SOCIETÀ ITALIANA DI GERONTOLOGIA E GERIATRIA
68° CONGRESSO NAZIONALE SIGG
Ritorno al futuro
FIRENZE, 13-16 DICEMBRE 2023
PALAZZO DEI CONGRESSI

I meccanismi di antibiotico-resistenza

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DISCLOSURE

In qualità di RELATORE, ai sensi dell'art.76 sul Conflitto di Interessi dell'Accordo Stato-Regioni del 2 febbraio 2017,

dichiara

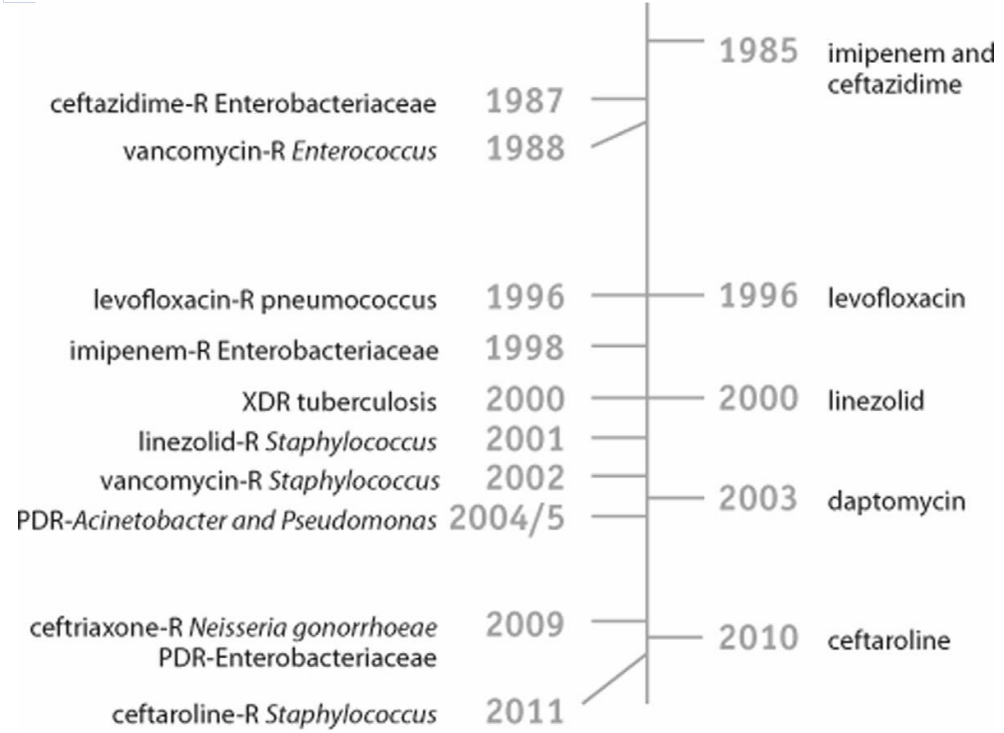
per l'evento in oggetto l'esistenza negli ultimi due anni di rapporti di natura finanziaria e/o lavorativa con le seguenti imprese commerciali operanti in ambito sanitario: MSD, Pfizer, B&D, Tillots, Termofisher, ImmuneMed, Qiagen, Takeda.

Dichiaro, inoltre, che i contenuti formativi esposti sono indipendenti da interessi commerciali.

Antimicrobials and Antimicrobial Resistance: A Brief History

- ✓ **Penicillin**, discovered by Alexander Fleming in 1928→ however, even before the use of penicillin, in **1940, the first penicillin resistant *Staphylococcus*** strains had already been described.
- ✓ To counteract the first penicillinases, **methicillin was introduced in 1959** and one year later, in **1960, a methicillin resistant *Staphylococcus* strain** was reported.
- ✓ **Vancomycin** was introduced in **1958** for the treatment of methicillin-resistant staphylococci. A couple of decades later, in **1979, coagulase-negative staphylococci resistant to vancomycin** were reported and ten years later resistance in **enterococci** was described.
- ✓ **Tetracycline** was introduced in **1950** followed by tetracycline-resistant *Shigella* strains being reported in **1959**.
- ✓ **Levofloxacin** was introduced into clinical practice in **1996** and in the **same year levofloxacin-resistant pneumococcus** was reported.

Christaki E et al. J Mol Evol 2020 ;88(1):26-40.



Morrison L et al. Gastrointest Endoscopy Clin N Am 2020; 30: 619–635

Fig. 1 ***Escherichia coli.*** **Percentage of invasive isolates resistant to fluoroquinolones (ciprofloxacin/levofloxacin/ofloxacin), by country, WHO European Region, 2021**

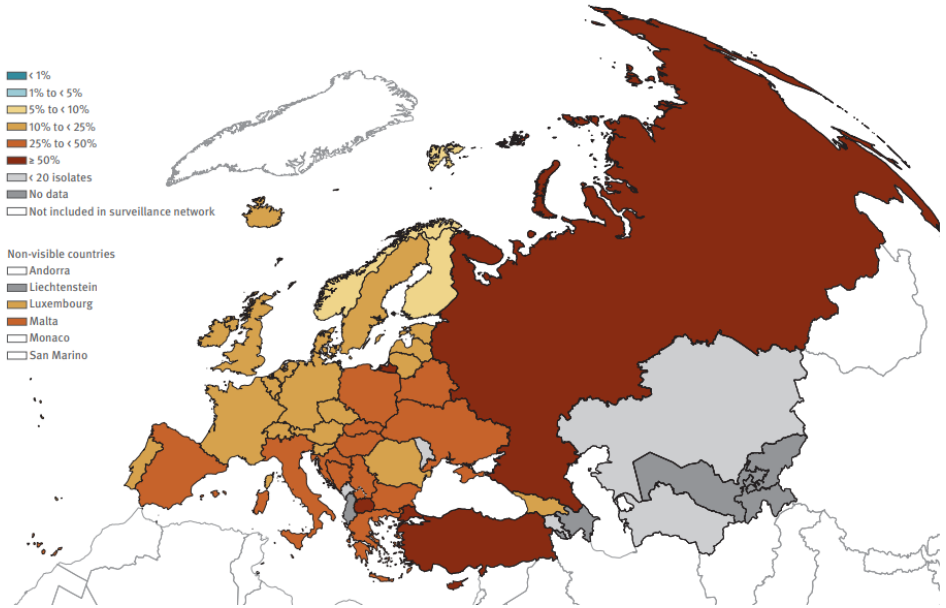


Fig. 2 ***Escherichia coli.*** **Percentage of invasive isolates resistant to third-generation cephalosporins (cefotaxime/ceftriaxone/ceftazidime), by country, WHO European Region, 2021**

