

Mechanisms of Antimicrobial Resistance

Karlslose Pedersen, Susanne

Publication date:
2011

Document Version
Publisher's PDF, also known as Version of record

[Link back to DTU Orbit](#)

Citation (APA):
Karlslose, S. (2011). Mechanisms of Antimicrobial Resistance [Sound/Visual production (digital)]. Global Foodborne Infections Network, Kolkata, India, 01/01/2011

DTU Library

Technical Information Center of Denmark

General rights

Copyright and moral rights for the publications made accessible in the public portal are retained by the authors and/or other copyright owners and it is a condition of accessing publications that users recognise and abide by the legal requirements associated with these rights.

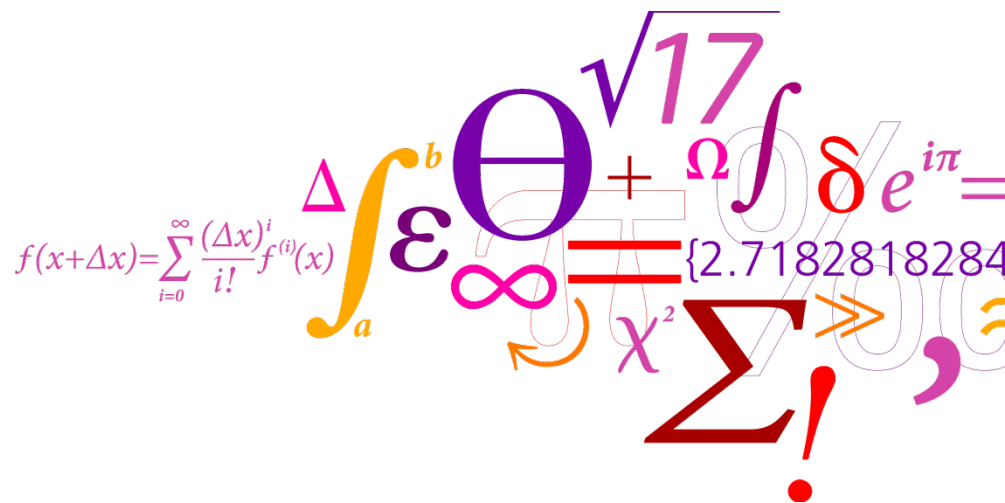
- Users may download and print one copy of any publication from the public portal for the purpose of private study or research.
- You may not further distribute the material or use it for any profit-making activity or commercial gain
- You may freely distribute the URL identifying the publication in the public portal

If you believe that this document breaches copyright please contact us providing details, and we will remove access to the work immediately and investigate your claim.

Mechanisms of antimicrobial resistance

March, 2011 – Kolkata, India

Susanne Karlsmose
suska@food.dtu.dk
DTU Food, Denmark



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	<i>Streptomyces</i> sp, <i>Micromonospora</i> sp	Bactericidal
Cephalosporins	<i>Cephalosporium</i> spp	Bactericidal
Macrolides	<i>Streptomyces</i> spp	Bacteriostatic
Penicillins	<i>Penicillium</i> sp	Bactericidal
Phenicol	<i>Streptomyces venezuelae</i>	Bacteriostatic
Quinolones	Synthetic	Bactericidal
Rifamycins	<i>Amycolatopsis mediterranei</i>	Bactericidal
Sulfonamides	Synthetic	Bacteriostatic
Tetracyclines	<i>Streptomyces</i> 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

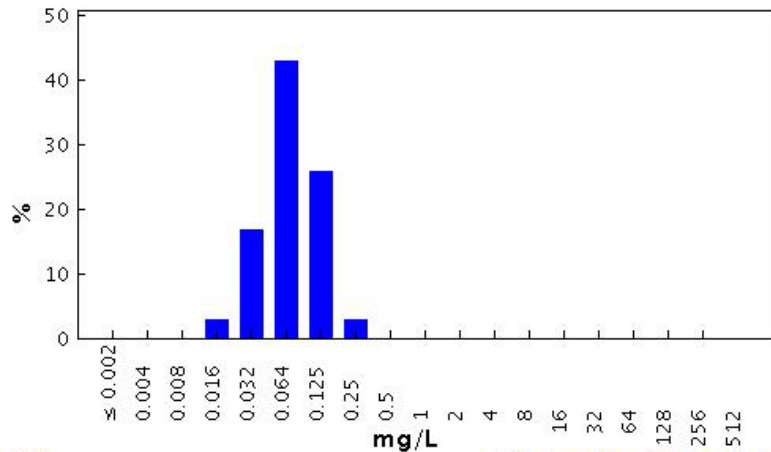
Resistance due to a structural or functional trait allowing tolerance by all members of a bacterial group (species, genus or even larger group)

