Antimicrobial resistance of ESKAPE pathogens: occurrence factors and general concepts

Alessandra Cornacchia, WOAH CC FH IZS-Teramo, Italy

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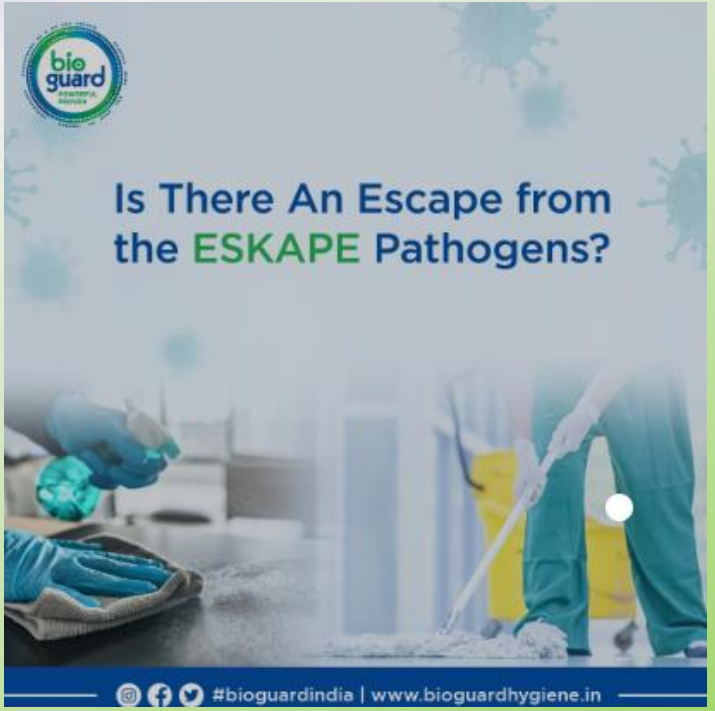
"Detection and characterization of *Listeria monocytogenes*, *Klebsiella pneumoniae* and *Salmonella* spp."

Antimicrobial resistance

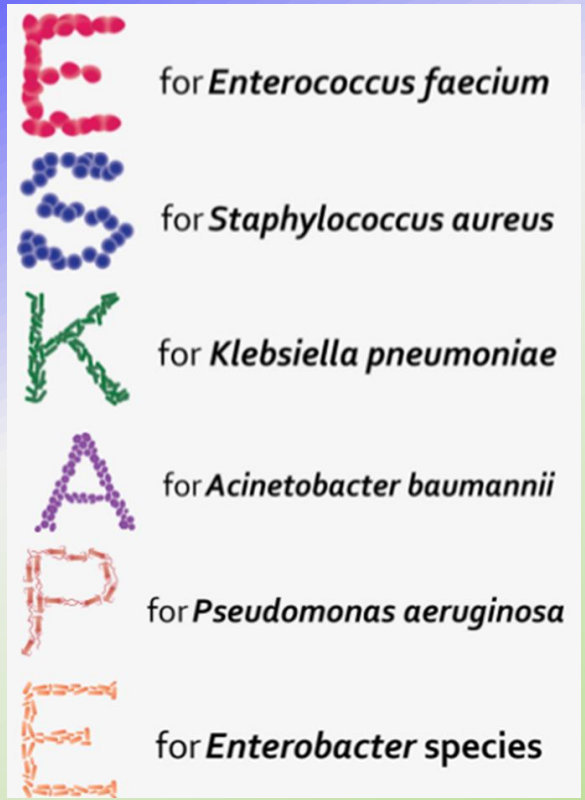
- Antimicrobial resistance (AMR) is one of the most serious public health threaths of the twenty-first century.
- Resistance to an antimicrobial agents has become a major source of morbidity and mortality worldwide.

ESKAPE Pathogens

- To systematize the surveillance and research on emerging drug-resistant pathogens, the World Health Organization (WHO) published a list of pathogens for which new effective treatment was urgently needed in February 2017.

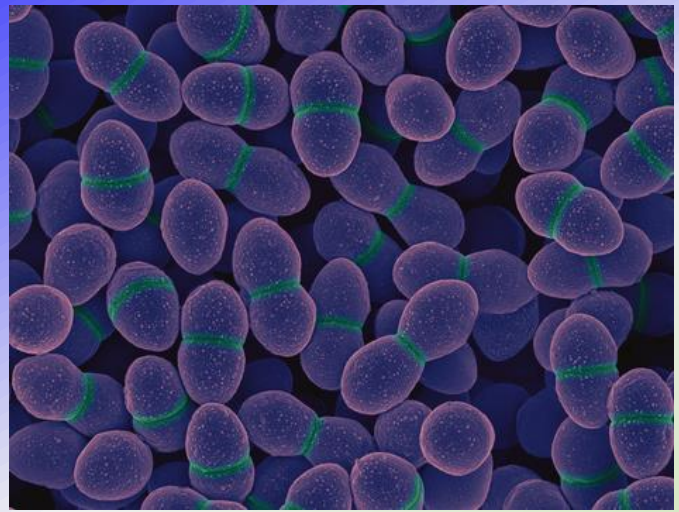


ESKAPE Pathogens



- According to the latest data from the Centers for Disease Control and Prevention (CDC), the six **ESKAPE** pathogens are responsible for two thirds of all health care-associated infections (HAIs).
- **ESKAPE** pathogens are considered the greatest threat for physicians, due to the emergence of strains that are resistant to all or most available antibiotics.