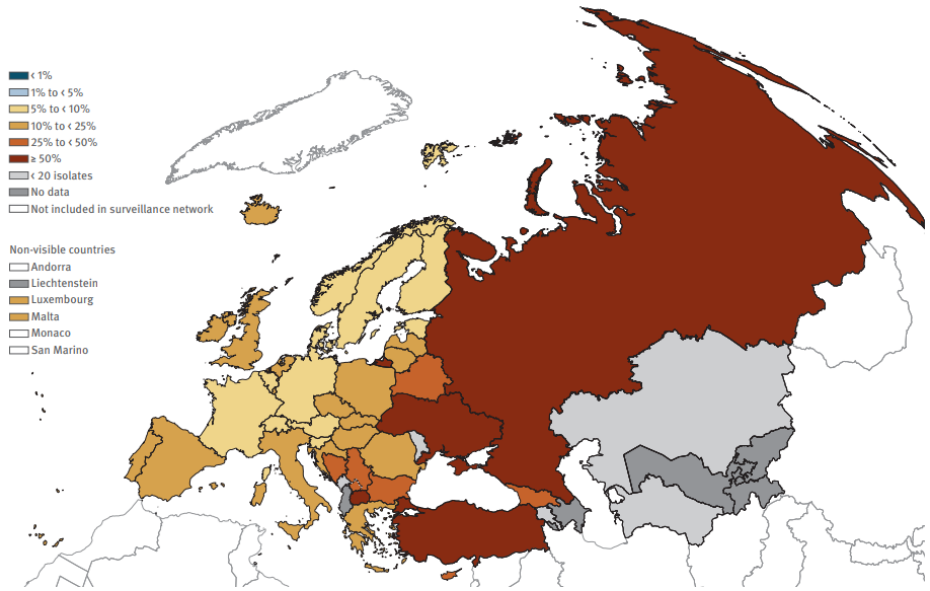
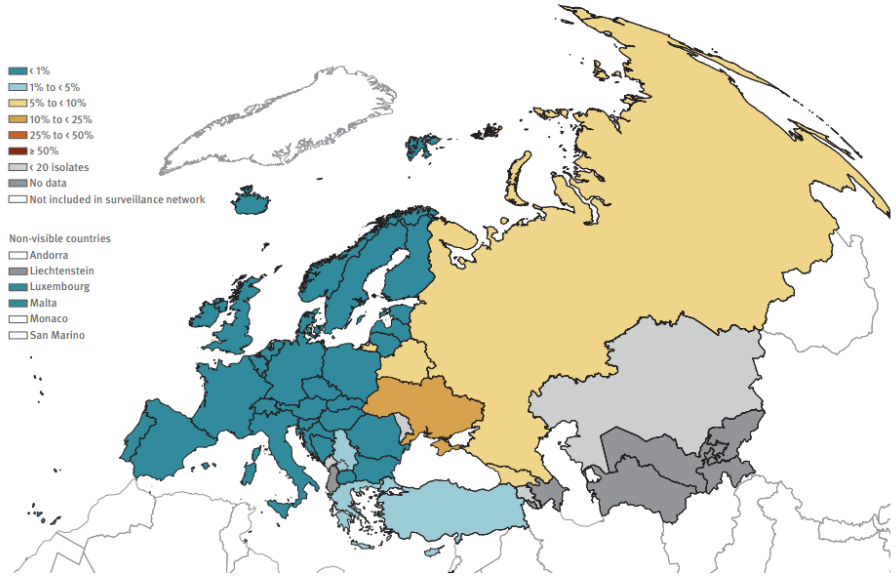


Fig. 3 ***Escherichia coli.*** **Percentage of invasive isolates resistant to carbapenems (imipenem/meropenem), by country, WHO European Region, 2021**



ecdc
EUROPEAN CENTRE FOR DISEASE PREVENTION AND CONTROL

World Health Organization
European Region

Fig. 4 *Klebsiella pneumoniae*. Percentage of invasive isolates resistant to third-generation cephalosporins (cefotaxime/ceftriaxone/ceftazidime), by country, WHO European Region, 2021

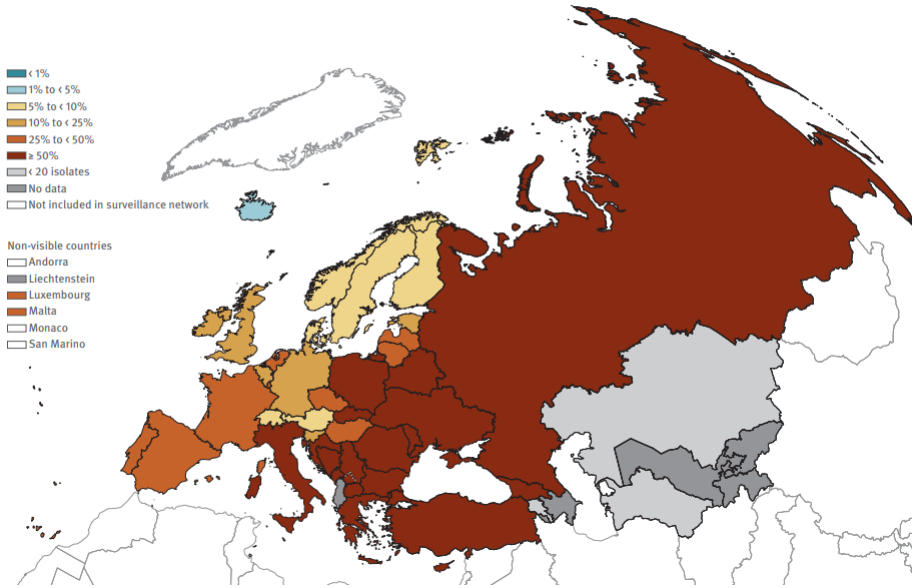
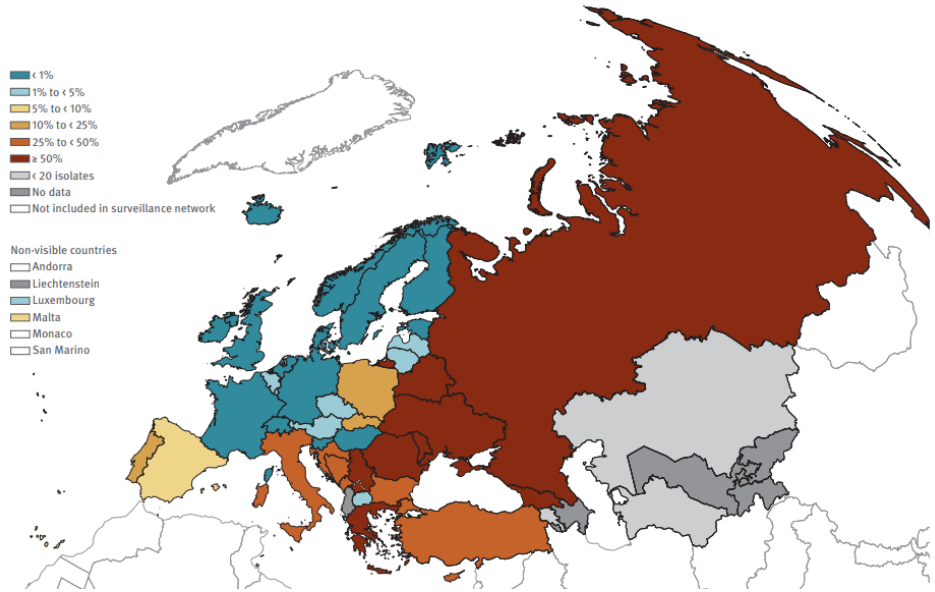


Fig. 5 *Klebsiella pneumoniae*. Percentage of invasive isolates resistant to carbapenems (imipenem/meropenem), by country, WHO European Region, 2021



ecdc EUROPEAN CENTRE FOR DISEASE PREVENTION AND CONTROL

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Fig. 6 *Pseudomonas aeruginosa*. Percentage of invasive isolates with resistance to carbapenems (imipenem/meropenem), by country, WHO European Region, 2021