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

Example of intrinsic resistance

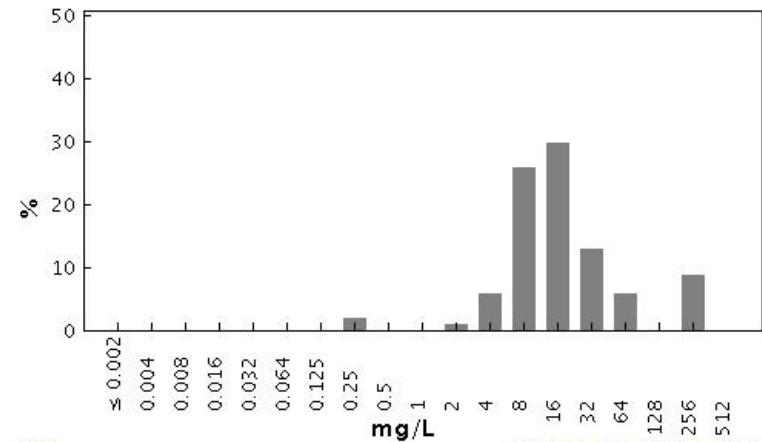
Cefotaxime susceptibility in *E. coli* and *Acinetobacter baumannii*

Cefotaxime / *Escherichia coli*
Antimicrobial wild type distributions of microorganisms - reference database
EUCAST



MIC
Epidemiological cut-off: WT ≤ 0.25 mg/L
3781 observations (11 data sources)
Clinical breakpoints: S ≤ - mg/L, R > - mg/L

Cefotaxime / *Acinetobacter baumannii*
Antimicrobial wild type distributions of microorganisms - reference database
EUCAST



MIC
Epidemiological cut-off: -
861 observations (2 data sources)
Clinical breakpoints: S ≤ - mg/L, R > - mg/L

Types of acquired resistance

Mutation (endogenous, vertical)

Gene transfer (exogenous, horizontal)

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

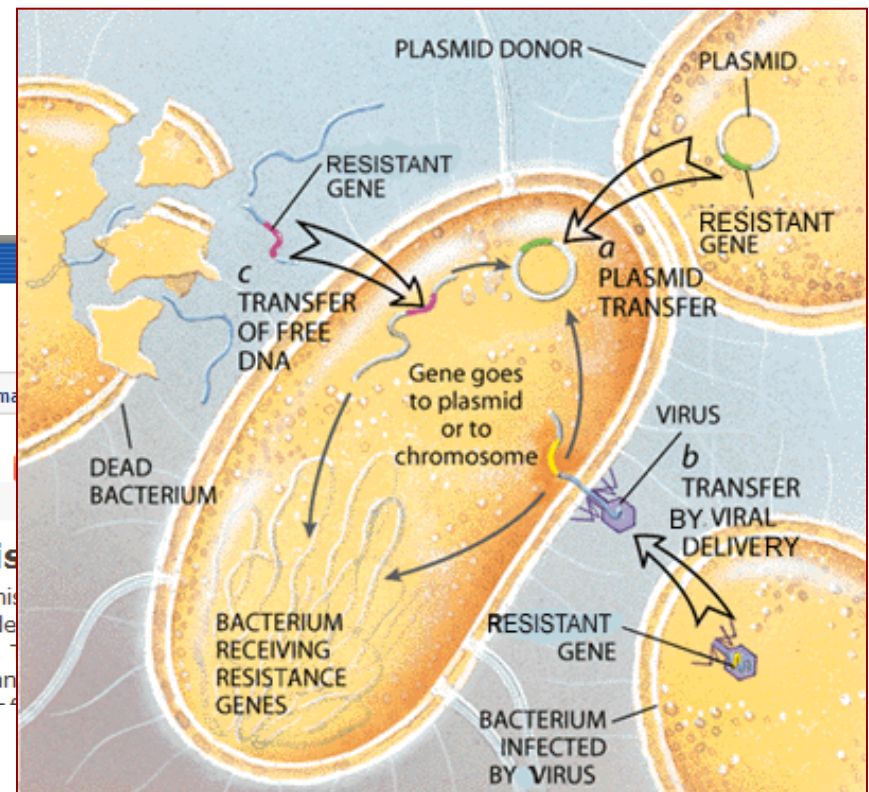


U.S. Department of Health & Human Services
FDA U.S. Food and Drug Administration
 Home | Food | Drugs | Medical Devices | Vaccines, Blood & Biologics | Animal Health

