Mechanisms of Antimicrobial Resistance

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Mechanisms of antimicrobial resistance

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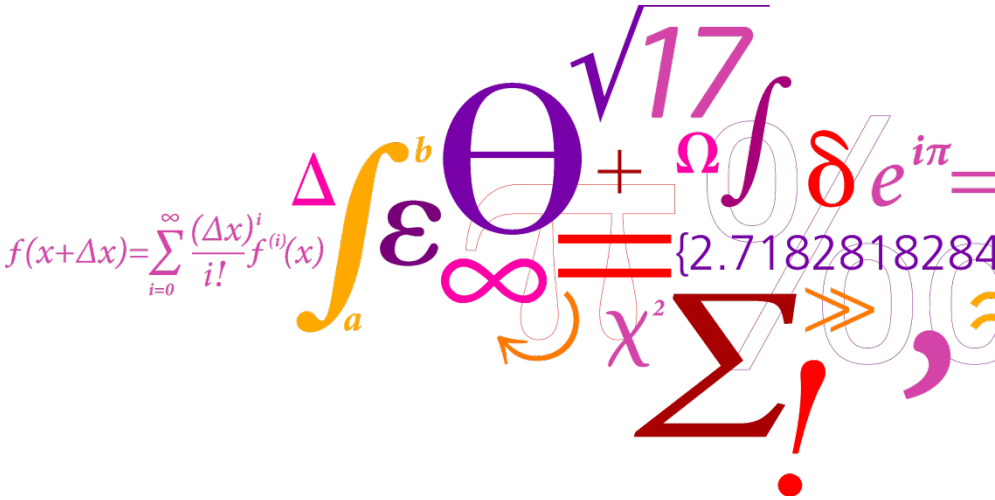

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An antibiotic

...is a substance produced by a microorganism, that has the capacity, in dilute solution, to selectively inhibit or kill other microorganisms (Paul Vuillemin 1941)

An ’antimicrobial agent’

…refers to any substance that can affect microbial life - including synthetic and semi-synthetic substances and compounds without selective toxicity (e.g. disinfectants)

Origin and activity

Class	Origin	Activity
Aminoglycosides	*Streptomyces* sp, *Micromonospora sp*	Bactericidal
Cephalosporins	*Cephalosporium* spp	Bactericidal
Macrolides	*Streptomyces* spp	Bacteriostatic
Penicillins	*Penicillium* sp	Bactericidal
Phenicols	*Streptomyces venezuelae*	Bacteriostatic
Quinolones	Synthetic	Bactericidal
Rifamycins	*Amycolatopsis mediterranei*	Bactericidal
Sulfonamides	Synthetic	Bacteriostatic
Tetracyclines	*Streptomyces* spp	Bacteriostatic

What is antimicrobial resistance?

Microbiological definition:

– Resistance is the property of a bacterial strain to survive at higher antibiotic concentrations compared to most other members of the same species (wild types)

Clinical definition:

– Resistance is the ability of a bacterial strain to survive antimicrobial therapy

