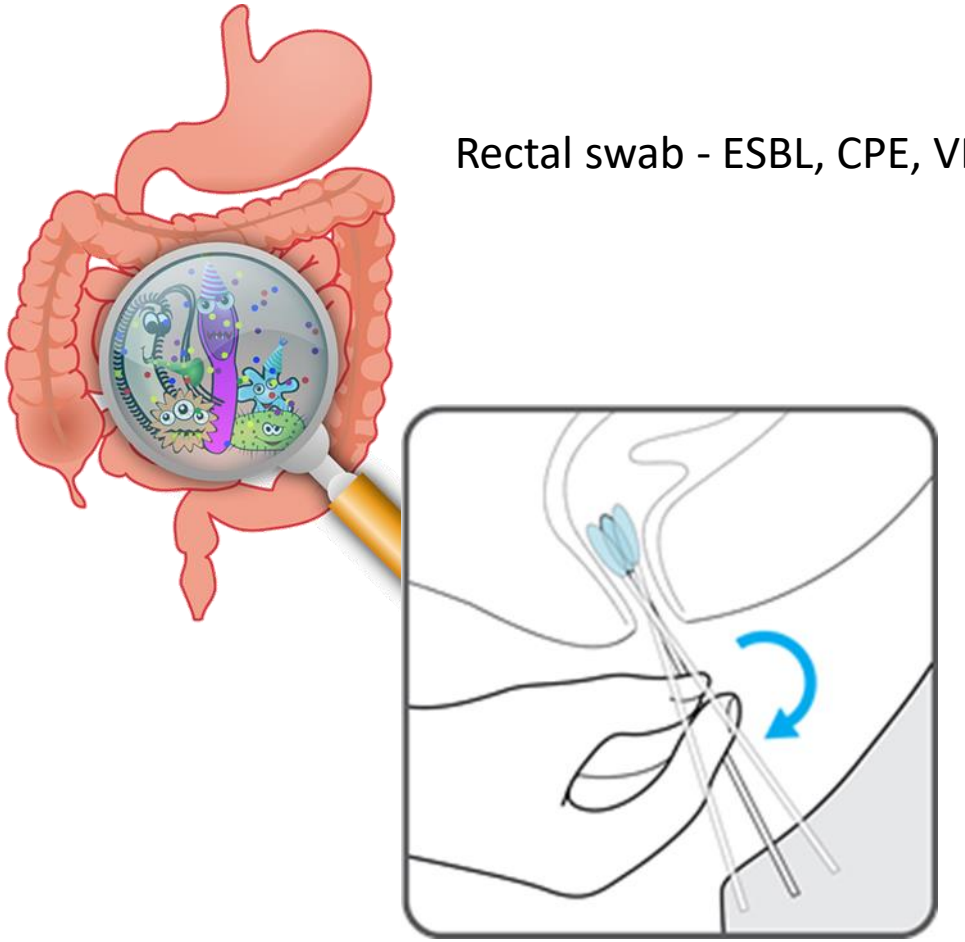
- Travellers – returning from high-risk countries
- Patients on ICU, and other wards with high antibiotic consumption
- Patients before surgery
  - MRSA screening followed by decolonisation (prevention of post-surgery infections)
  - Universal MRSA decolonisation without screening (chlorhexidine bathing, nasal mupirocin)?
    Short term effective, Long term selection of resistance.
- Contacts of positive patients (familly, staff)