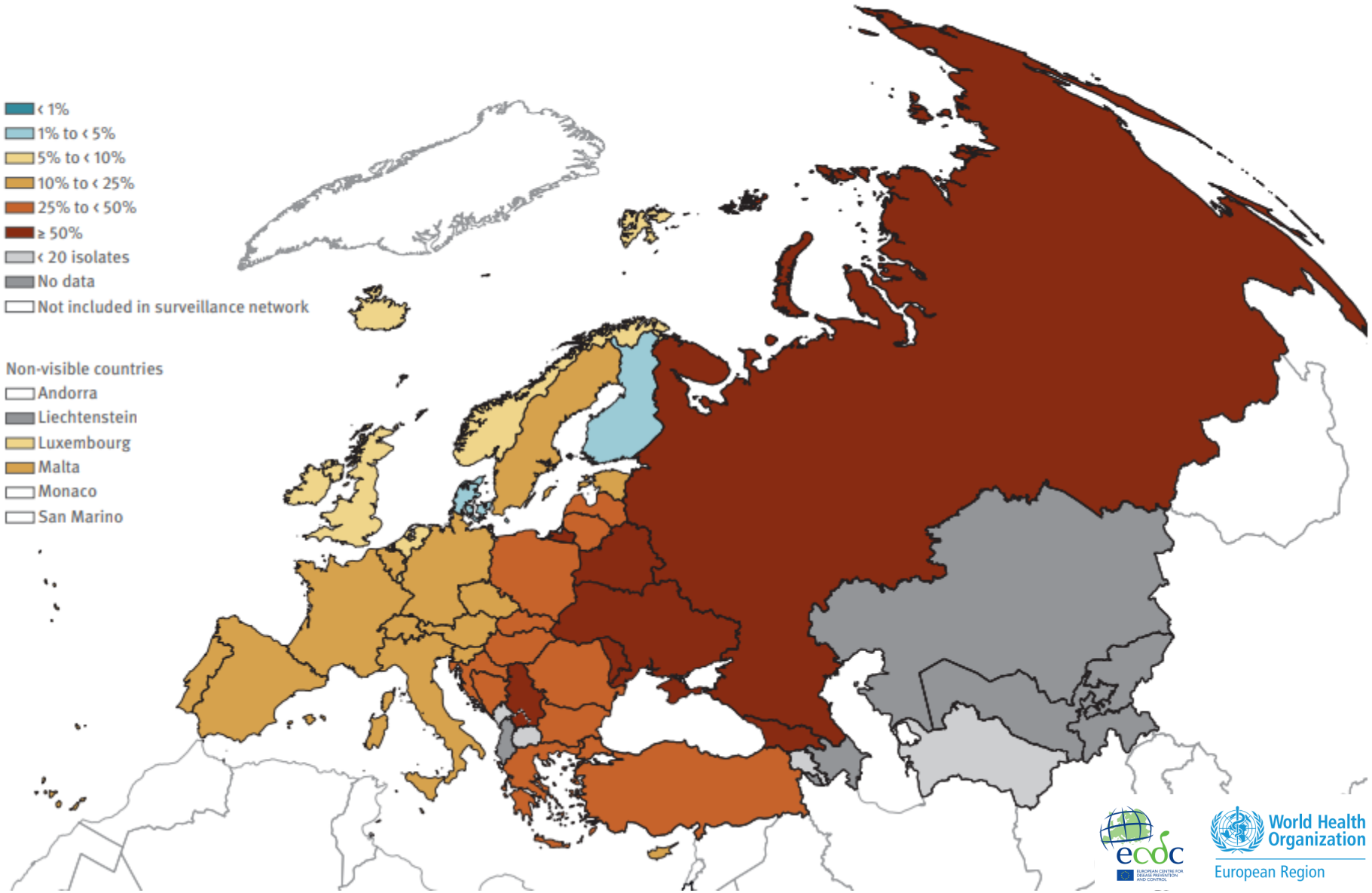


Fig. 7 *Acinetobacter* species. Percentage of invasive isolates with resistance to carbapenems (imipenem/meropenem), by country, WHO European Region, 2021

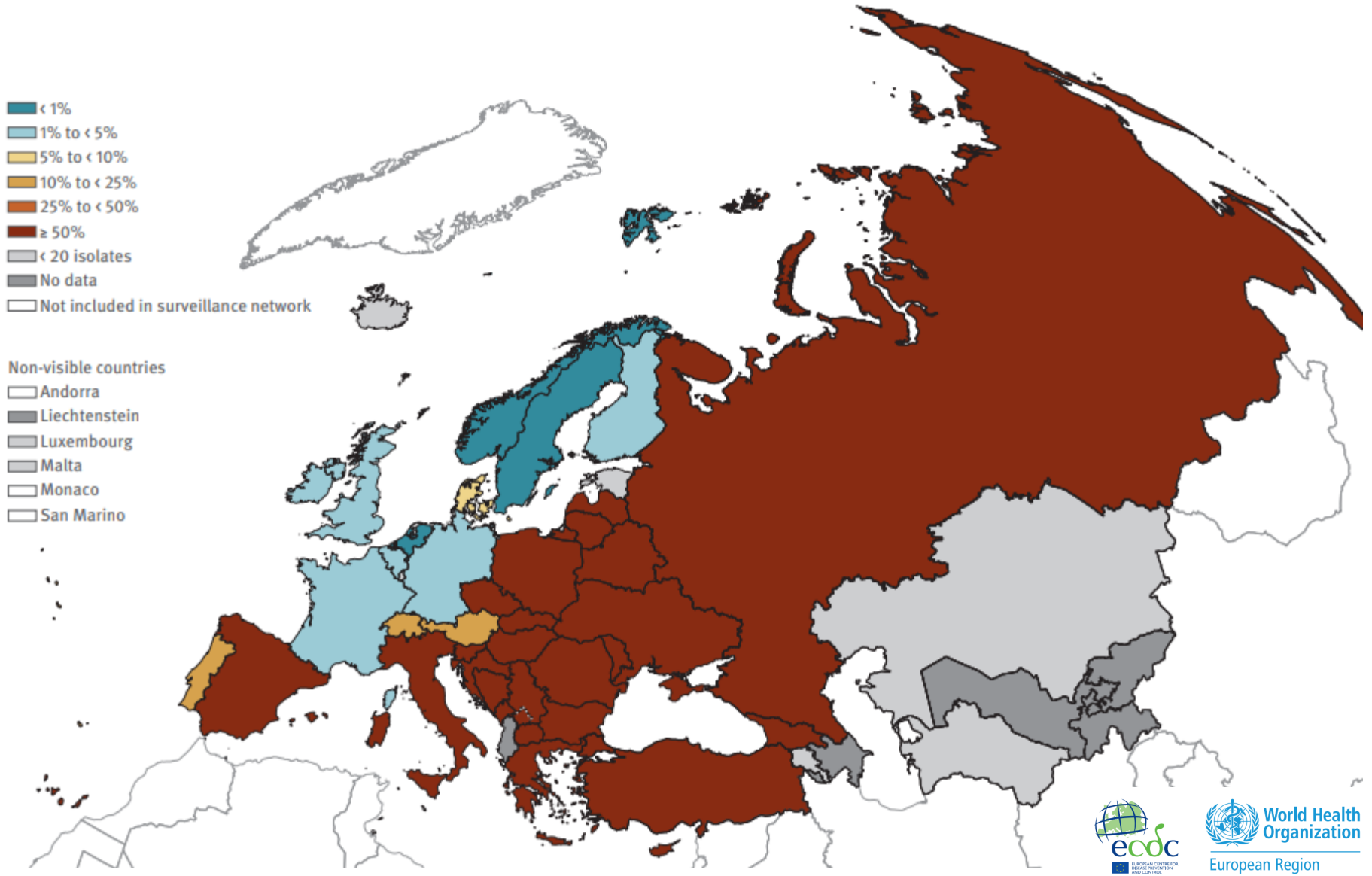


Fig. 8 *Staphylococcus aureus*. Percentage of invasive isolates resistant to meticillin (MRSA),[a] by country, WHO European Region, 2021