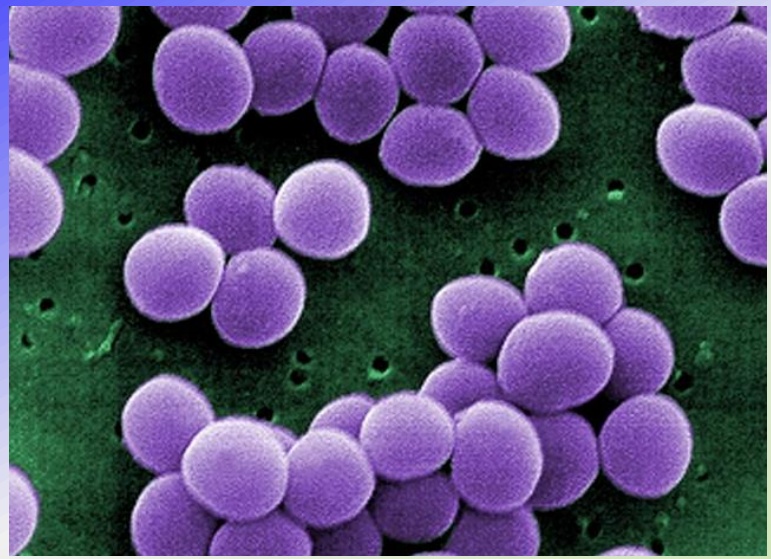
Enterococcus faecium



- Gram-positive cocci bacteria in the genus *Enterococcus* of the family *Enterococcaceae*.
- Being a part of the human microbiome, it is found in the gastrointestinal tract (GI tract) of humans.
- Can develop biofilm and hence are involved in medical device-associated infections.

Vancomycin-resistant strains of *E. faecium* (VR *E. faecium*) are reported as a major cause of device-associated infections like ventilator-associated pneumonia and other respiratory tract infections (RTIs), catheter-associated UTIs, catheter-associated surgical wound infections, and bloodstream infections.

Staphylococcus aureus MRSA



- *S. aureus* is a gram-positive, catalase-positive, facultatively anaerobic, cocci bacterium in the genus *Staphylococcus*.

- It is the most abundant normal flora of the skin and nasal cavity. However, it is frequently reported as opportunistic pathogens causing skin infections, food poisoning, UTIs, bacteremia, sepsis, RTIs, etc.

- *S. aureus* can develop biofilm in medical devices.

- Due to resistance to most available treatments account for the majority of nosocomial infections worldwide.

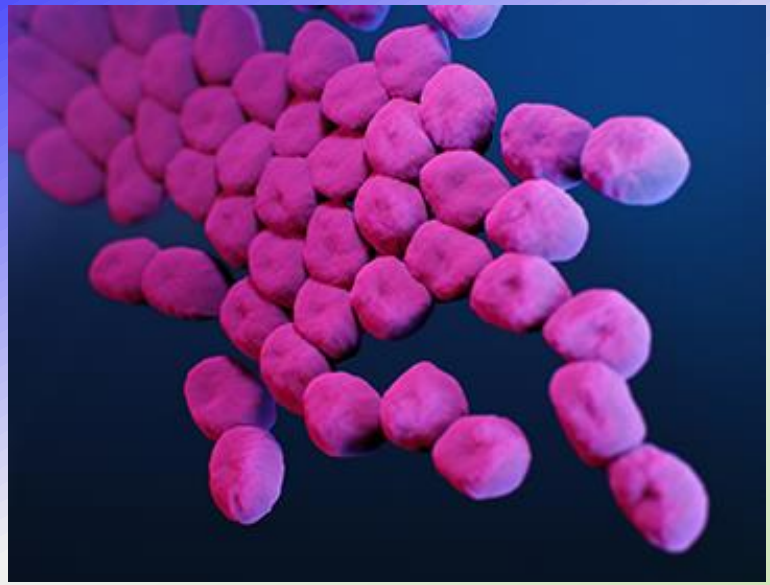
Methicillin-Resistant *Staphylococcus aureus* (MRSA) is the most common drug-resistant strain of *S. aureus*, accounting for almost 50% of Staphylococcal infections. MRSA is regarded as a superbug and is frequently associated with skin and soft tissue infections, UTIs, and sepsis.

Klebsiella pneumoniae

- *Kp* are intrinsically resistant to ampicillin.
- Resistance to most of ESBL extended-spectrum beta-lactams.
- **Carbapenem-Resistant *K. pneumoniae* (CRKP)** is the pathogen on the urgent threat list.

Usually susceptible only to colistin, tigecycline, some aminoglycosides and possibly miscellaneous agents like trimethoprim.