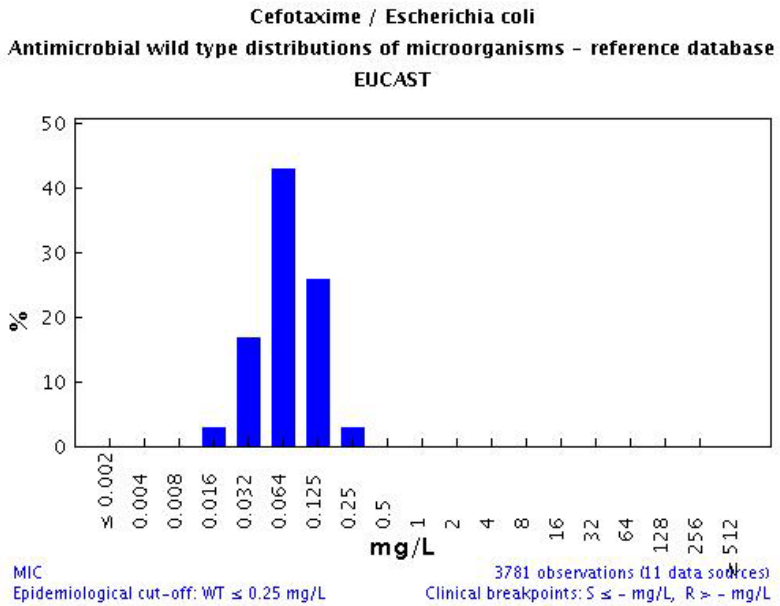
Intrinsic resistance

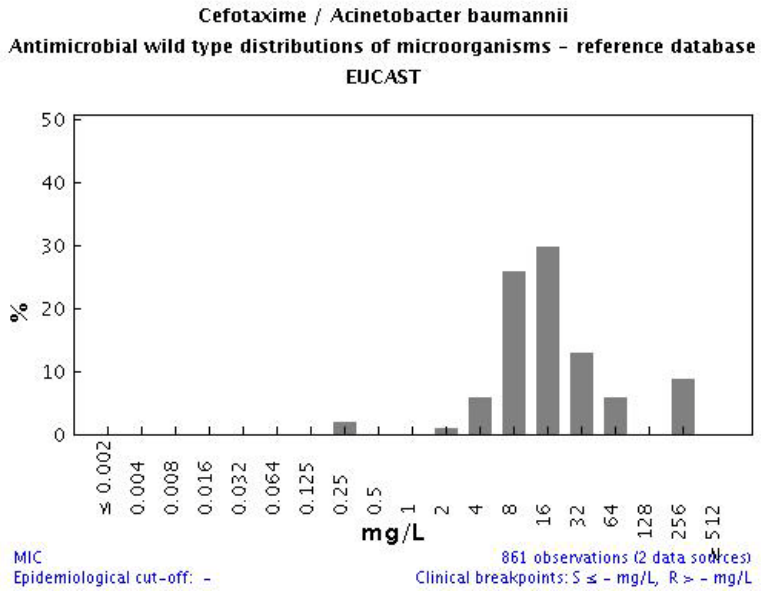
Resistance due to a structural or functional trait allowing tolerance by all members of a bacterial group (species, genus or even larger group)

- Impermeability
- Active exporters
- Enzymatic degradation
- Low affinity of the target

Example of intrinsic resistance

Cefotaxime susceptibility in *E. coli* and *Acinetobacter baumannii*



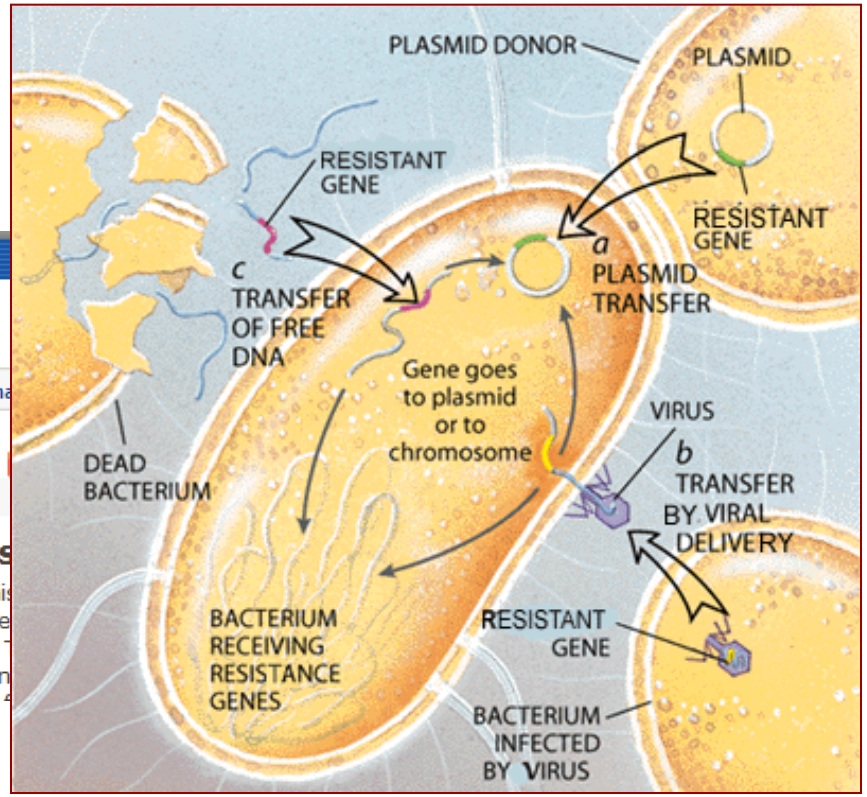


Types of acquired resistance

Mutation (endogenous, vertical)

Gene transfer (exogenous, horizontal)

- Transformation (free DNA)
- Transduction (with phages)
- Conjugation (plasmids)



Targets of antimicrobial action

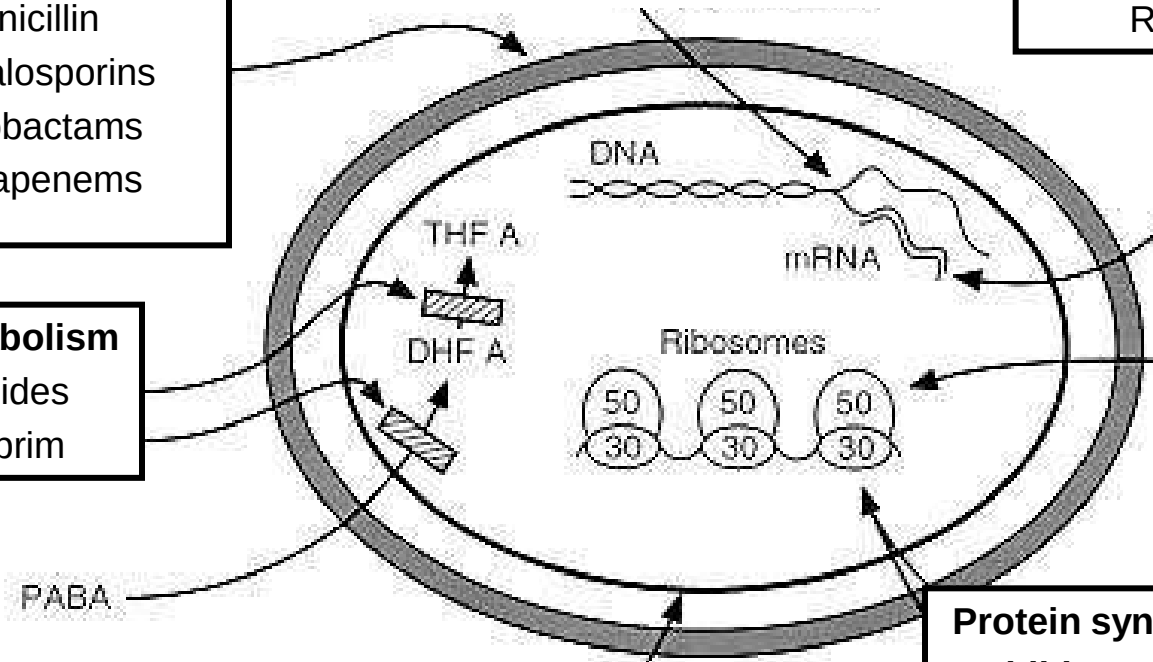
Cell wall synthesis
Vancomycin
β-lactams, e.g.:
Penicillin
Cephalosporins
Monobactams
Carbapenems