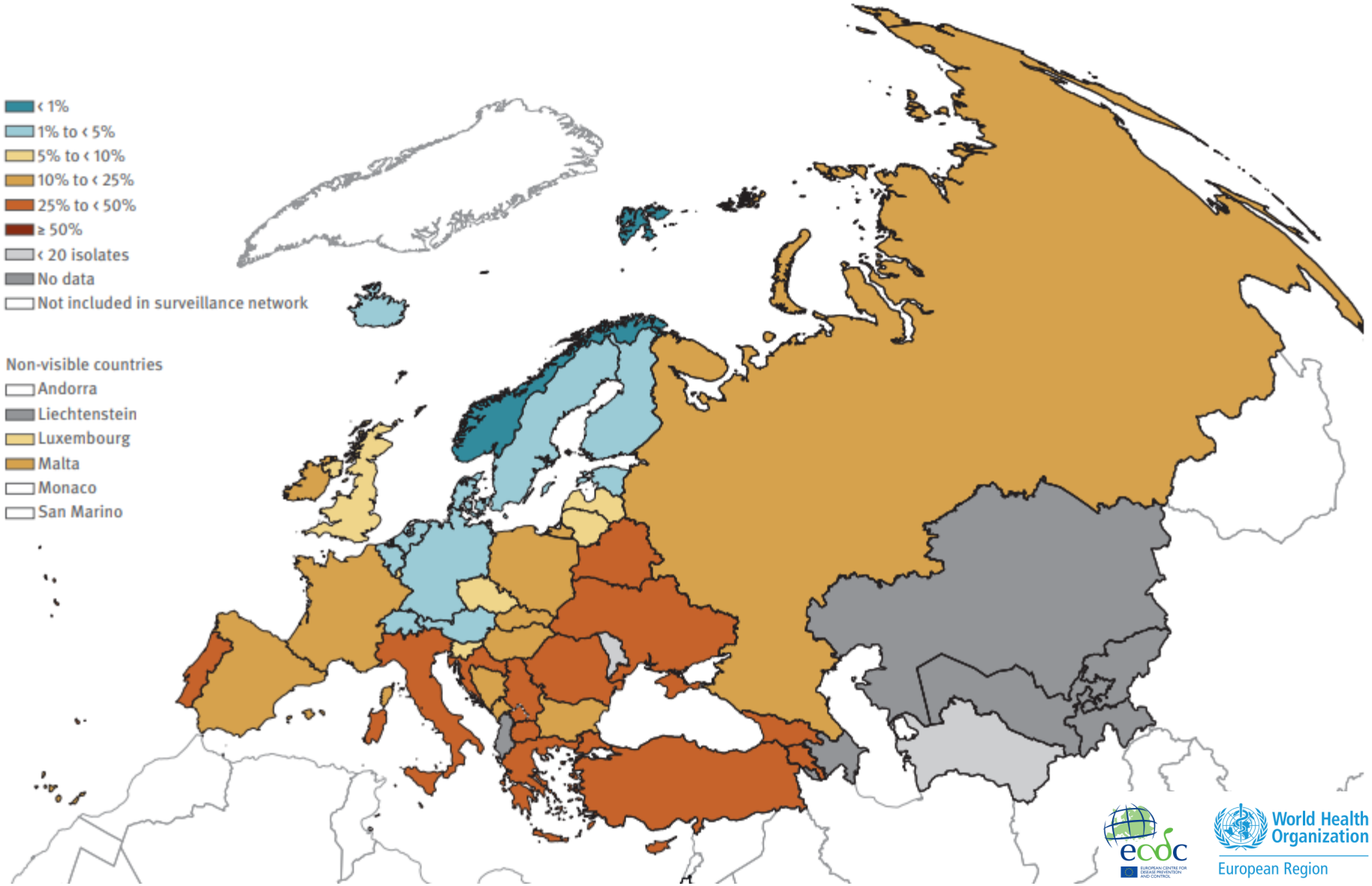


Fig. 9 *Streptococcus pneumoniae*. Percentage of penicillin[a] non-wild-type[b] invasive isolates, by country, WHO European Region, 2021

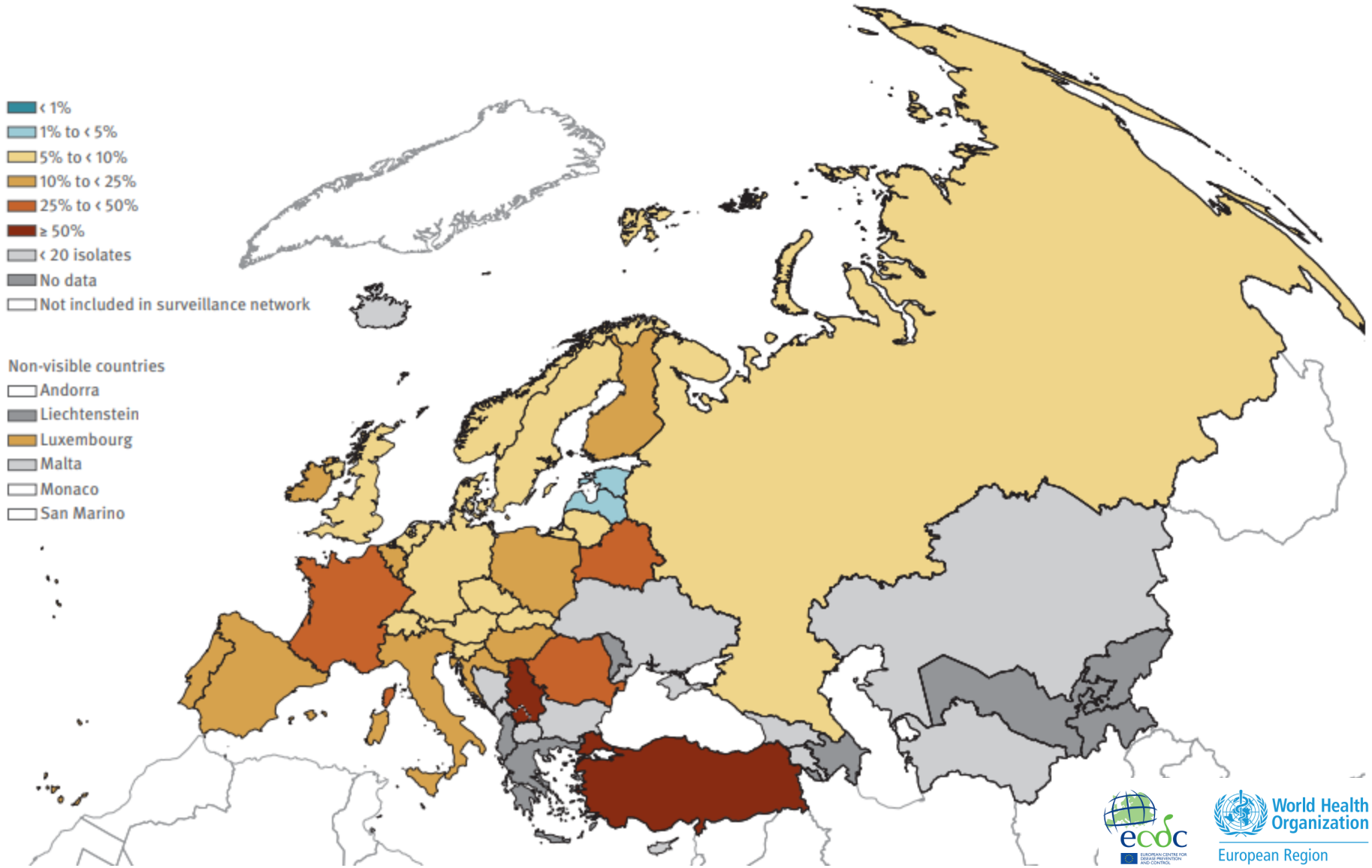
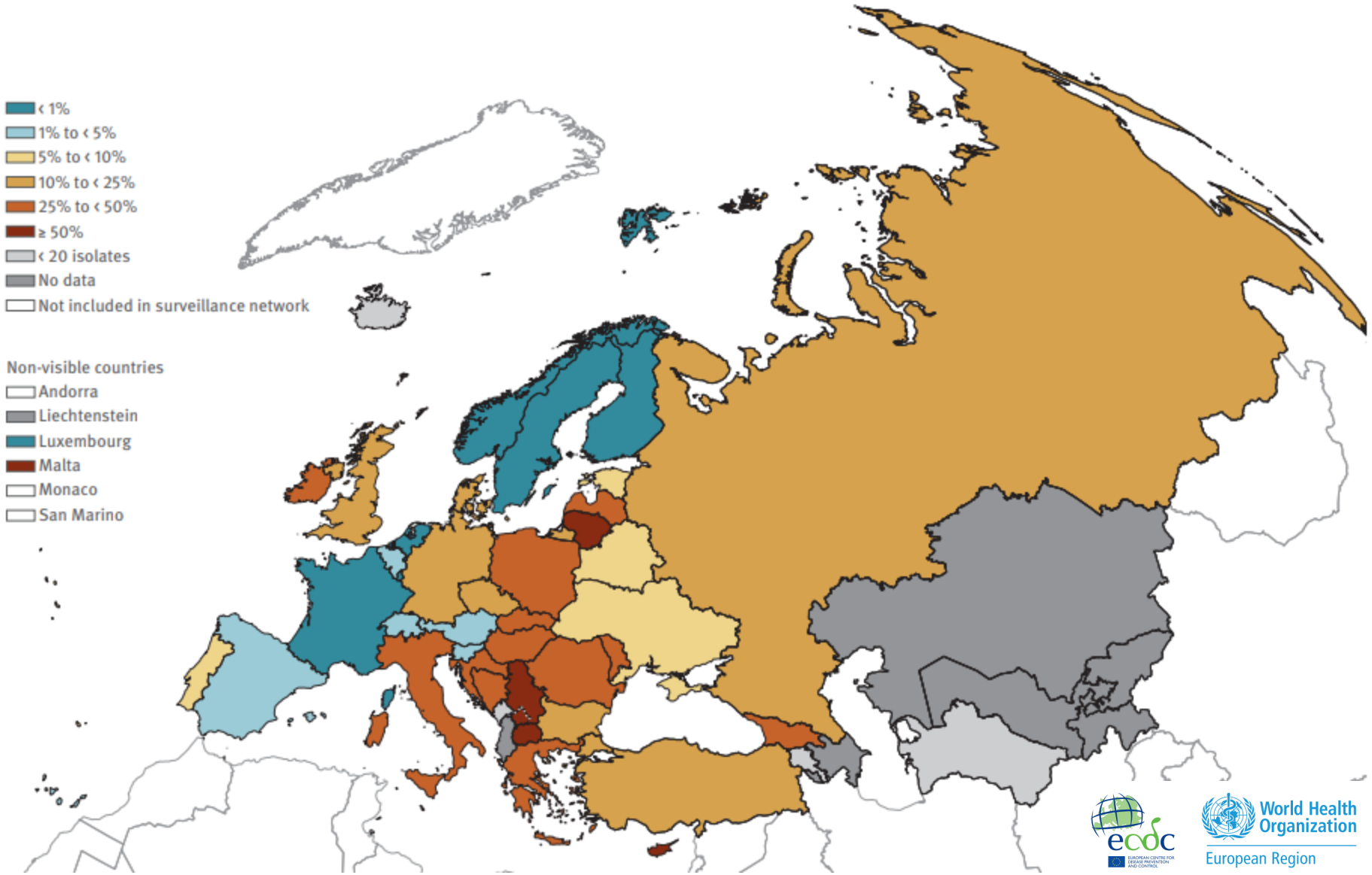