Acinetobacter baumannii

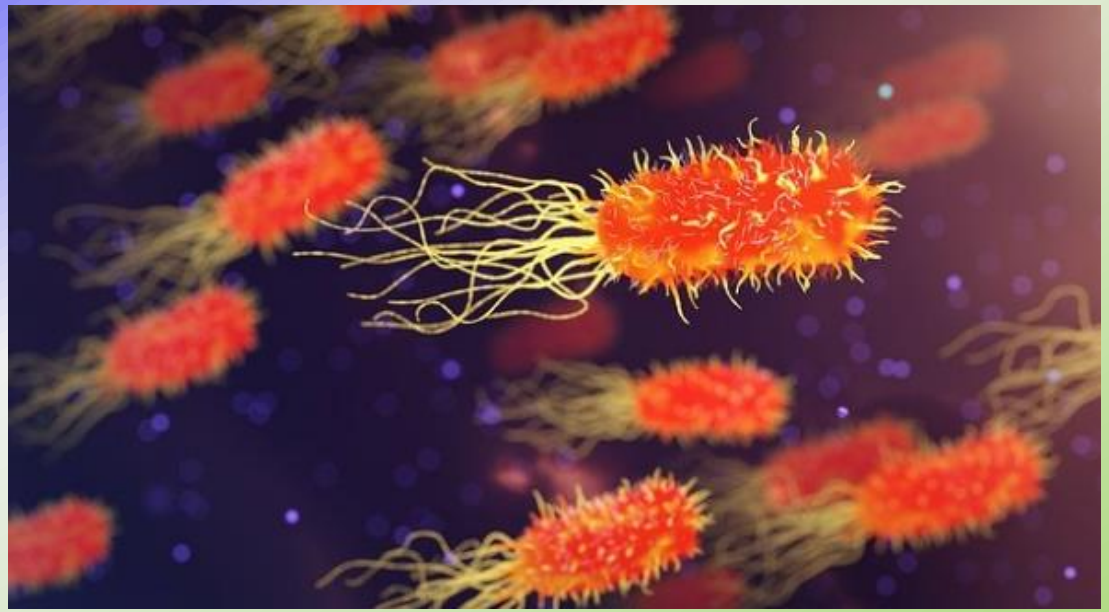


- *A. baumannii* is a Cocco-bacilli, Gram-negative bacteria in the genus *Acinetobacter* of the family *Moraxellaceae*.
- It is normally found in soil and water and as transient flora in human skin.
- Nosocomial infections by *A. baumannii*, specially RTIs, UTIs, and wound infections.

Carbapenem-Resistant *A. baumannii* (CRAB) is under the urgent threat list of WHO and CDC. CRAB is mainly associated with ventilator-associated pneumonia (VAP), UTIs, and wound infection in hospitalized patients.

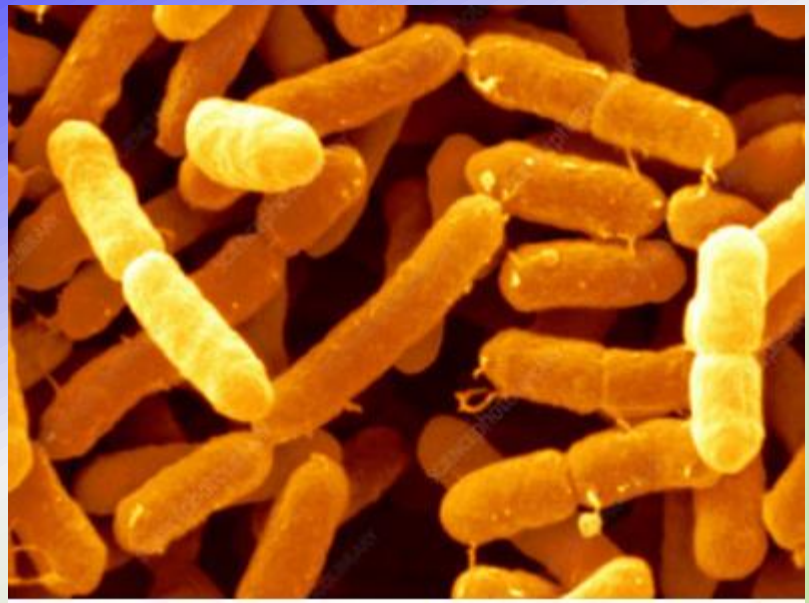
Pseudomonas aeruginosa

P. aeruginosa is a Gram-negative, rod-shaped, encapsulated bacteria of the genus *Pseudomonas* in the family *Pseudomonadaceae* of phylum *Pseudomonadota*.



- *P. aeruginosa* is an opportunistic nosocomial pathogen causing serious, RTIs, UTIs, blood and wounds infections.
- Can have a mortality rate of up to 60%.
- Resistant to carbapenems, ciprofloxacin and levofloxacin.

Enterobacter spp



• *Enterobacter* is a genus of Gram-negative, facultatively anaerobic, lactose-fermenting, rod-shaped bacteria of the family Enterobacteriaceae.

• *Enterobacter* includes several pathogenic species which mainly cause opportunistic infection in immune-compromised patients.: *E. aerogenes, E. cloacae,* and *E. sakazakii.*

•*Enterobacter spp*. are commonly associated with UTIs and RTIs.

• Multidrug-resistant species are resistant to most of the β-lactams and cephalosporins, which makes them very hard to treat.

Factors contributing to AMR

1. Environmental factors
2. Drug related factors
3. Patient related factors
4. Physician relatre factors

Factors contributing to AMR

1. Environmental factors

- Huge populations and overcrowding
- Rapid spread, increased national and international travelling
- Poor sanitation
- Increased community acquired resistance
- Ineffective infection control program
- Widespread use of antibiotics in animal husbandry and agriculture
- Land spreading of animal manure and sewage sludge
- Municipal and industrial wastewater

Factors contributing to AMR

2. Drug related factors

- Quality of the drug
- Soaring use of antimicrobials
- Availability of antimicrobials
- Irrational fixed dose combination of antimicrobials

3. Patient related factors

- Poor adherence of dosage regimens
- Poverty and lack of sanitation concepts
- Lack of education
- Self-medication

Factors contributing to AMR

4. Physician/prescriber related factors

- Inappropriate use of available drugs
- Increased empiric poly-antimicrobials use
- Overuse of antimicrobials
- Inadequate dosing
- Lack of current knowledge and training

We need to remember there is NATURAL resistance of bacteria against antimicrobials, so it is not fault on these four factors