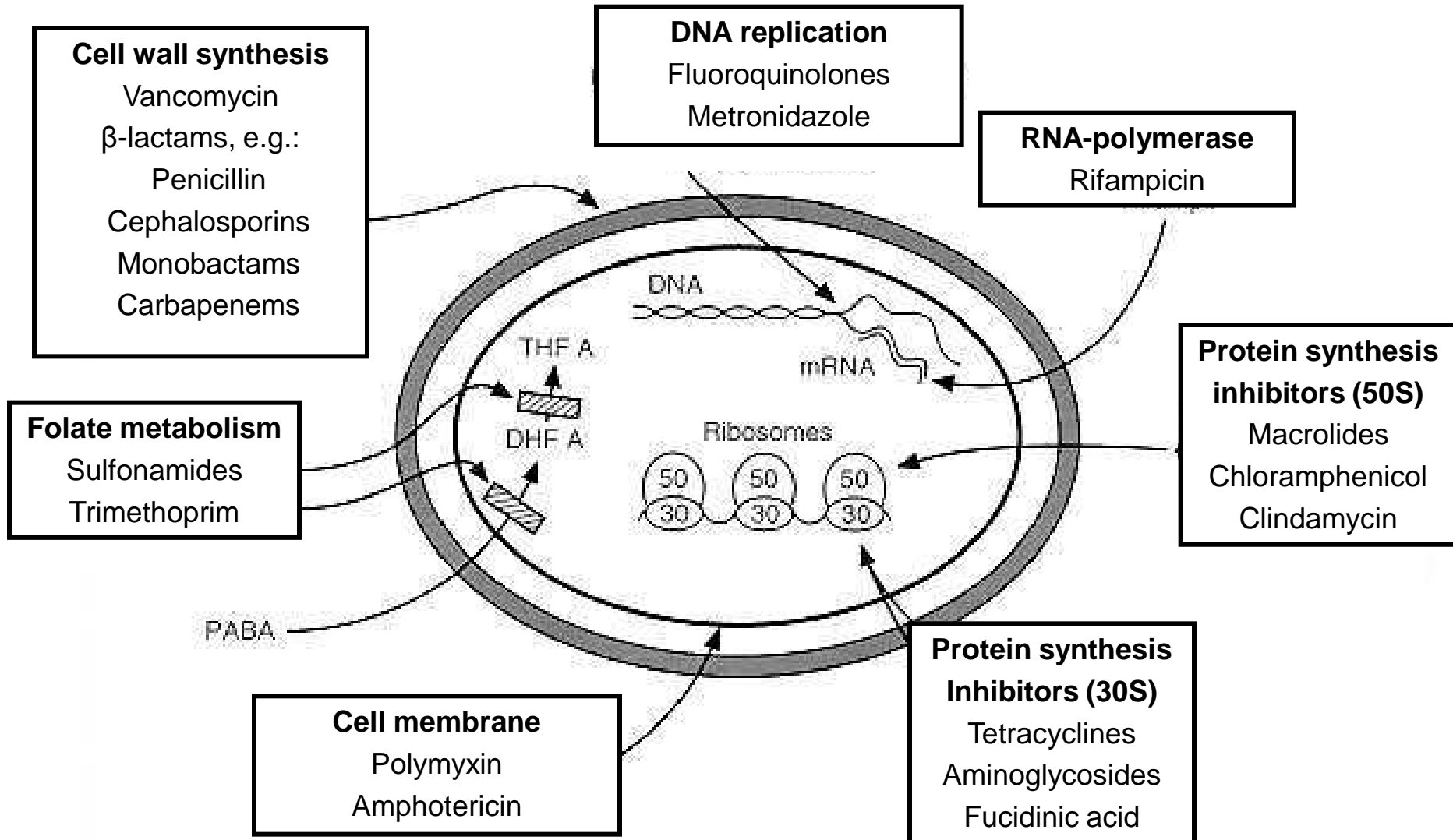
Animal & Veterinary
 Home > Animal & Veterinary > Safety & Health > Antimicrobial Resistance

Safety & Health
 ▶ **Antimicrobial Resistance**
 Antimicrobial Resistance Public Meetings

Antimicrobial Resistance
 Bacteria and other microorganisms are remarkably resilient and can develop resistance to drugs meant to kill or weaken them. This is known as antimicrobial resistance.