Fig. 10 ***Enterococcus faecium.*** **Percentage of invasive isolates resistant to vancomycin, by country, WHO European Region, 2021**



- ✓ **In the period from 2014 to 2020, the incidence of multidrug-resistant bacteria in war wounds in Ukraine was higher than that in Ukrainian civilian hospitals and other European countries.**

- ✓ **The detection of carbapenemase-producing Pseudomonas aeruginosa, Acinetobacter baumannii, and Klebsiella pneumoniae is of particular importance.**

- ✓ **Since March, 2022, the European Centers for Disease Control have advised that people with traumatic wounds in Ukraine might have multidrug-resistant A baumannii and K pneumoniae, among other multidrug-resistant organisms,8 and have recommended pre-emptive isolation and screening for carriage of multidrug-resistant bacteria (particularly carbapenem-restant Enterobacterales) for patients transferred from hospitals in Ukraine or with a history of hospital admission in Ukraine in the past 12 months**

Petrosillo N et al. Lancet Infect Dis 2023 Jun;23(6):653-654.

What is antimicrobial resistance?

Antibiotic resistance exhibited by bacteria can be intrinsic, acquired, or adaptive

- ***Intrinsic resistance*** **is defined as the resistance exhibited due to the inherent properties of the bacterium.**

Examples of intrinsic resistance include the glycopeptide resistance exhibited by Gram-negative bacteria due to the impermeability of the outer membrane present in the Gram-negative bacterial cell envelope.

- ***Acquired resistance*** **is defined as the resistance exhibited when a previously sensitive bacterium acquires a resistance mechanism by either a mutation or the acquisition of new genetic material from an exogenous source (horizontal gene transfer).**

Joon-Hee Lee.J Microbiol 2019 57(3):181–184

Antibiotic resistance exhibited by bacteria can be intrinsic, acquired, or adaptive

- ***Adaptive resistance*** **is defined as the resistance to one or more antibiotics induced by a specific environmental signal (e.g., stress, growth state, pH, concentrations of ions, nutrient conditions, sub-inhibitory levels of antibiotics).**

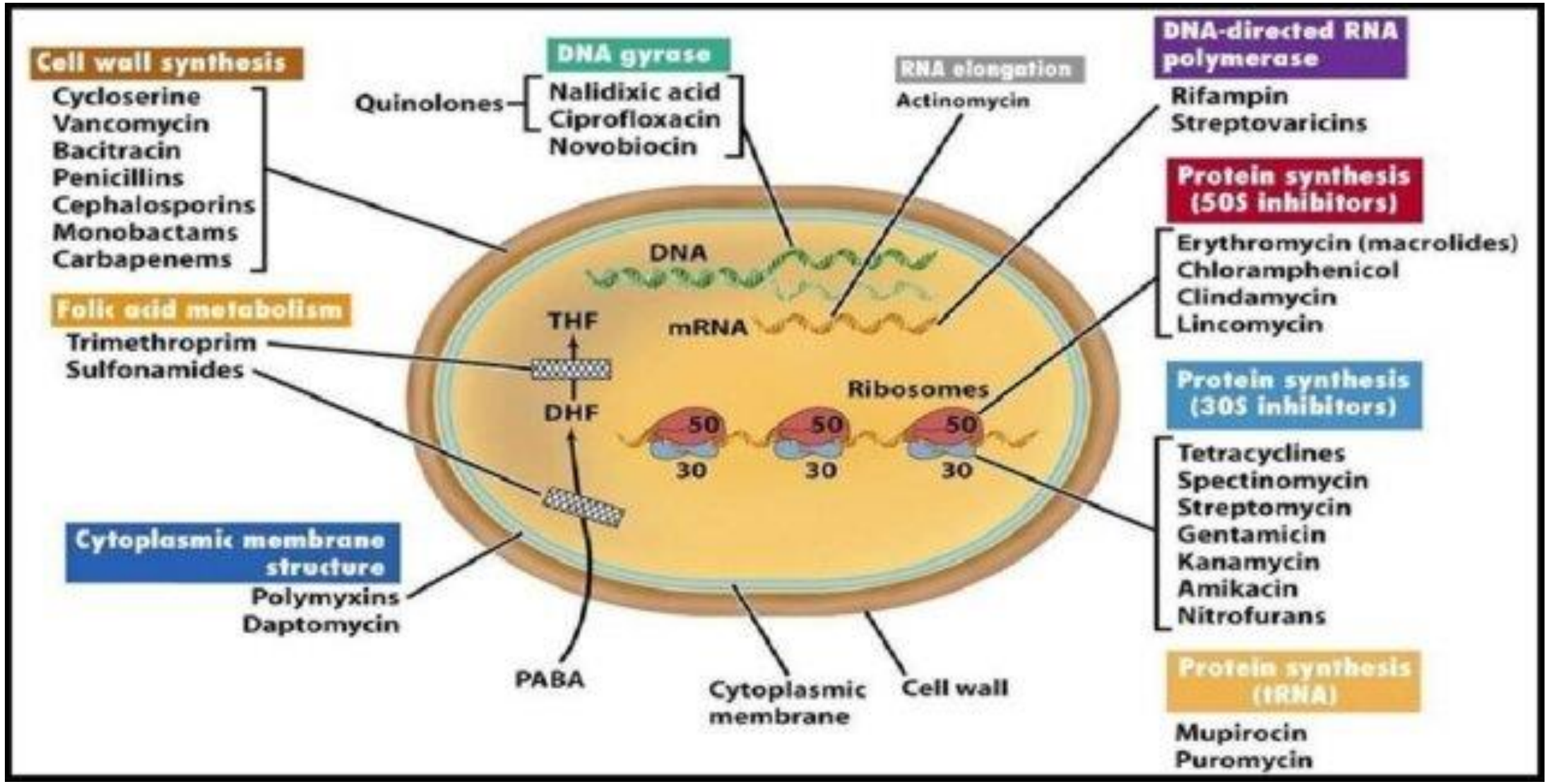
In contrast to intrinsic and acquired resistance, adaptive resistance is transient.