Carriage of resistant bacteria – which samples

- **Colonisation**:
  - Nose
  - GIT
  - Skin
  - Upper airways
  - throat

    …

Nasal swab - MRSA



Rectal swab - ESBL, CPE, VRE

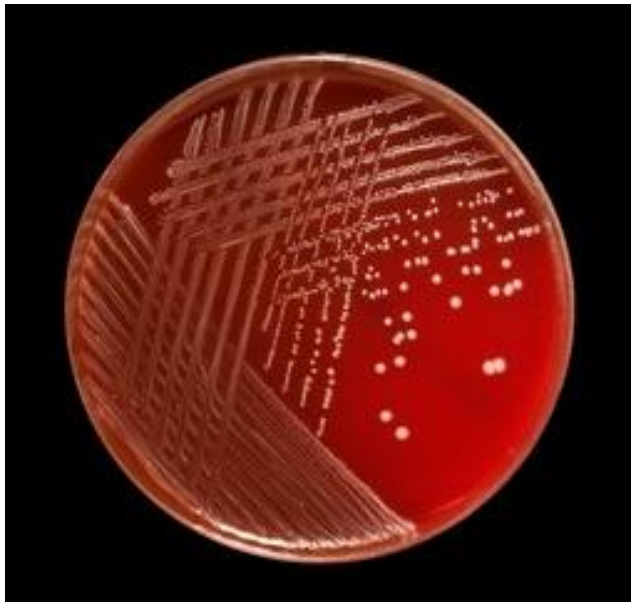
Methods for resistance screening

- **Selective culture** – not blood agars…

Yersinia pestis

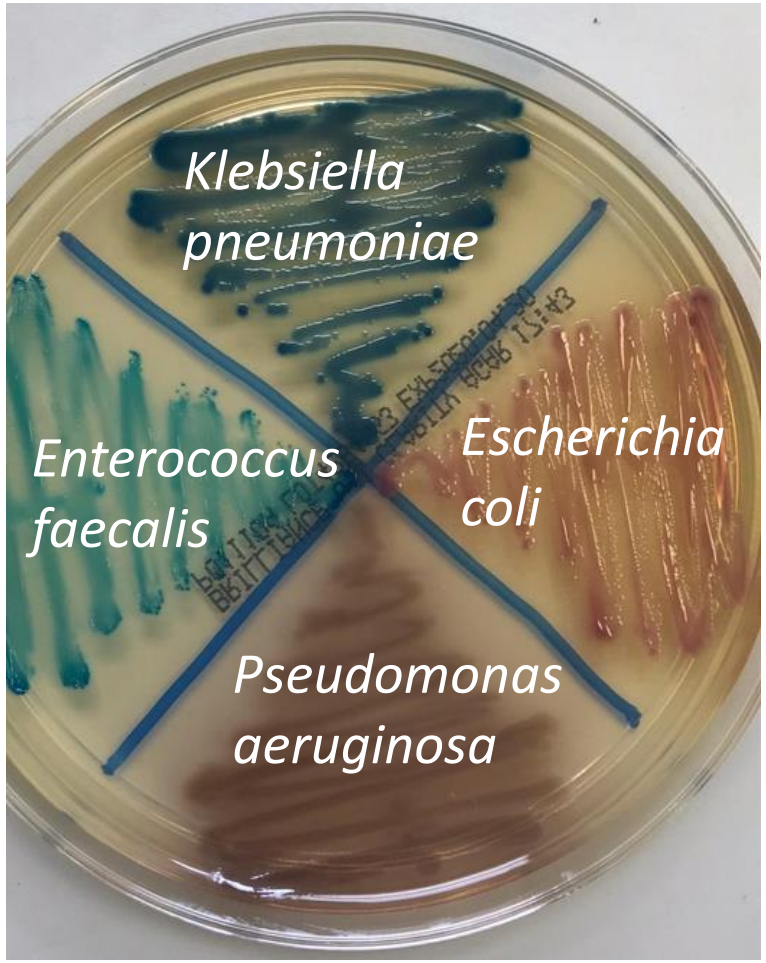
Staphylococcus epidermidi