DNA replication
Fluoroquinolones
Metronidazole

RNA-polymerase
Rifampicin

Folate metabolism
Sulfonamides
Trimethoprim

Protein synthesis inhibitors (50S)
Macrolides
Chloramphenicol
Clindamycin

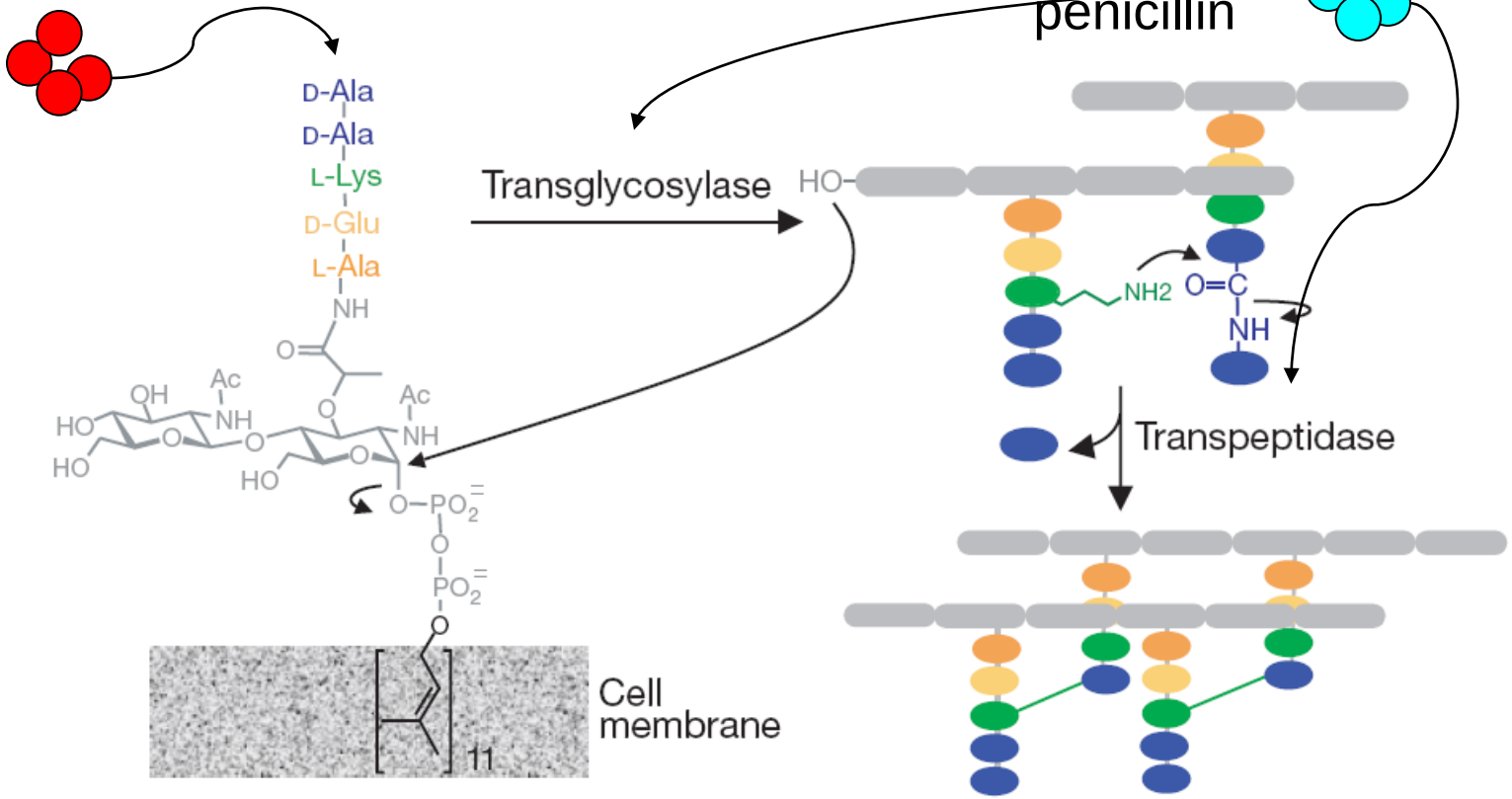


Cell membrane
Polymyxin
Amphotericin

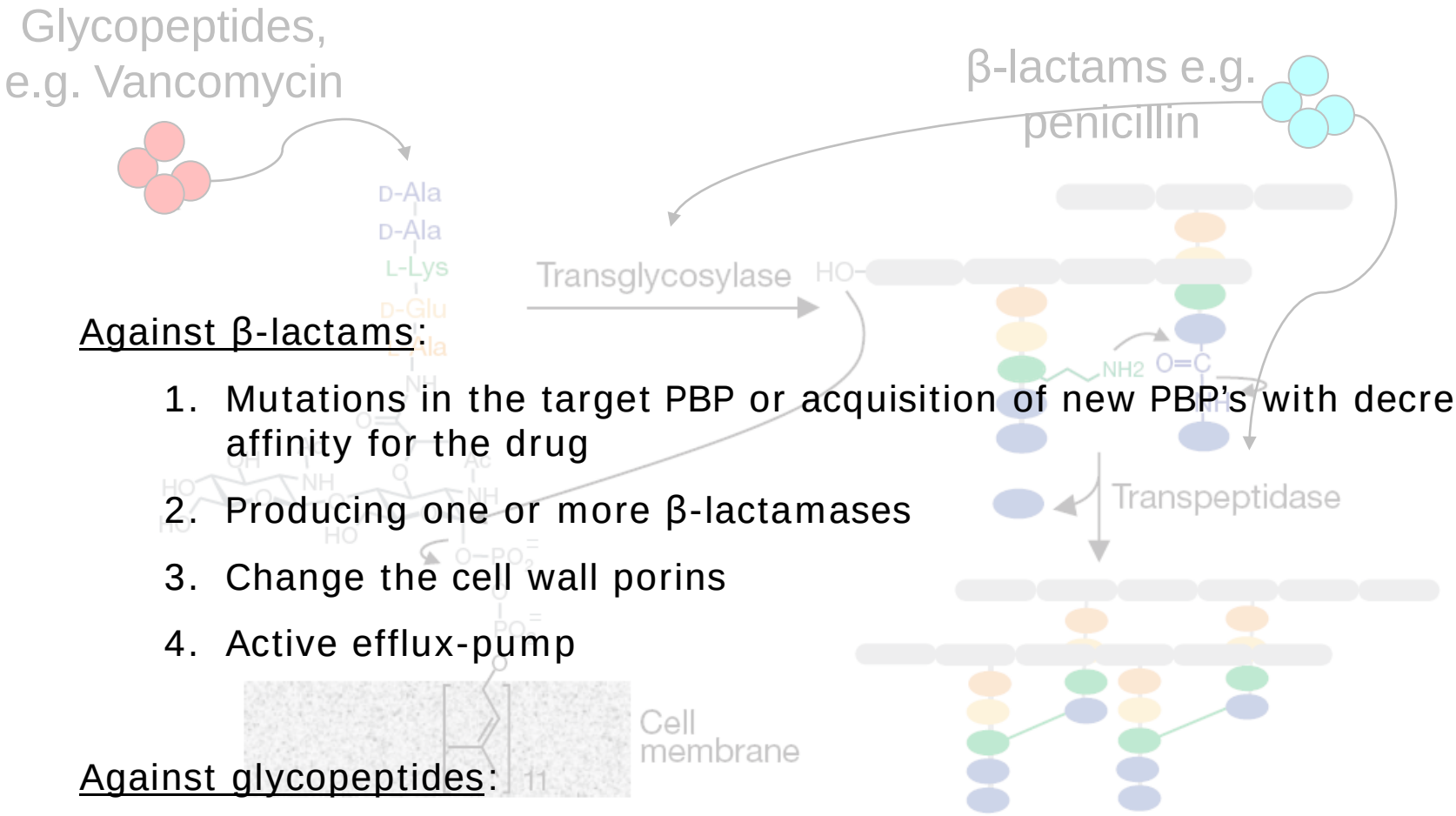
Protein synthesis Inhibitors (30S)
Tetracyclines
Aminoglycosides
Fucidinic acid

Inhibition on cell wall synthesis

Glycopeptides,
e.g. Vancomycin



Resistance mechanism



Against β-lactams:

1. Mutations in the target PBP or acquisition of new PBP's with decreased affinity for the drug
2. Producing one or more β-lactamases
3. Change the cell wall porins
4. Active efflux-pump

Against glycopeptides:

1. Synthesis of D-Ala-D-Lac in stead of D-Ala-D-Ala

Folate pathway inhibitor

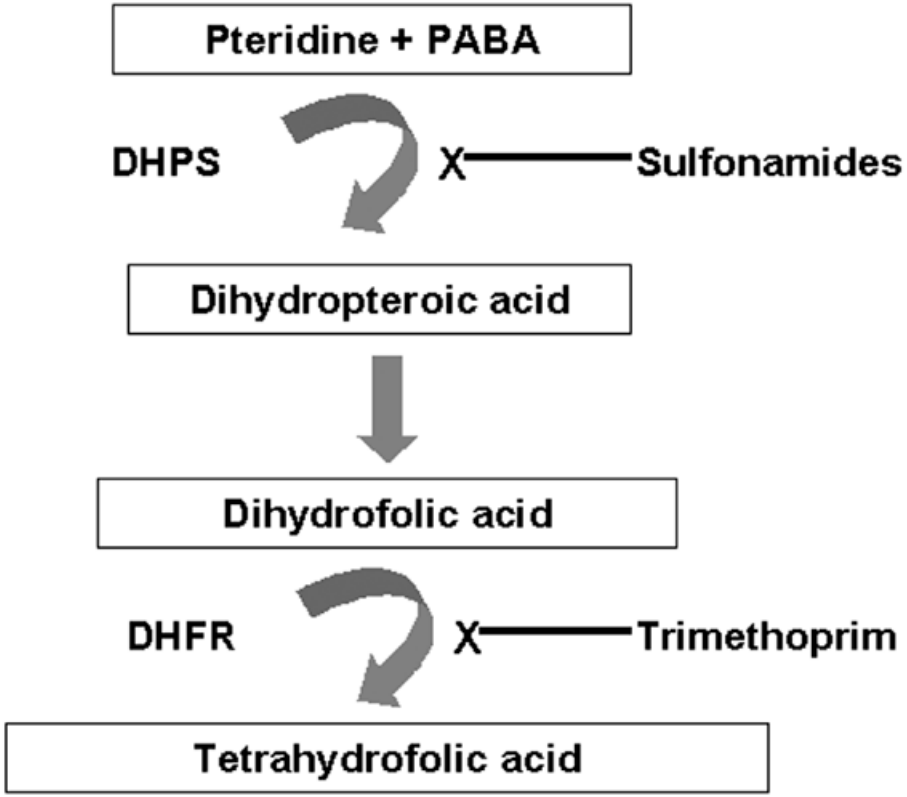


Figure from cdc.gov:

PABA paraaminobenzoic acid

DHPS, dihydropteroate synthase

DHFR, dihydrofolate reductase

Folate pathway

Against sulfonamides:

1. Sulfonamide-insensitive enzymes are produced

Against trimethoprim:

1. Trimethoprim-insensitive enzymes are produced

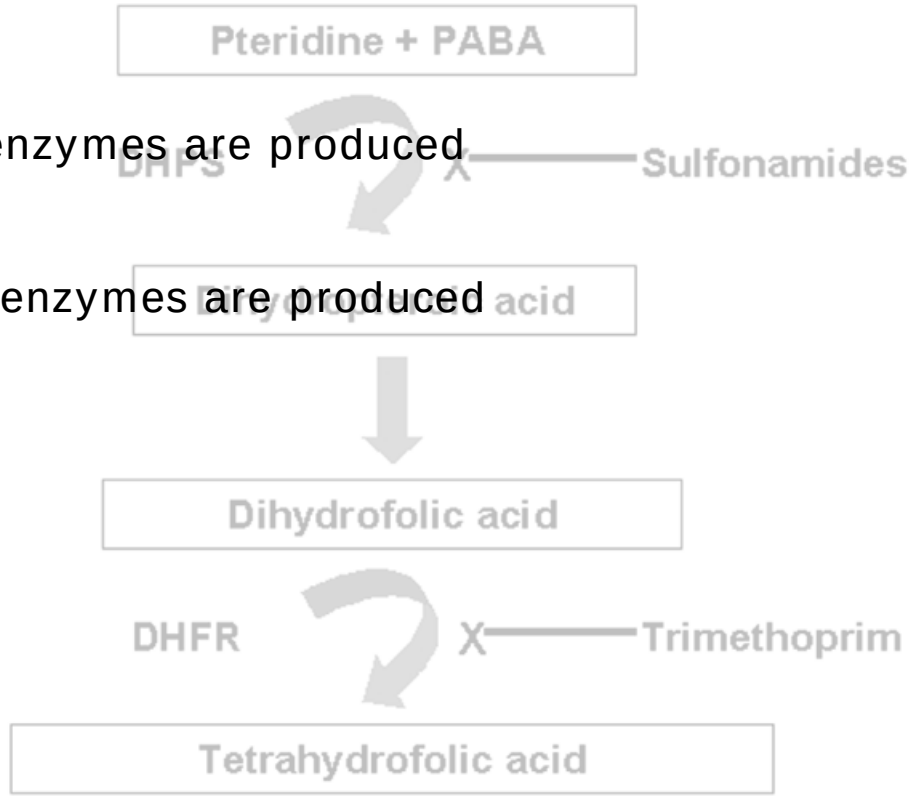


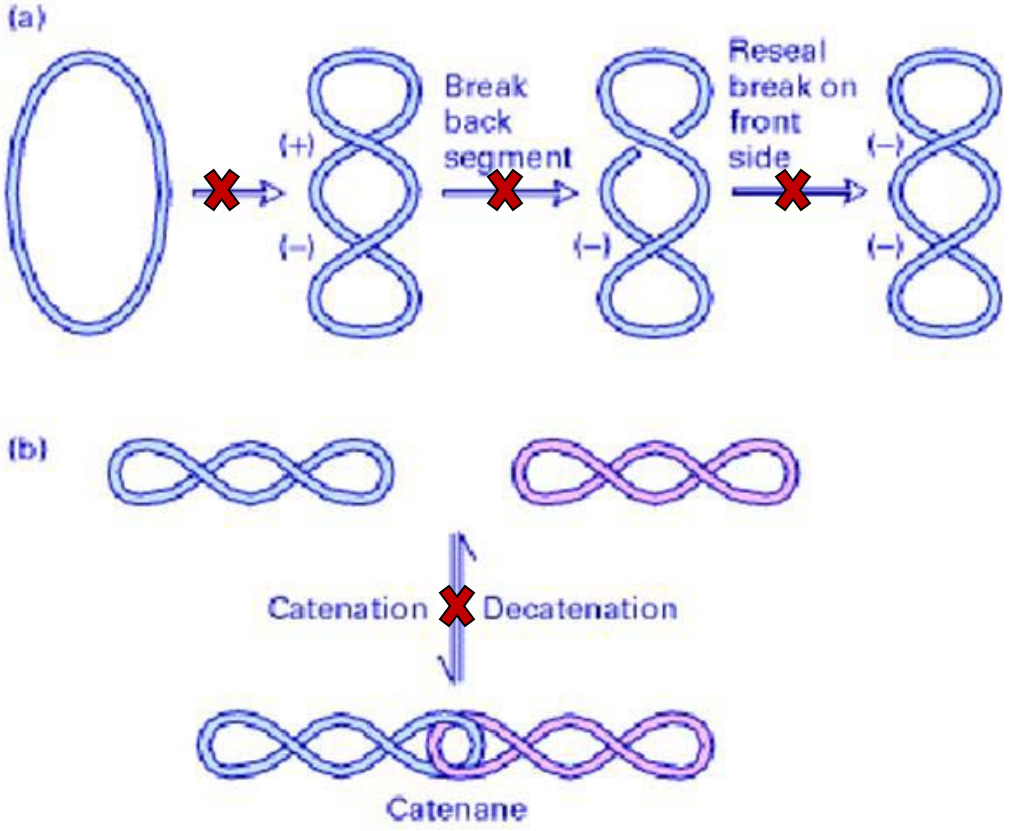
Figure from cdc.gov:

PABA paraaminobenzoic acid

DHPS, dihydropteroate synthase

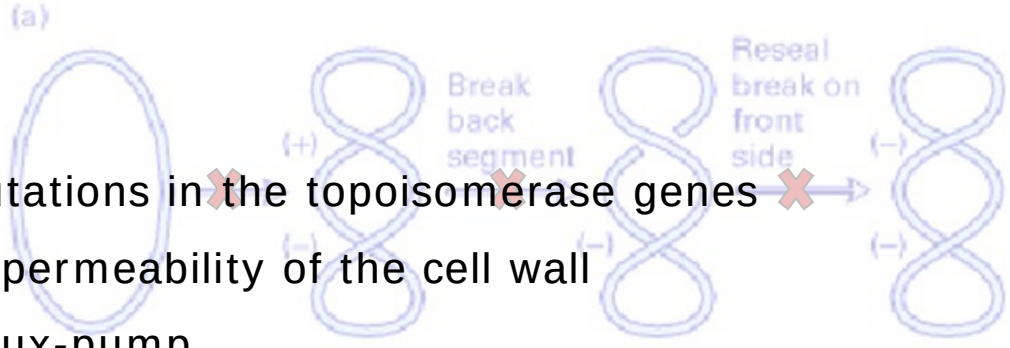
DHFR, dihydrofolate reductase

Inhibition of DNA synthesis



Quinolones appear to mainly target gyrA in G- and parC in G+

Resistance mechanism



1. Target mutations in the topoisomerase genes
2. Decrease permeability of the cell wall
3. Active efflux-pump

High-level fluoroquinolone-resistance: primarily due to mutations in gyrA and parC-genes