Adaptive resistance, which allows bacteria to respond more rapidly to antibiotic challenge, generally reverts to the original state once the inducing signal is removed.

Adaptive resistance seems to be the result of modulations in gene expression as a response to environmental changes.

In particular, modulation of the expression of efflux pumps and porins have been implicated in the emergence of adaptive resistance

Joon-Hee Lee.J Microbiol 2019 57(3):181–184


Cell wall synthesis
Cycloserine
Vancomycin
Bacitracin
Penicillins
Cephalosporins
Monobactams
Carbapenems
DNA gyrase
Quinolones
Nalidixic acid
Ciprofloxacin
Novobiocin
RNA elongation
Actinomycin
DNA-directed RNA polymerase
Rifampin
Streptovaricins
Protein synthesis (50S inhibitors)
Erythromycin (macrolides)
Chloramphenicol
Clindamycin
Lincomycin
Folic acid metabolism
Trimethroprim
Sulfonamides
DNA
mRNA
THF
DHF
Ribosomes
50
30
Protein synthesis (30S inhibitors)
Tetracyclines
Spectinomycin
Streptomycin
Gentamicin
Kanamycin
Amikacin
Nitrofurans
Cytoplasmic membrane structure
Polymyxins
Daptomycin
PABA
Cytoplasmic membrane
Cell wall
Protein synthesis (tRNA)
Mupirocin
Puromycin

MECHANISMS OF ANTIBIOTIC RESISTANCE

Generally speaking, there are 4 types of resistance mechanisms. These mechanisms include:

1. **Decreased drug accumulation by either decreased outer membrane permeability or increased active efflux of the drugs across the cell surface.**

2. **Drug inactivation or modification through production of enzymes that either destroy or alter the antibiotic, rendering it ineffective.**

3. **Alteration of target or binding sites such alteration of penicillin-binding proteins, or alteration of ribosomal-binding proteins.**

4. **Alteration of metabolic pathways, such as the ability of enterococci to absorb folic acid from the environment, which allows them to bypass the effects of trimethoprim-sulfamethoxazole.**

Morrison L et al. Gastrointest Endoscopy Clin N Am 2020; 30: 619–635

GENETIC BASIS OF ANTIMICROBIAL RESISTANCE

- ✓ **Bacteria have a remarkable genetic plasticity that allows them to respond to a wide array of environmental threats, including the presence of antibiotic molecules that may jeopardize their existence.**

- ✓ **Bacteria sharing the same ecological niche with antimicrobial-producing organisms have evolved ancient mechanisms to withstand the effect of the harmful antibiotic molecule and, consequently, their intrinsic resistance permits them to thrive in its presence.**

GENETIC BASIS OF ANTIMICROBIAL RESISTANCE

From an evolutionary perspective, bacteria use two major genetic strategies to adapt to the antibiotic "attack":

(i) mutations in gene(s) often associated with the mechanism of action of the compound

and

(ii) acquisition of foreign DNA coding for resistance determinants through horizontal gene transfer (HGT).

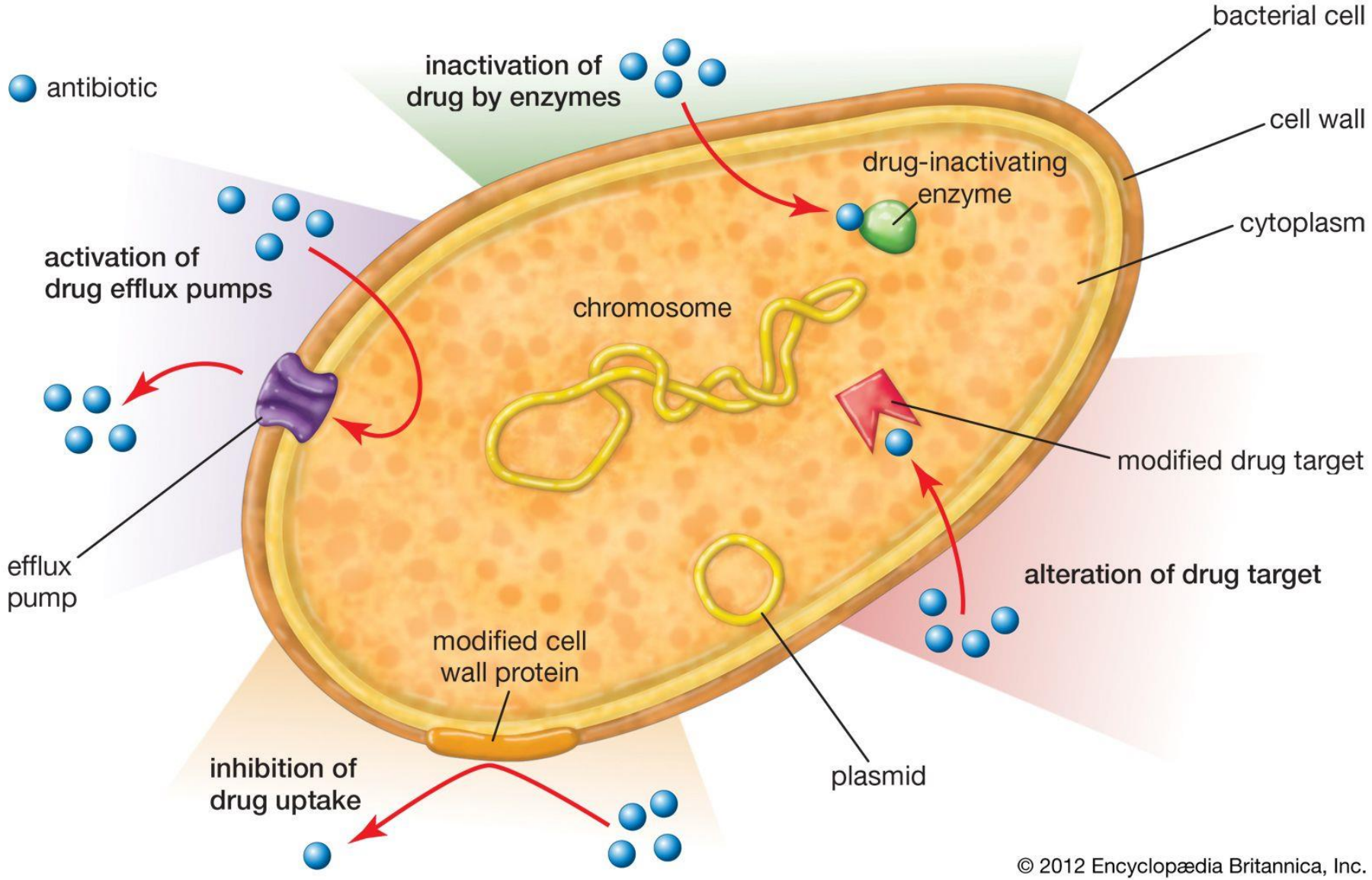
Mutational Resistance

- ✓ In this scenario, a subset of bacterial cells derived from a susceptible population develops mutations in genes that affect the activity of the drug, resulting in preserved cell survival in the presence of the antimicrobial molecule.