Escherichia coli

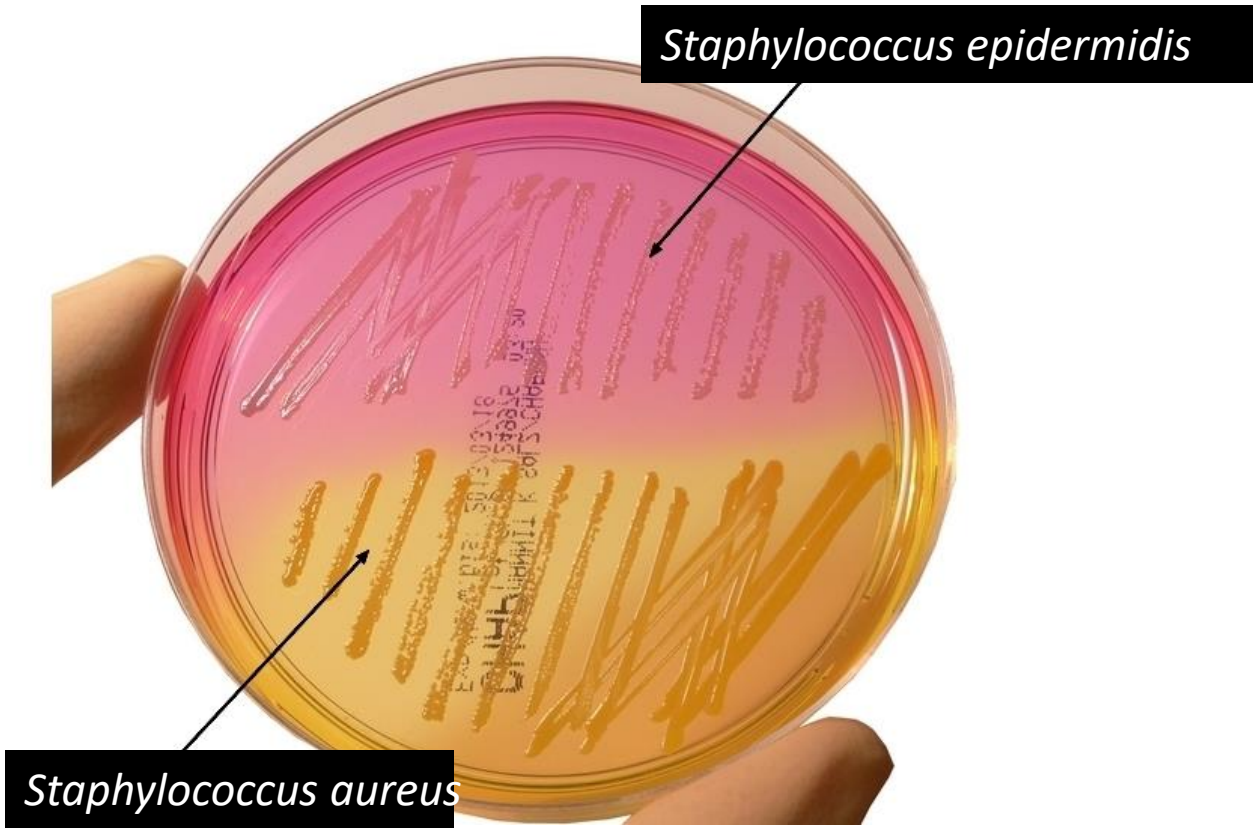


Selective differential media

Chromogenic media



Manitol Salt agar

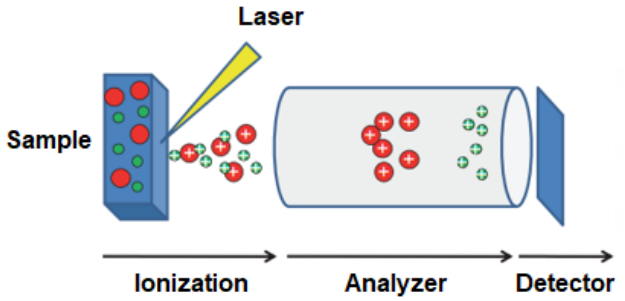


Screening of patients

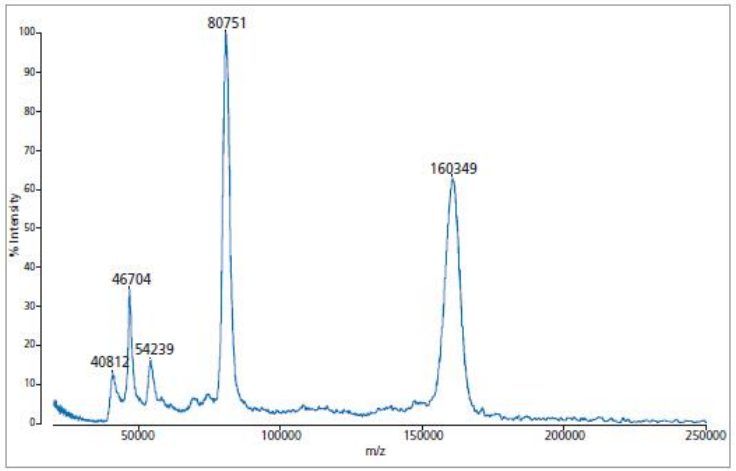
- **Methods for resistance screening**
  - **Selective culture** – monitoring the spread
    - *Speciec confirmation* by mass spectrometry (MALDI-TOF)