AMR Mechanisms

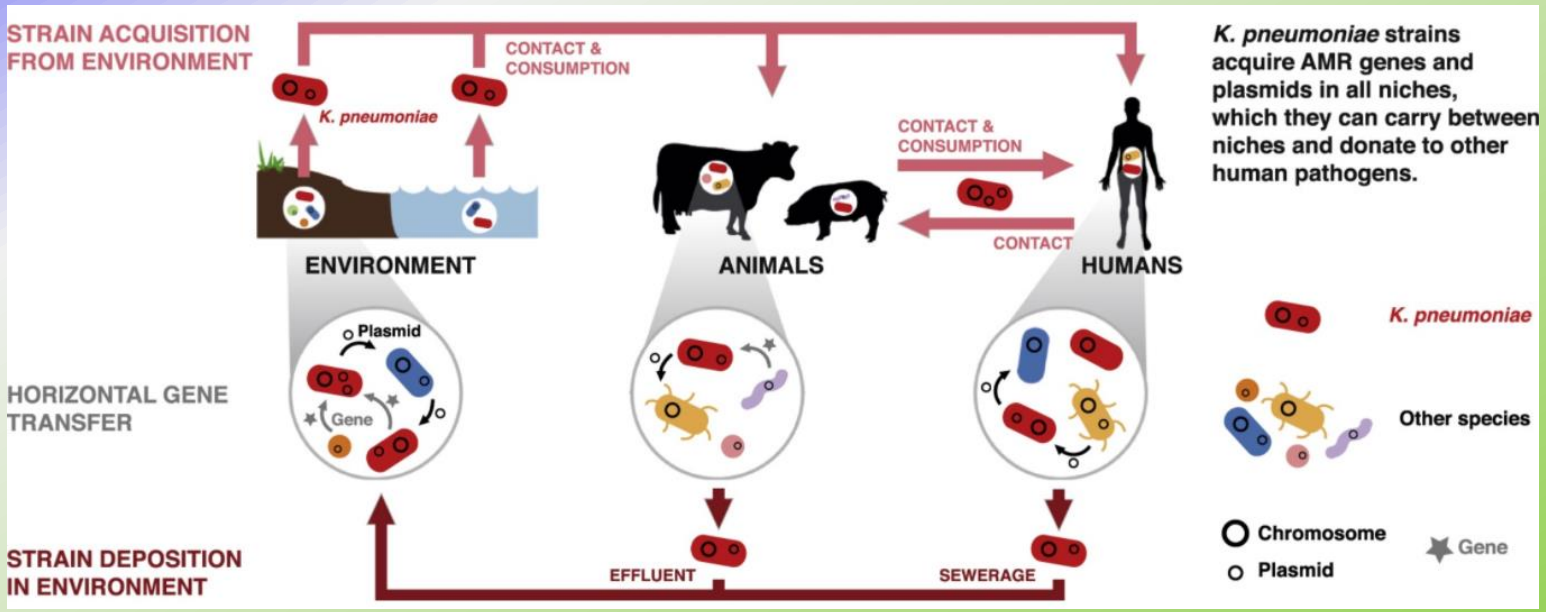
Antimicrobial resistance can be: **intrinsic** or **acquired.**

Intrinsic resistance: innate ability of a bacterium to resist to a class of antimicrobials. The most common bacterial mechanisms involved in intrinsic resistance are reduced permeability of the outer membrane (LPS) and the natural activity of efflux pumps.

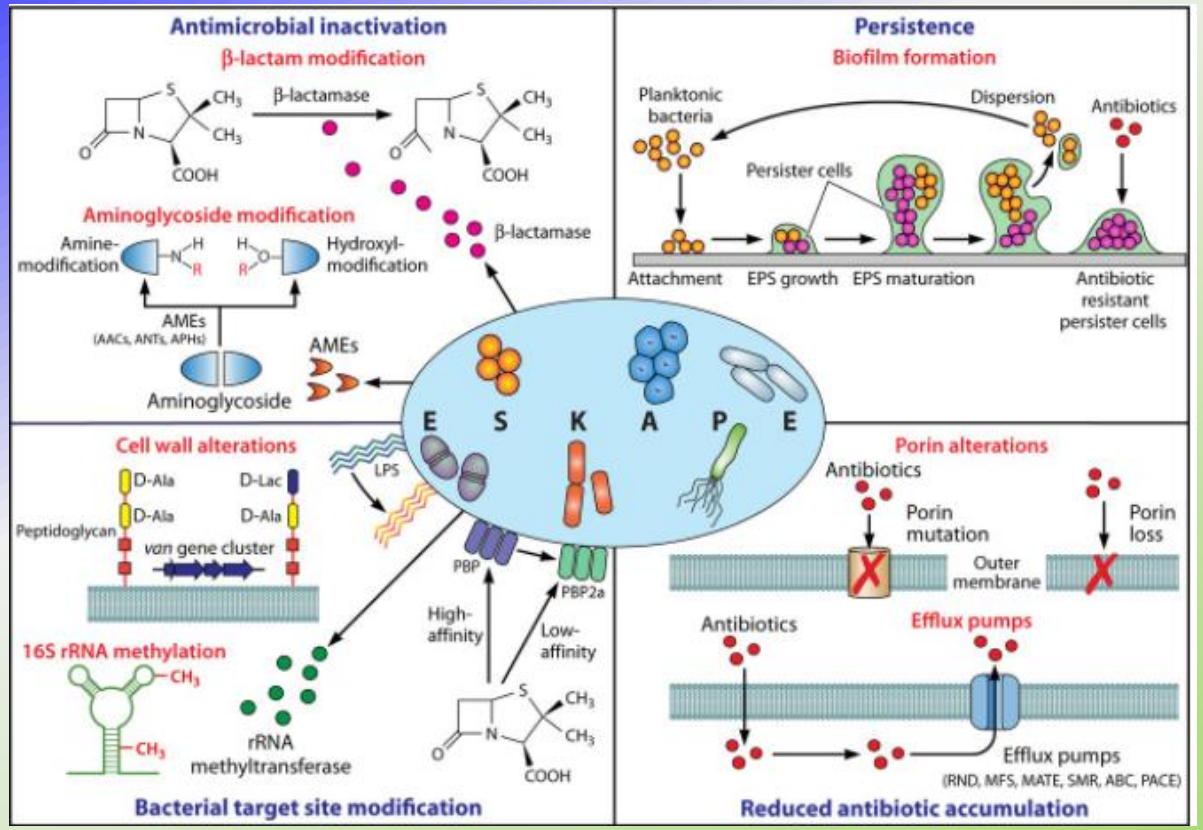
Acquired resistance: microorganism acquires ways to escape to the action of a drug. Acquisition of AMR genes via Horizontal Gene Transfer (HGT), mainly by PLASMIDS and MOBILE GENETIC ELEMENTS or by MUTATIONS to chromosomal DNA.