- ✓ Once a resistant mutant emerges, the antibiotic eliminates the susceptible population, and the resistant bacteria predominate.

- ✓ In many instances, mutational changes leading to resistance are costly to cell homeostasis (i.e., decreased fitness) and are only maintained if needed in the presence of the antibiotic.

Examples of mechanisms of antibiotic resistance

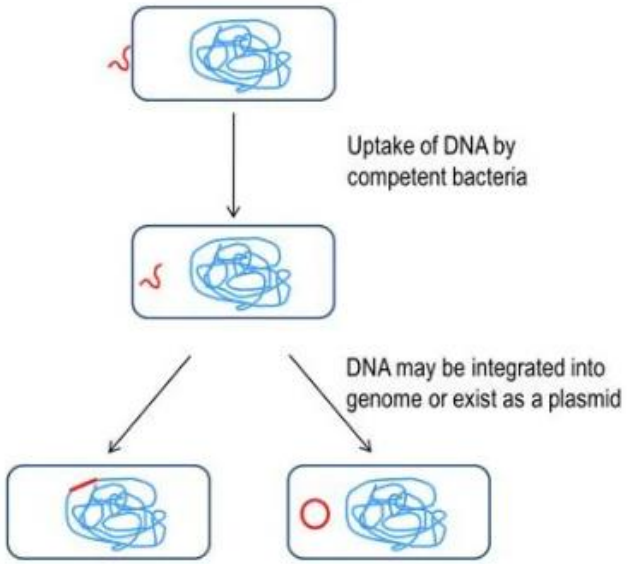


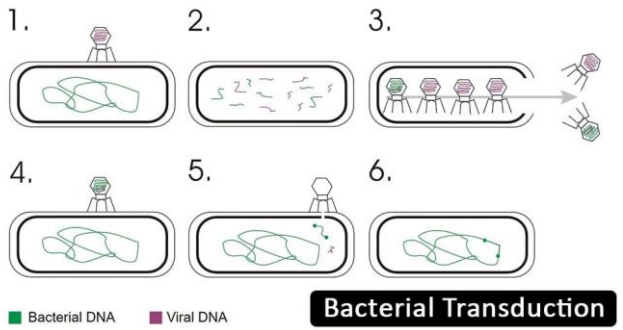
Horizontal Gene Transfert (HGT)

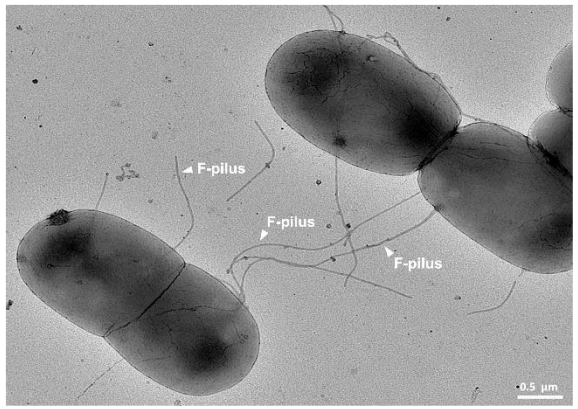
- ✓ Acquisition of foreign DNA material through HGT is one of the most important drivers of bacterial evolution, and it is frequently responsible for the development of antimicrobial resistance.
- ✓ Most antimicrobial agents used in clinical practice are (or derive from) products naturally found in the environment (mostly soil).
- ✓ Bacteria sharing the environment with these molecules harbor intrinsic genetic determinants of resistance, and there is robust evidence suggesting that such "environmental resistome" is a prolific source of the acquisition of antibiotic resistance genes in clinically relevant bacteria.
- ✓ Furthermore, this genetic exchange has been implicated in the dissemination of resistance to many frequently used antibiotics.

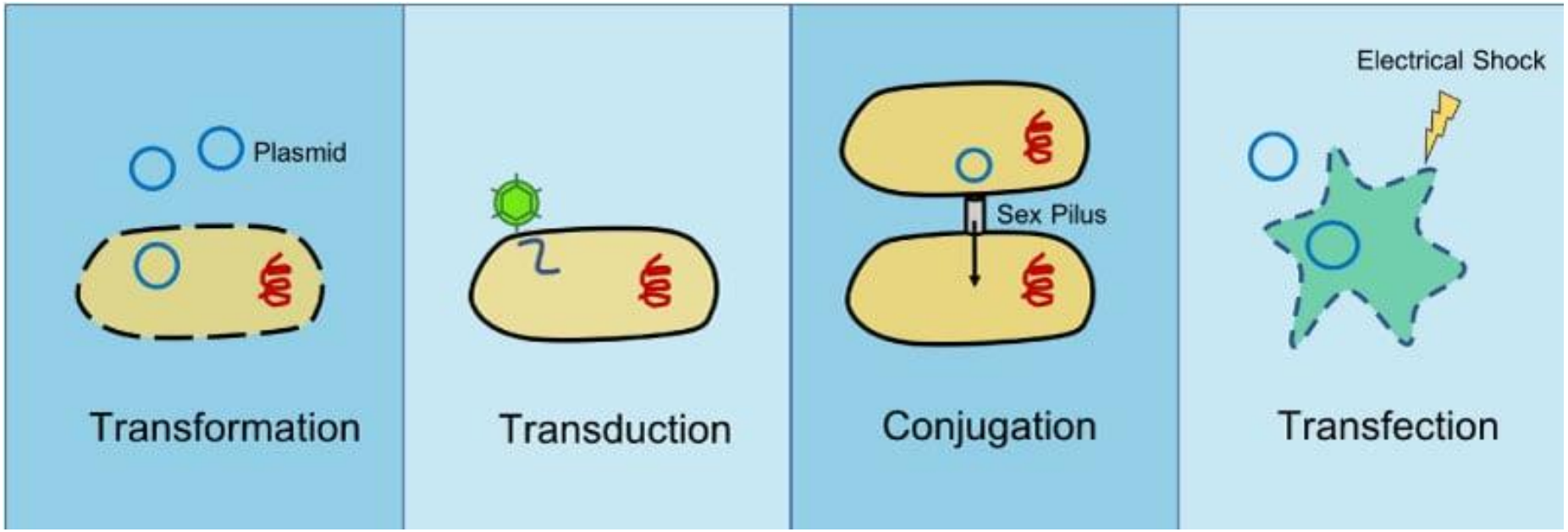
Classically, bacteria acquire external genetic material through three main strategies:

(i) transformation (incorporation of naked DNA),
(ii) transduction (phage mediated), and
(iii) conjugation (bacterial "sex").








Plasmid
Transformation
Transduction
Sex Pilus
Conjugation
Electrical Shock
Transfection

- ✓ **Transformation is perhaps the simplest type of HGT, but only a handful of clinically relevant bacterial species are able to naturally incorporate naked DNA to develop resistance.**

- ✓ **Emergence of resistance in the hospital environment often involves conjugation, a very efficient method of gene transfer that involves cell-to-cell contact and is likely to occur at high rates in the gastrointestinal tract of humans under antibiotic treatment.**