Culture

Mass spectrometry
MALDI-TOF



Excitation by laser –
flight throught vacuum



The weight to charge ratio is species specific

Screening of patients

- **Methods for resistance screening**
  - **Selective culture** – monitoring the spread
    - *Speciec confirmation* by mass spectrometry (MALDI-TOF)
    - *Resistance confirmation* (AST)
    - *Mechanism of the* resistance (PCR, sequencing)
    - *Typing* (clonal spread)
  - **Direct PCR** – direct detection of resistance genes

Controling prescription

Classification of antimicrobials according preference of usage
- AWARE classification

Consultations – optimal treatment
- Microbiologist, infectious disease specialist, pharmacist

Controling prescription
- Antibiotic centres – microbiologist has to approave the prescription
- Point prevalence studies/audit of prescription
  - Selected patients – retrospective revision of their therapy
  - Regular
  - **<u>feedback</u>** to clinicians

Measuring antimicrobial usage
- Is there exces in some dept.?
- What is the reason?

ATB consumption in European hospitals

Figure 4. Hospital sector consumption of antibacterials for systemic use (ATC gro countries, 2021 (expressed as DDD per 1 000 inhabitants per day)

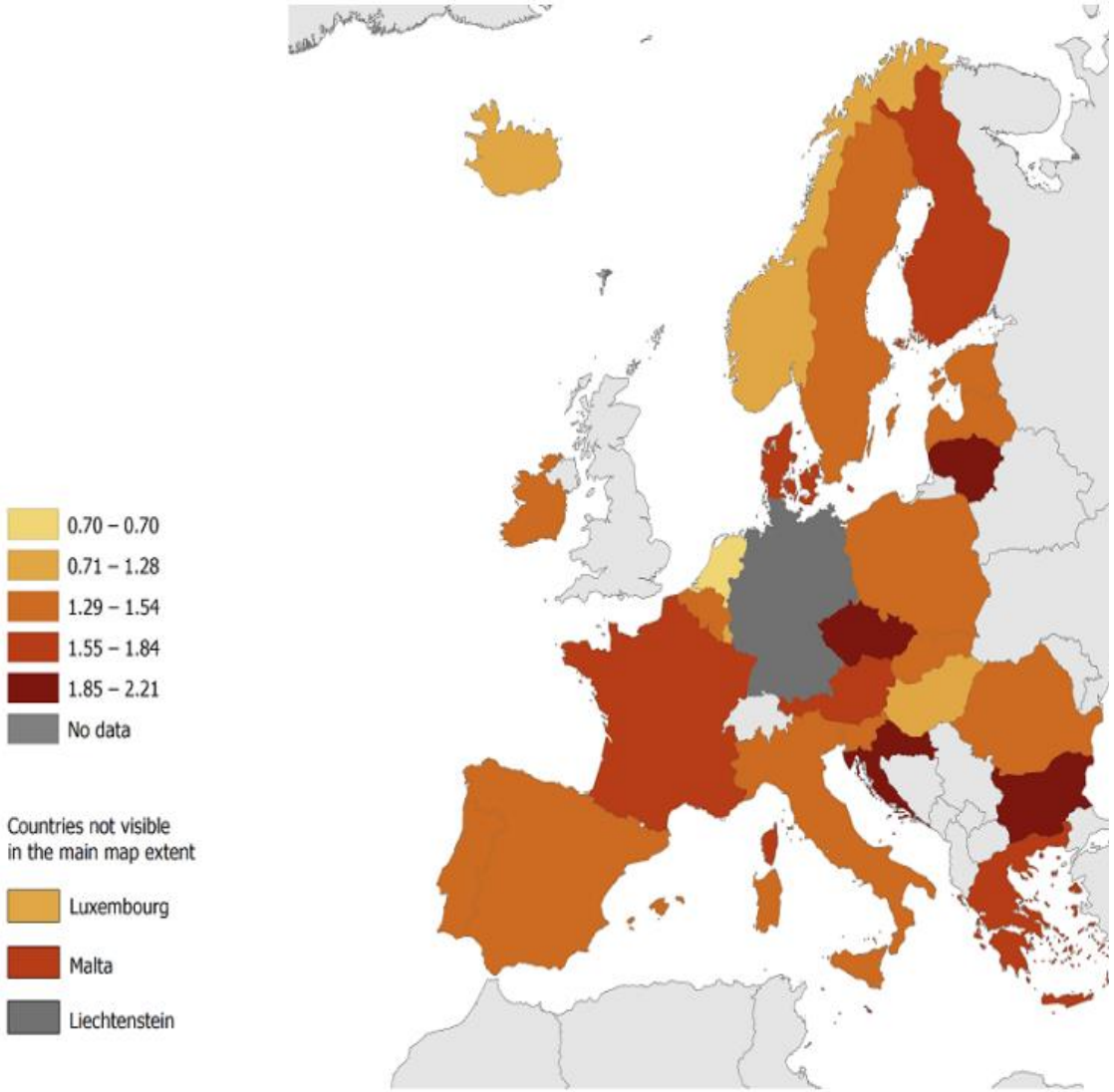
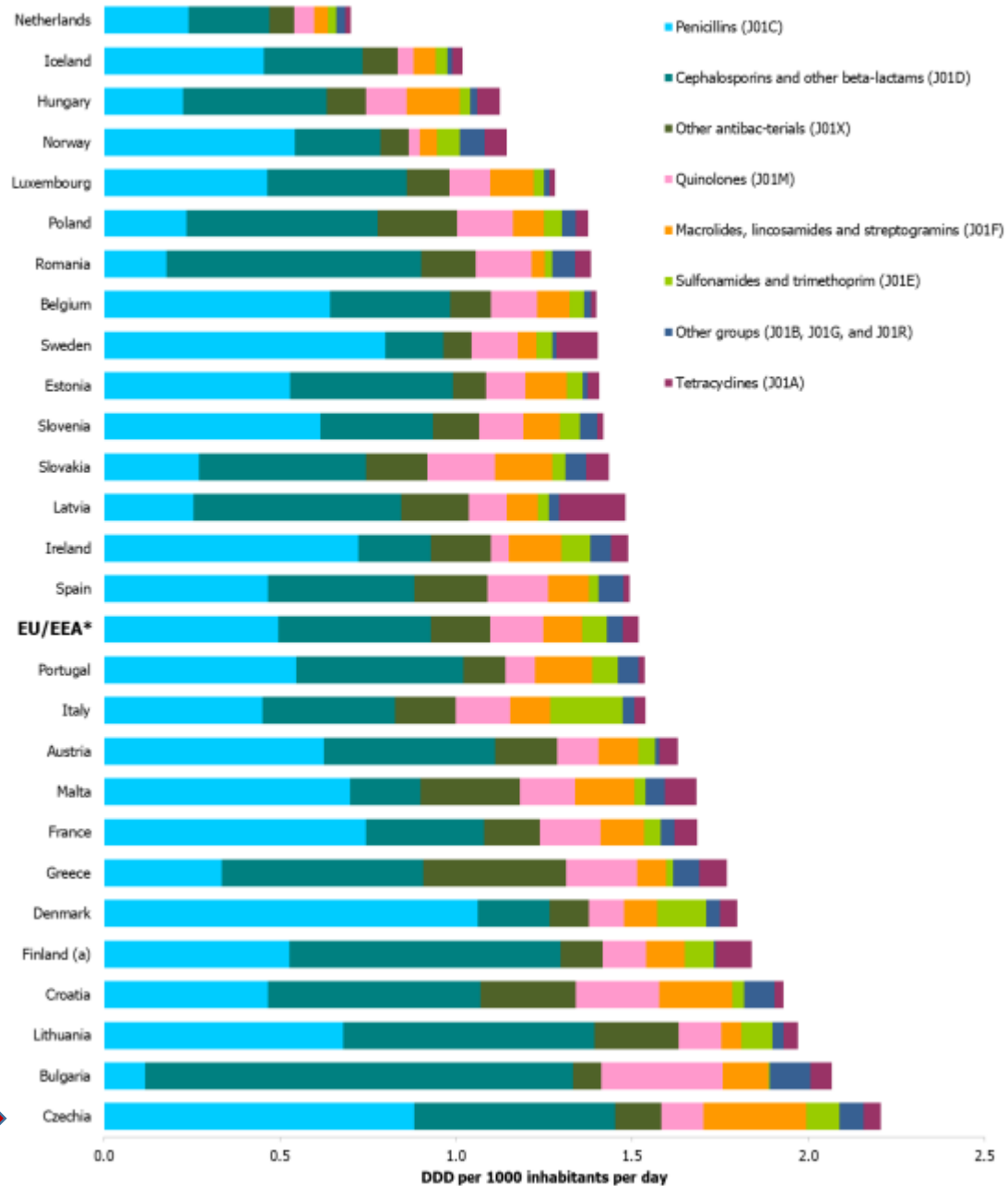