=> reduce binding of the drug, and DNA replication can continue

Quinolones appear to mainly target gyrA in G- and parC in G+

Inhibition of protein synthesis I

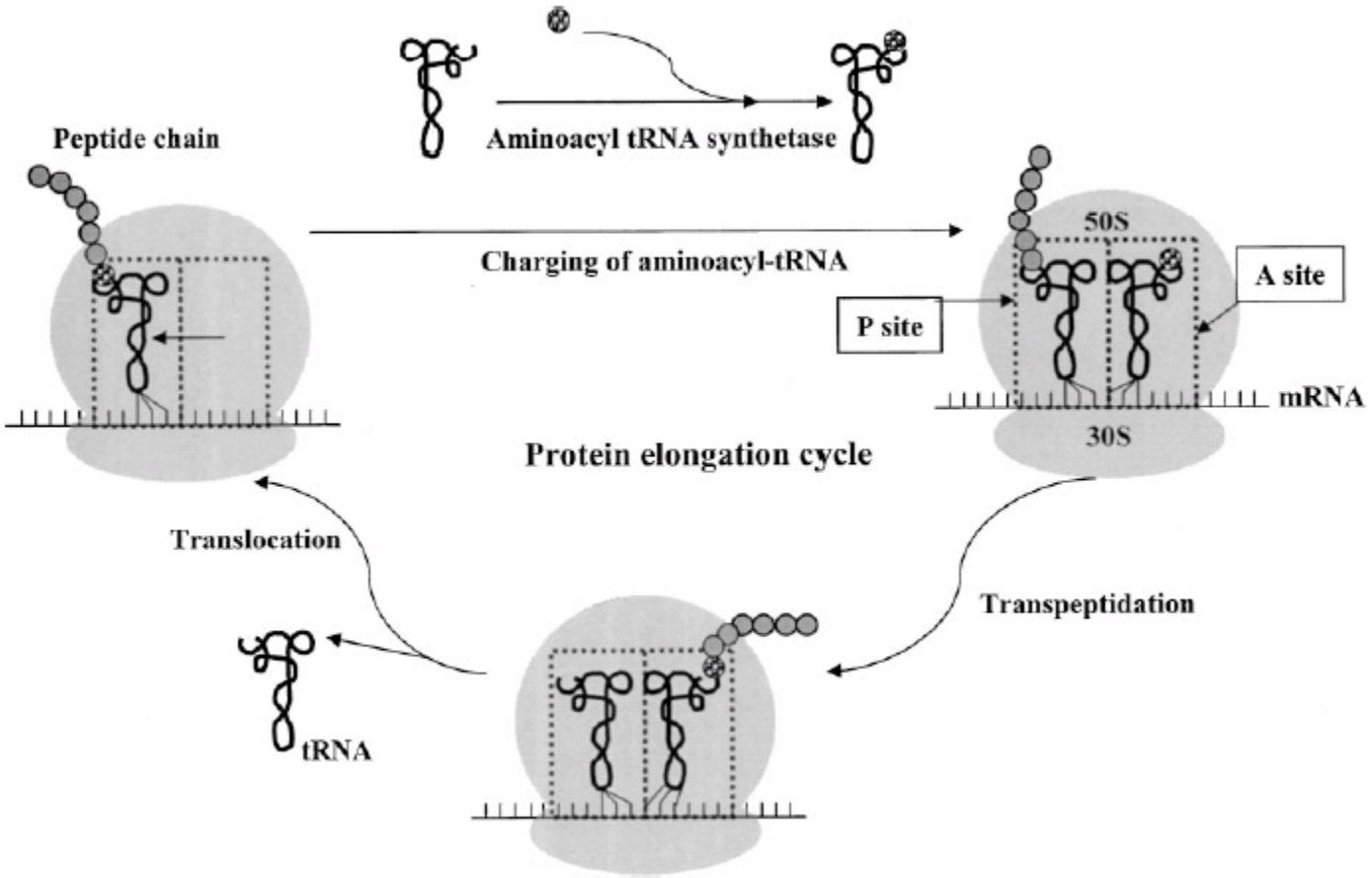


Figure from McDermott *et. al.*, 2003, International Journal of Toxicology, 22:135–143