AMR Mechanisms

Model for AMR gene and plasmid trafficking by *K. pneumoniae*. Individual *K. pneumoniae* strains can move between niches in the environment, human and/or animal hosts, carrying with them acquired AMR genes and/or plasmids. Strains can move from the environment to human/animal hosts via contact or consumption of contaminated water sources or plant matter; between human and animal hosts via contact or consumption; and from hosts back to the environment via effluent or sewerage.



AMR Mechanisms

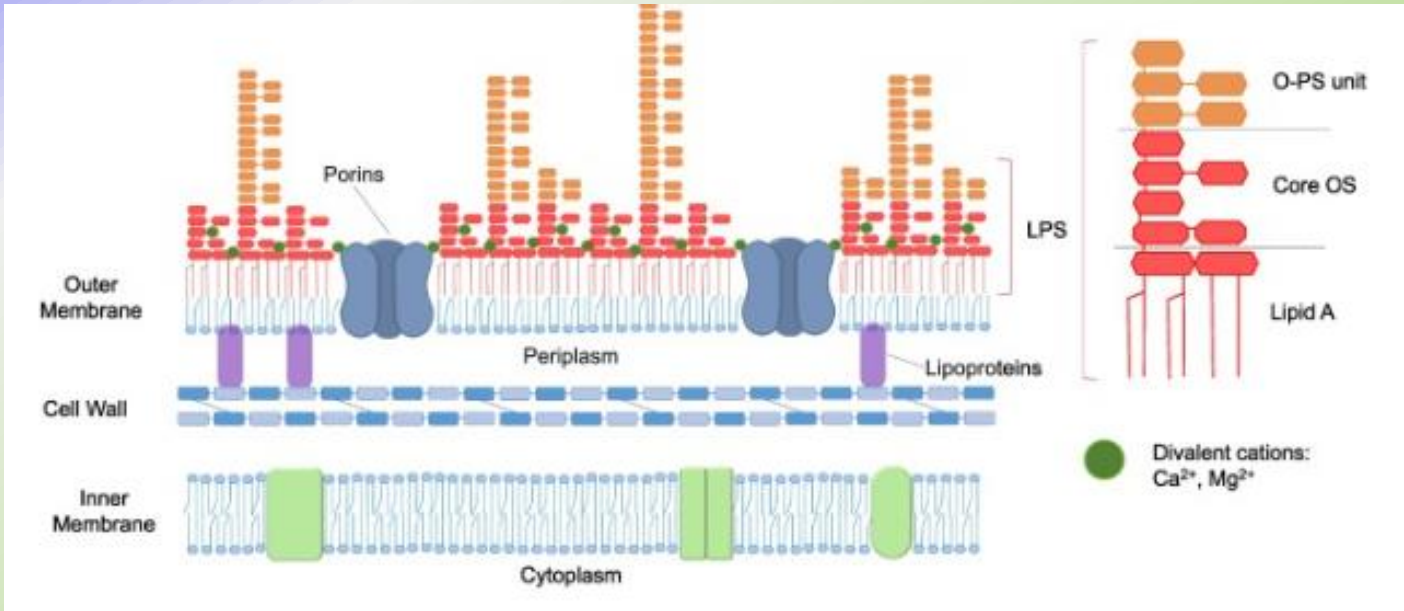


- Limiting uptake (natural)
- Antimicrobial inactivation
- Biofilm formation
- Bacterial target site modification
- Porin alterations and efflux pumps activation

Gram-negative make use of all these mechanisms. Gram-positive without a LPS less commonly use limitingthe uptake of a drug.

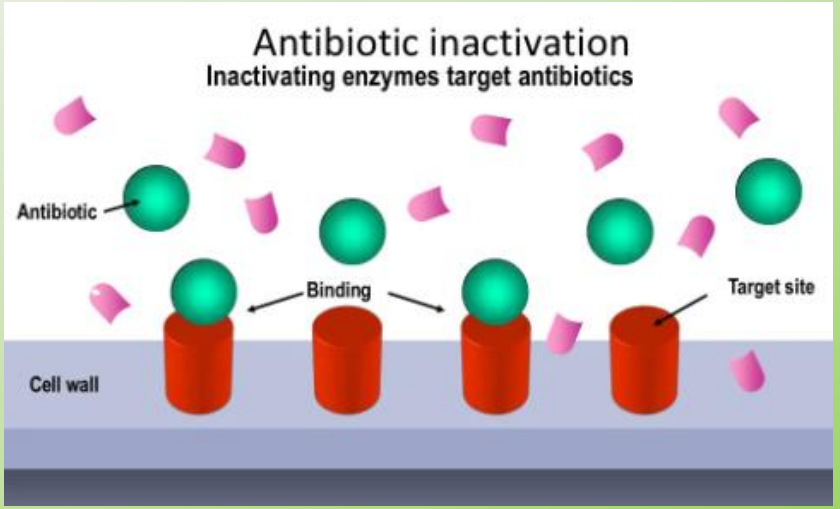
AMR Mechanisms: Limiting uptake of a drug