Figure 5. Hospital sector consumption of antibacterials for systemic use (ATC group J01) at ATC level 3 sub-group, EU/EEA countries, 2021 (expressed as DDD per 1 000 inhabitants per day)



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

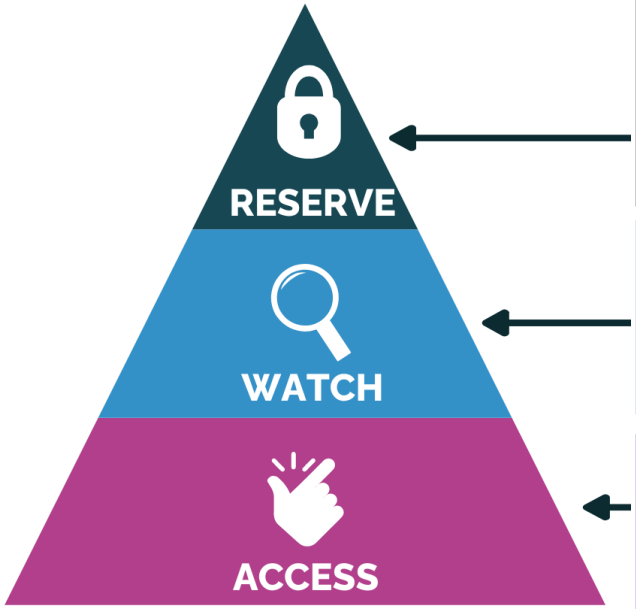
Targetted – known cause end its susceptibility

Deescalation – switch to targetted therapy after identification of cause

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

AWARE classification

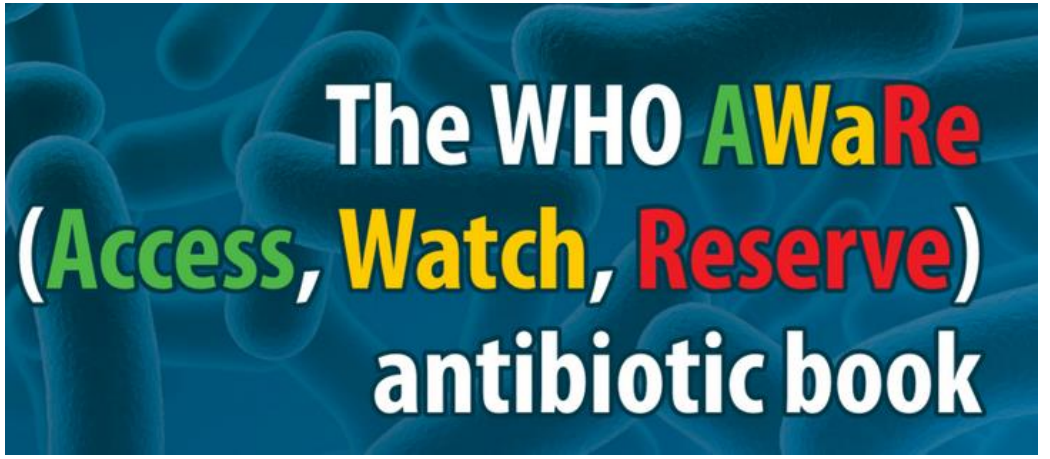
The AWaRe classification is intended as a tool for monitoring antibiotic consumption, defining targets and monitoring the effects of stewardship policies that aim to optimize antibiotic use and curb antimicrobial resistance.