Inhibition of protein synthesis II

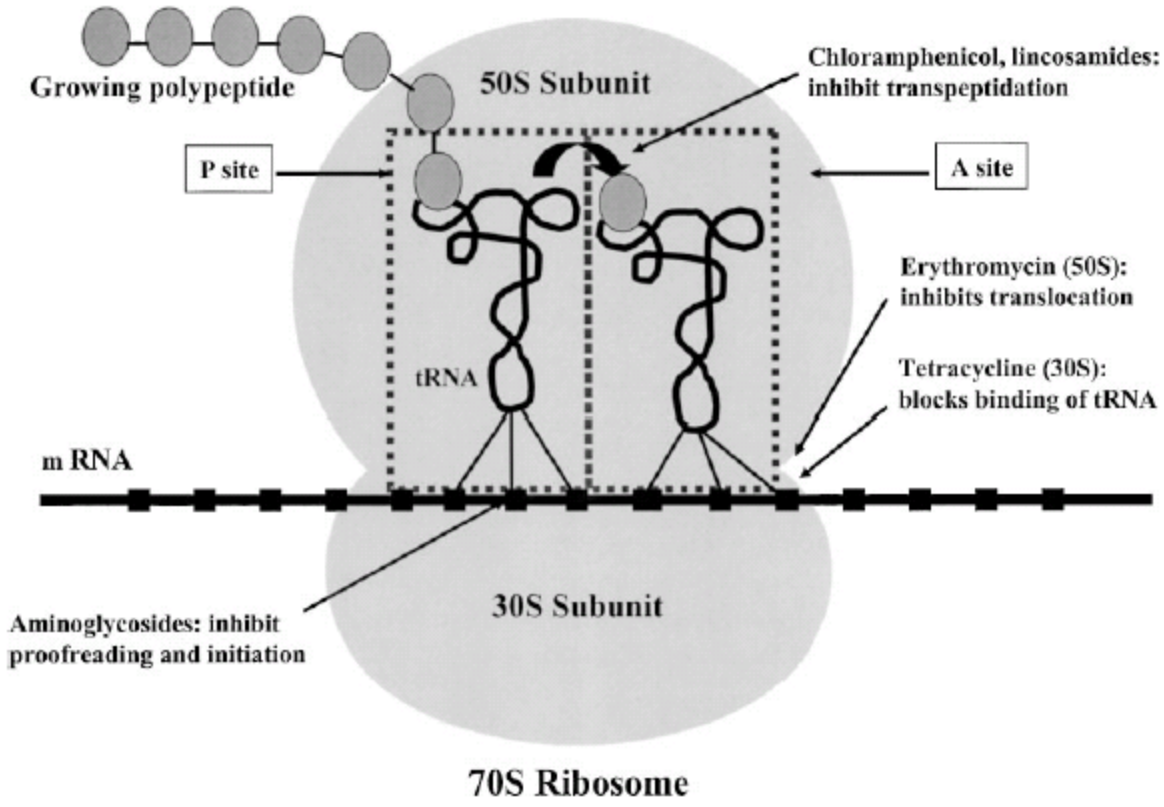


Figure from McDermott *et. al.*, 2003, International Journal of Toxicology, 22:135–143

Resistance mechanism

Against aminoglycosides (e.g. strep, gen):

1. Structural mutations in the 30S ribosomal sub-unit
2. Production of modifying enzymes (a large number of diverse enzymes have been identified)

Against chloramphenicol:

1. Inactivation of the drug by acetylation of the two hydroxyl groups
2. Efflux mechanisms

Against macrolides (e.g. ery):

1. G- are intrinsically resistant
2. Mutations or modifications (methylation) of the 23S ribosomal RNA subunit
3. Efflux-pump

Against tetracycline:

1. Modifications of the ribosome
2. Efflux-pump

Against streptogramins:

1. Inactivation by acelylation
2. Ribosomal mutations

Against linezolid:

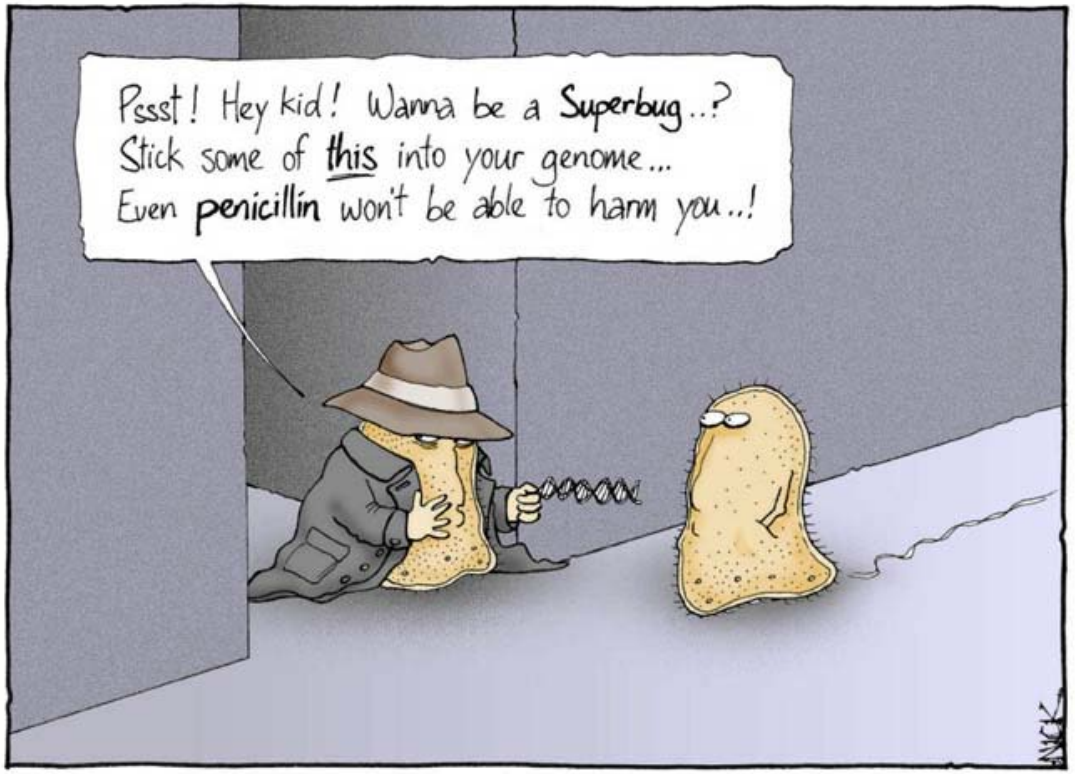
1. Mutations in the 23S rRNA subunit

Mechanisms of resistance

1. Alteration of the antimicrobial agent	Aminoglycosides, chloramphenicol, β-lactams, Streptogramins
2. Mutation in the target site	Aminoglycosides, β-lactams, macrolides, quinolones, rifampicin, trimethoprim, tetracycline, mupirocin
3. Decreased antibiotic accumulation - Decreased uptake - Increased efflux	 Many antibiotics Tetracycline, macrolides, chloramphenicol and quinolones
4. Acquisition of drug-insensitive enzyme	Sulfonamides, trimethoprim

Cross resistance

Resistance to two related (avoparcin / vancomycin) or unrelated drugs (erythromycin / lincosamides) is due to a single biological mechanism



Thanks for your attention!