The structure and functions of the LPS layer present in Gram-negative bacteria provides a barrier to certain types of molecules

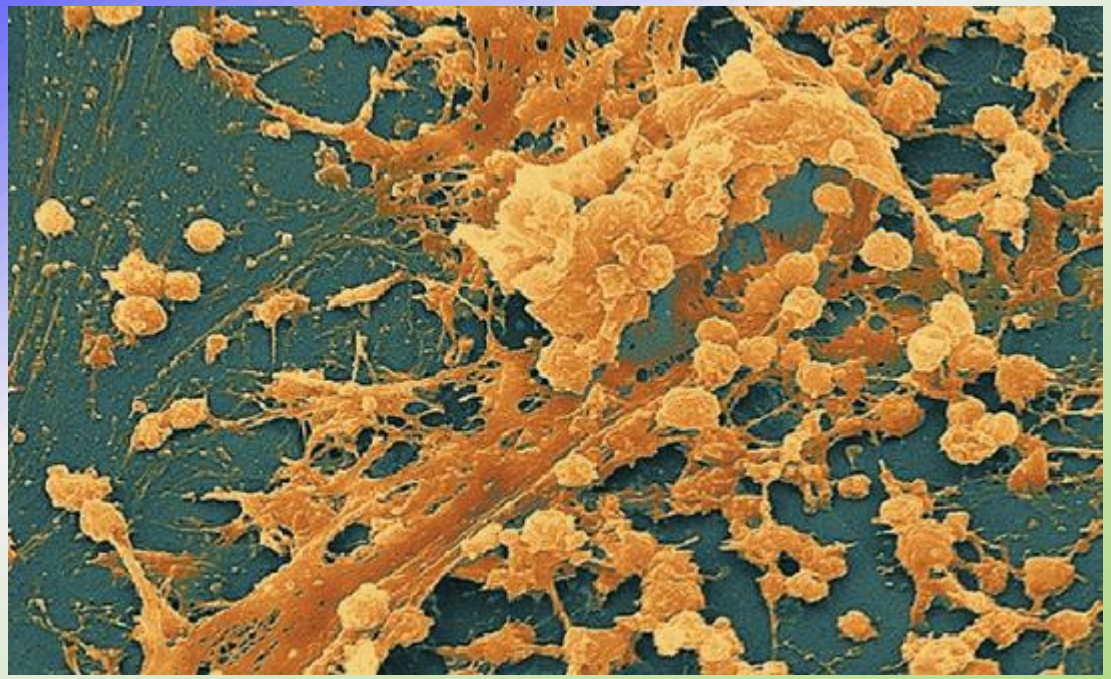


AMR Mechanisms: Antimicrobial inactivation

There are two main ways in which bacteria inactivate drugs by:
1- Degradation of the drug as β-lactamases a very large group of drug hydrolyzing enzymes.
2- Transfer of a chemical group to the drug (ex. Acetyl group). A large group of Transferase as been identified.



AMR Mechanisms: Biofilm formation



Biofilm is a complex structure of microbiome having different bacterial colonies or single type of cells in a group. These cells are embedded in extracellular polymeric substances, a matrix which is generally composed of eDNA, proteins and polysaccharides, showed high resistance to antibiotics.

Biofilm similarly enables bacterial tolerance to environmental threats, and also encourages the transfer of antibiotic resistance genes between bacterial species.

AMR Mechanisms: Bacterial target site modification

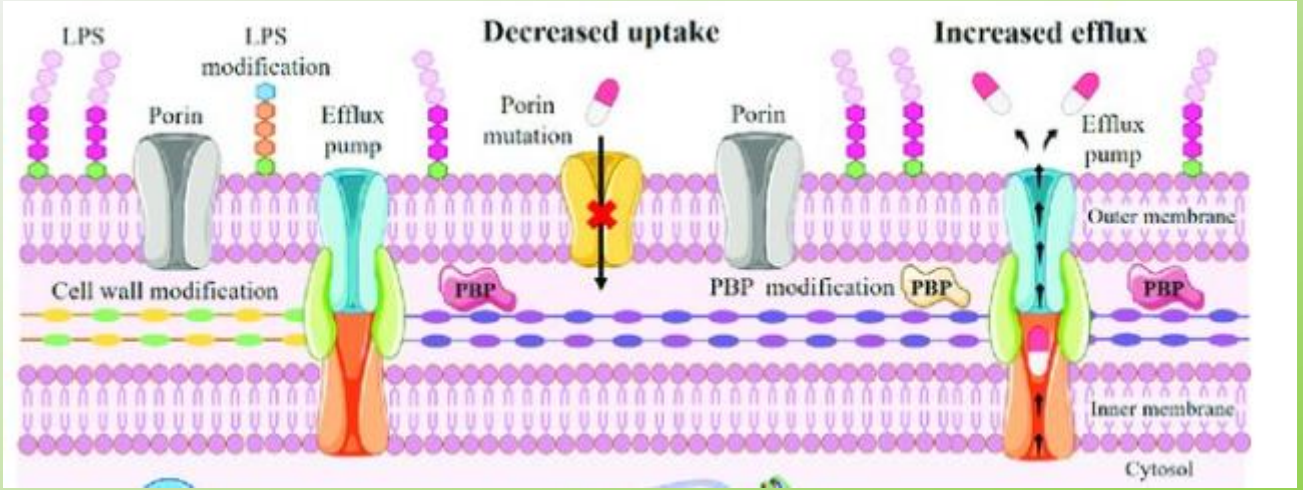
Multiple components in the bacterial cell can be targets of antimicrobial agents. These targets may be modified by the bacteria to enable resistance.
Exemple: Alteration of the structure of Penicillin-binding proteins (PBPs) involved in the construction of peptidoglycan in the cell wall.