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

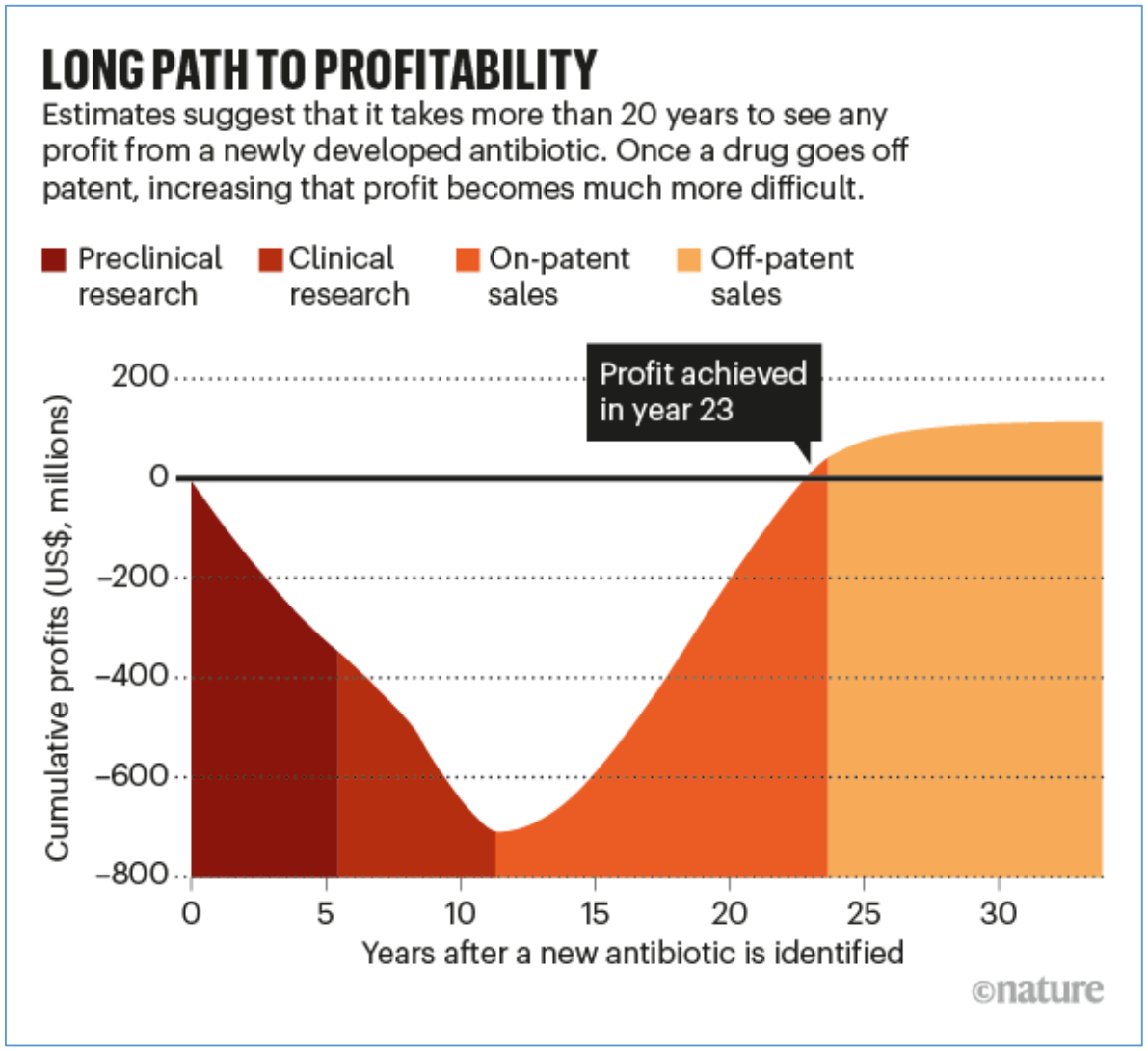
HEALTH, EUROPE