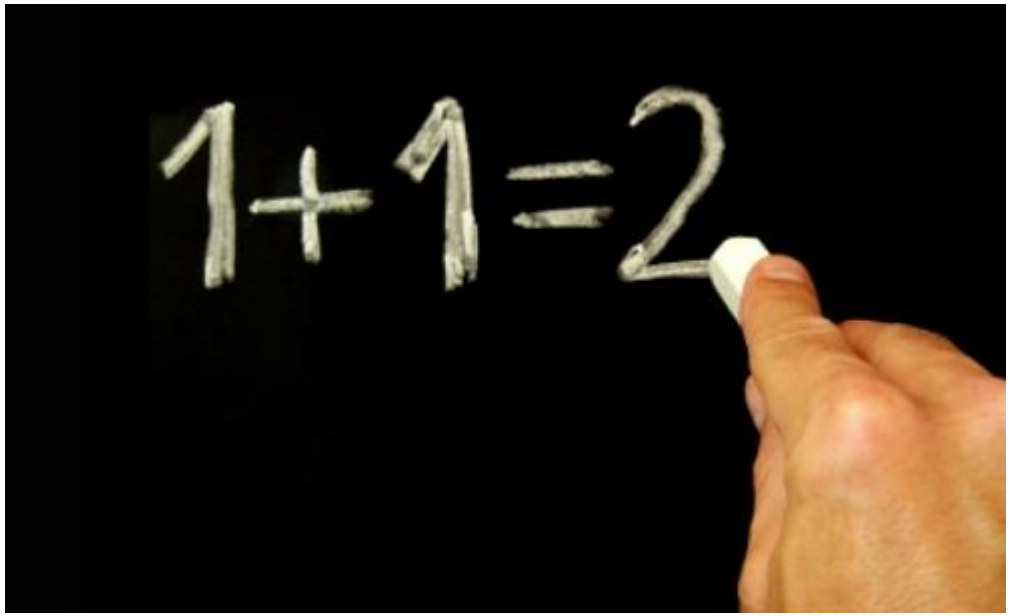
- ✓ As a general rule, conjugation uses mobile genetic elements (MGEs) as vehicles to share valuable genetic information, although direct transfer from chromosome to chromosome has also been well characterized.

- ✓ The most important MGEs are plasmids and transposons, both of which play a crucial role in the development and dissemination of antimicrobial resistance among clinically relevant organisms.

- ✓ **Finally, one of the most efficient mechanisms for accumulating antimicrobial resistance genes is represented by integrons, which are site-specific recombination systems capable of recruiting open reading frames in the form of mobile gene cassettes.**

- ✓ **Integrons provide an efficient and rather simple mechanism for the addition of new genes into bacterial chromosomes, along with the necessary machinery to ensure their expression: a robust strategy of genetic interchange and one of the main drivers of bacterial evolution.**

How simple is antimicrobial resistance?



Antibiotic Resistance Is Prevalent in an Isolated Cave Microbiome

- ✓ **Antibiotic resistance is a global challenge that impacts all pharmaceutically used antibiotics.**
- ✓ **The origin of the genes associated with this resistance is of significant importance to our understanding of the evolution and dissemination of antibiotic resistance in pathogens.**
- ✓ **A growing body of evidence implicates environmental organisms as reservoirs of these resistance genes; however, the role of anthropogenic use of antibiotics in the emergence of these genes is controversial.**

Bhullar K et al. PLoS One 2012;7(4):e34953.

Antibiotic Resistance Is Prevalent in an Isolated Cave Microbiome

- ✓ The AA. report a screen of a sample of the culturable microbiome of Lechuguilla Cave, New Mexico, in a region of the cave that has been isolated for over 4 million years.

- ✓ They report that, like surface microbes, these bacteria were highly resistant to antibiotics; some strains were resistant to 14 different commercially available antibiotics.

- ✓ Resistance was detected to a wide range of structurally different antibiotics including daptomycin, an antibiotic of last resort in the treatment of drug resistant Gram-positive pathogens.

- ✓ Enzyme-mediated mechanisms of resistance were also discovered for natural and semi-synthetic macrolide antibiotics via glycosylation and through a kinase-mediated phosphorylation mechanism.

Bhullar K et al. PLoS One 2012;7(4):e34953.

Antibiotic Resistance Is Prevalent in an Isolated Cave Microbiome

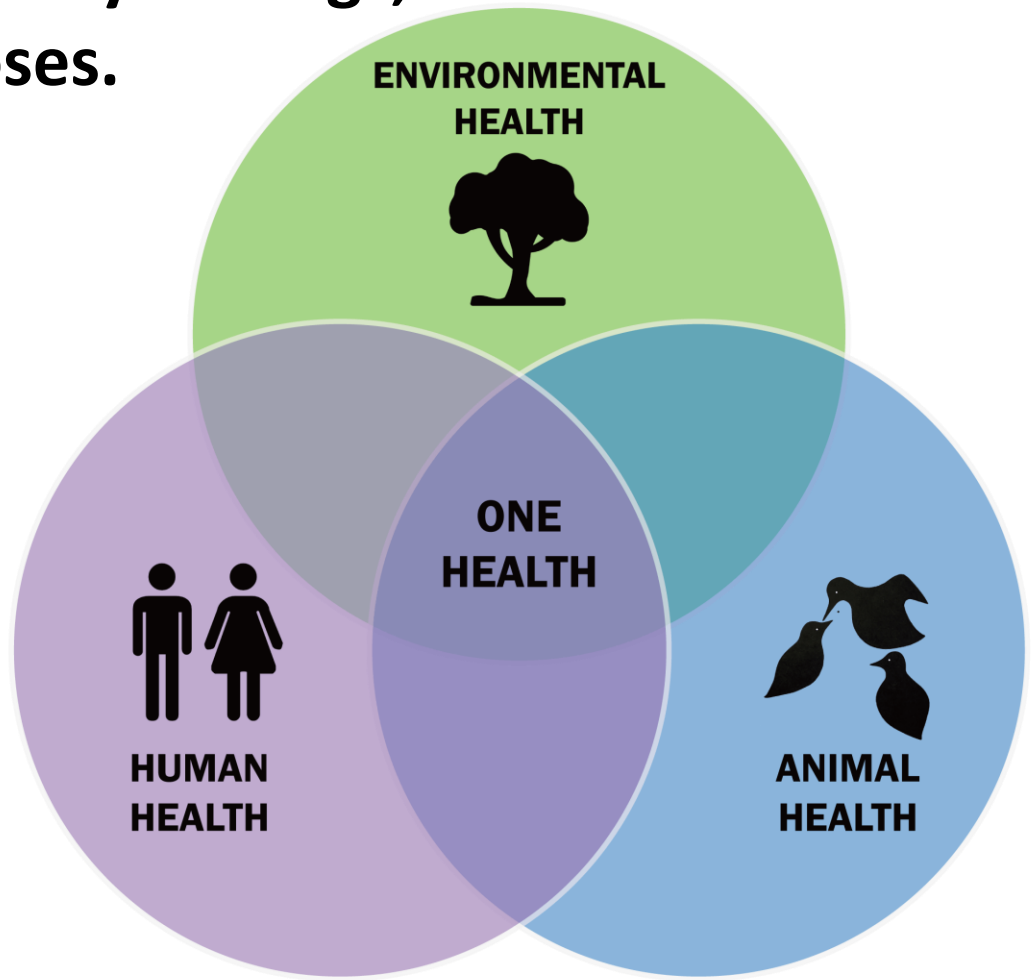
- ✓ **Sequencing of the genome of one of the resistant bacteria identified a macrolide kinase encoding gene and characterization of its product revealed it to be related to a known family of kinases circulating in modern drug resistant pathogens.**

- ✓ **The implications of this study are significant to our understanding of the prevalence of resistance, even in microbiomes isolated from human use of antibiotics.**

- ✓ **This supports a growing understanding that antibiotic resistance is natural, ancient, and hard wired in the microbial pangenome**

Bhullar K et al. PLoS One 2012;7(4):e34953.

Currently, the major drivers behind the occurrence and spread of antimicrobial resistance are represented by the use of antibiotics in human and veterinary settings, and in the environment, mainly for agricultural purposes.



- ✓ **The healthcare setting represents the melting pot and the sounding board for several multidrug-resistant orgasnisms.**

- ✓ **Indeed, while antimicrobial overuse/misuse determines ecological pressure on bacteria and contributes to the emergence and selection of antimicrobial resistance, poor infection prevention and control procedures, overcrowding, understaffing, and limited of lacking antimicrobial stewardship programmes greatly contribute to the growth and the spread of life threatening organisms.**