For antimicrobials taht target nucelic acid synthesis (fluoroquinolones), resistance is due to modification in DNA gyrase (Gram - *gyrA*) or topoisomerase IV (Gram + grlA)

AMR Mechanisms:Porin alterations,efflux pumps activation

• Two main ways to limit drug uptake: decrease in the number of **porins** present or mutations that change the selectivity of the porin channel (*Pseudomonas, Klebsiella, Enterobacter*).
• For **efflux pumps** bacteria have chromosomally encoded genes. Some are expressed constitutively, other are induced and overexpressed (a mutation modifies the transport channel) under certain environmenatl conditions

The efflux pumps primaly function is to rid the bacterial cell of toxic substances and transport a large variety of compunds (MDR multi-drug efflux pumps).



AMR Surveillance

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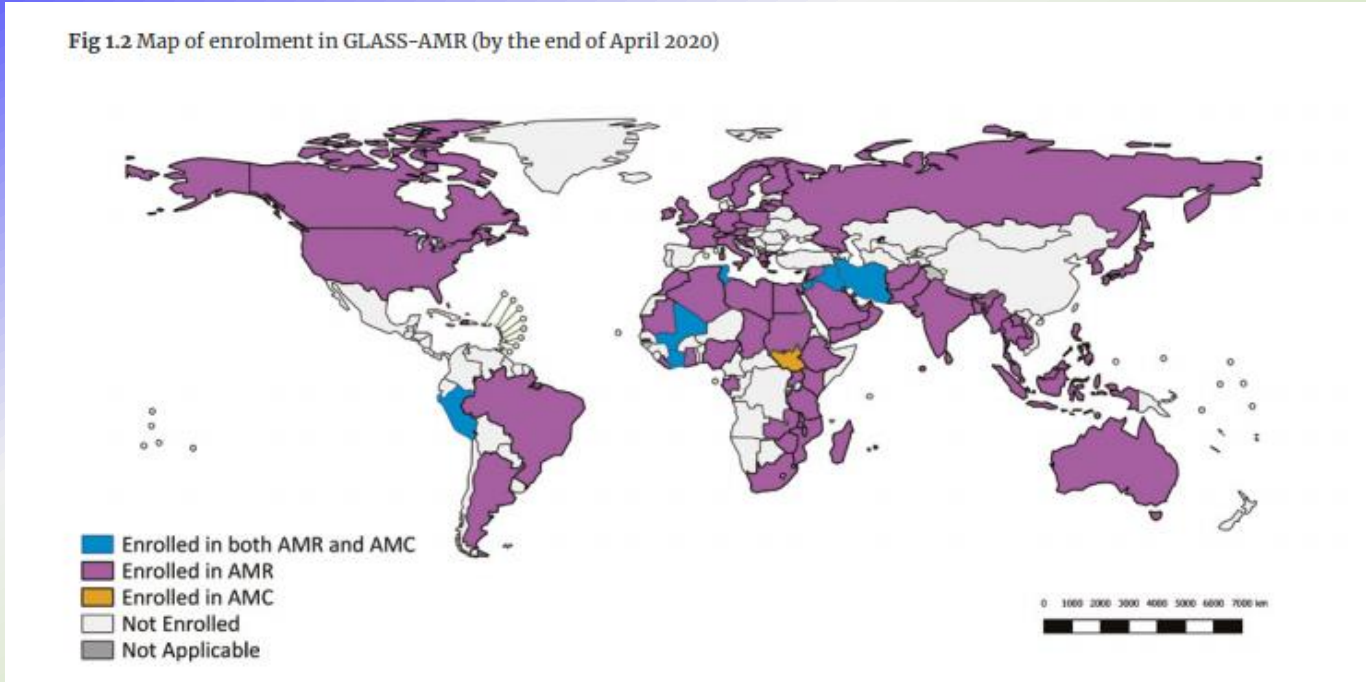
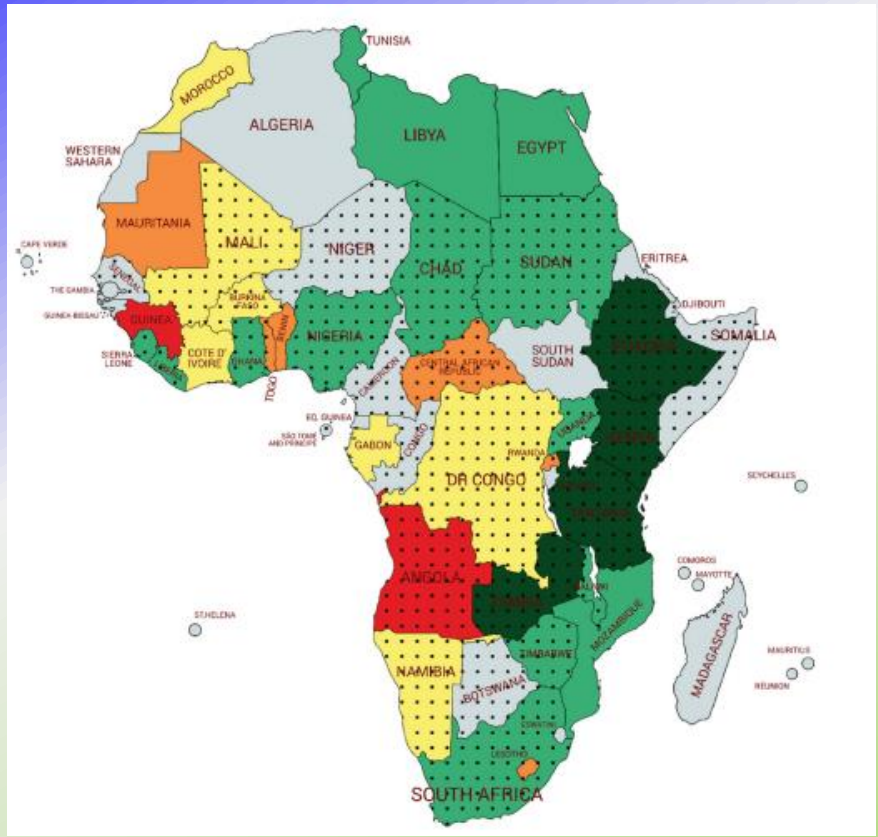