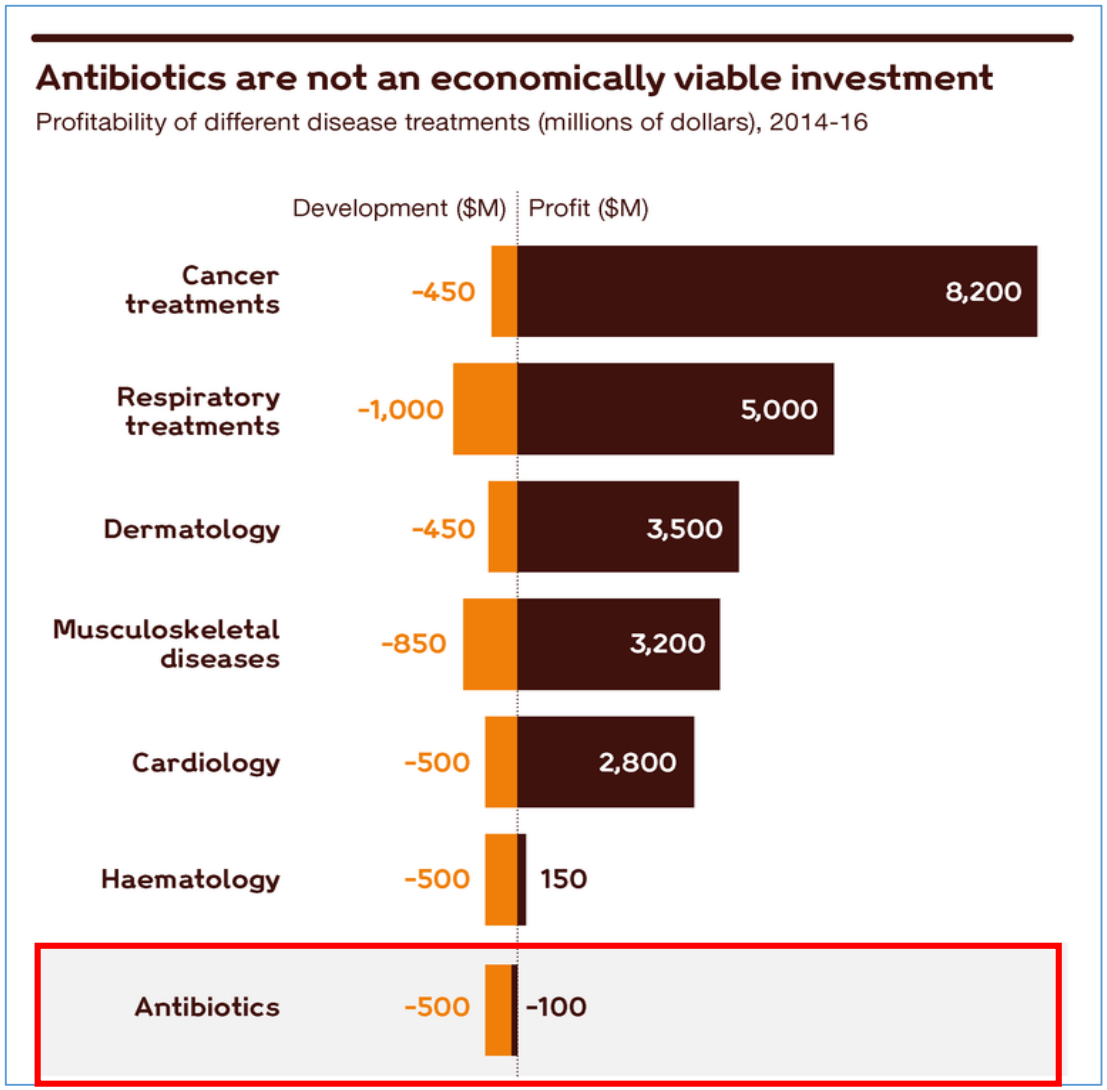
Antibiotics shortage crisis deepens in Germany

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!