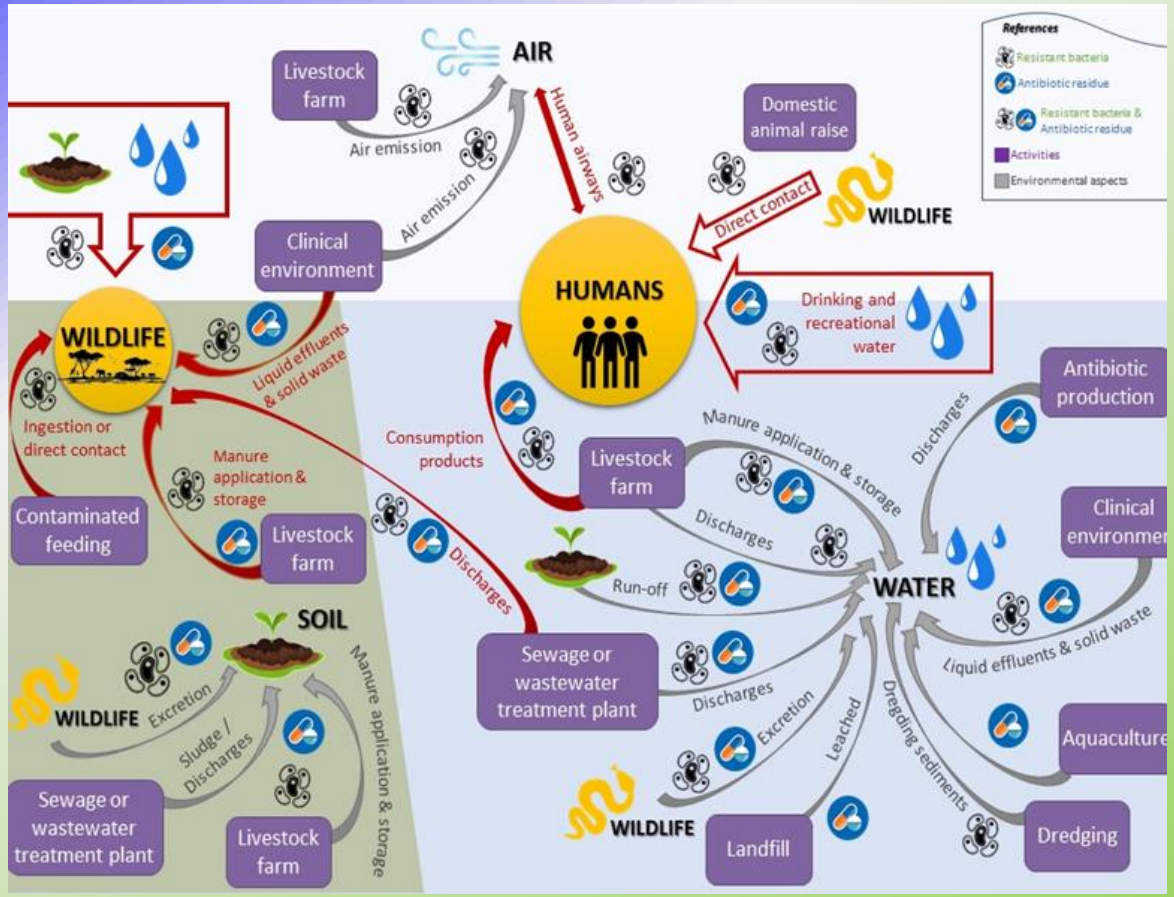
Pathogens currently included in GLASS-AMR are: Acinetobacter spp., E. coli, K. pneumoniae, N. gonorrhoeae, Salmonella spp., Shigella spp., S. aureus, and S. pneumoniae.

AMR Surveillance



- No national AMR action plan.
- National AMR action plan under development
- National AMR action plan developed.
- National AMR action plan approved by government that reflects Global Action Plan objectives, with an operational plan and monitoring arrangements.
- National AMR action plan has funding sources identified, is being implemented and has relevant sectors involved with a defined monitoring and evaluation process in place.
- No data
- Dots represent countries where CSO participants are working

AMR Surveillance



THANK YOU FOR YOUR ATTENTION!

Alessandra Cornacchia
a.cornacchia@izs.it