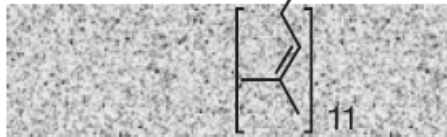
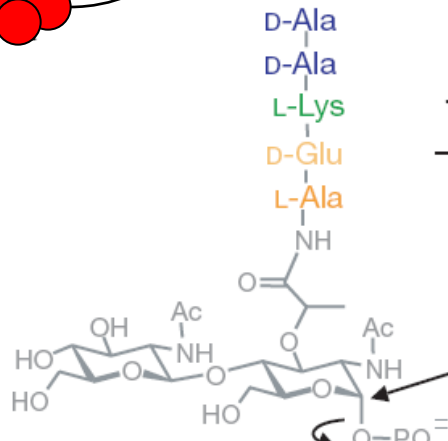
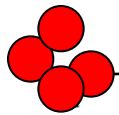


Targets of antimicrobial action



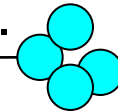
Inhibition on cell wall synthesis

Glycopeptides,
e.g. Vancomycin



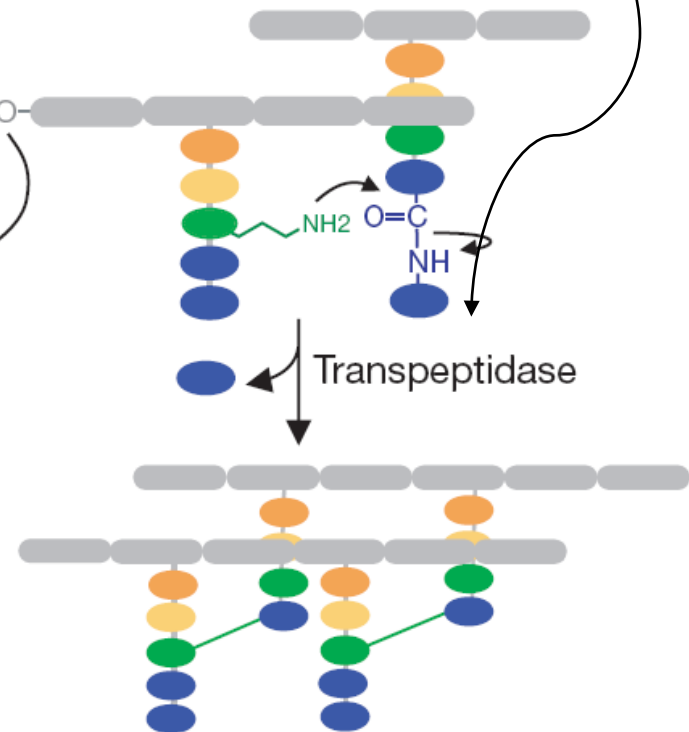
Cell membrane

β-lactams e.g.
penicillin



Transglycosylase

Transpeptidase



Resistance mechanism

Glycopeptides,
e.g. Vancomycin



D-Ala
D-Ala
L-Lys
D-Glu
Ala

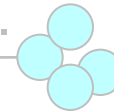
Against β -lactams:

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

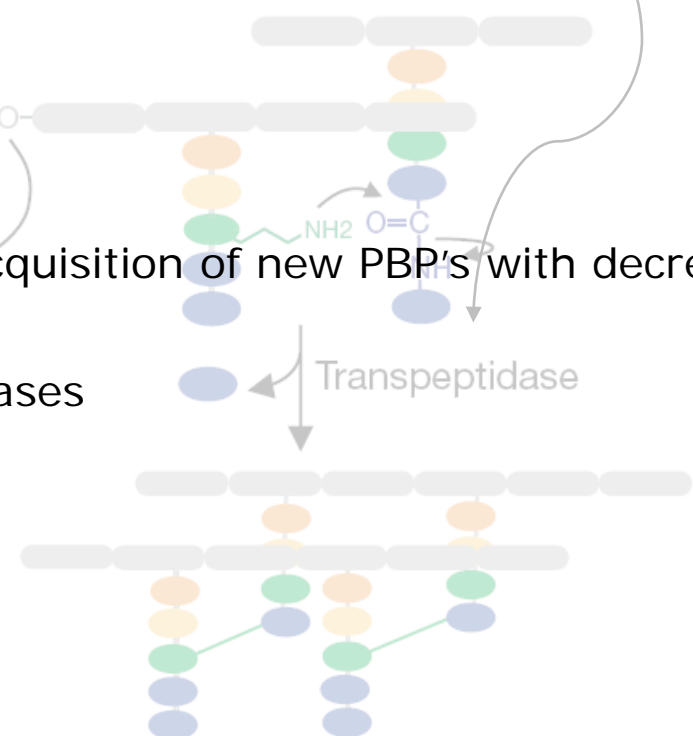
Against glycopeptides:

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

β -lactams e.g.
penicillin

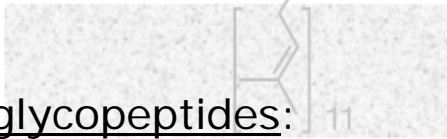


Transglycosylase



Transpeptidase

Cell membrane



Folate pathway inhibitor

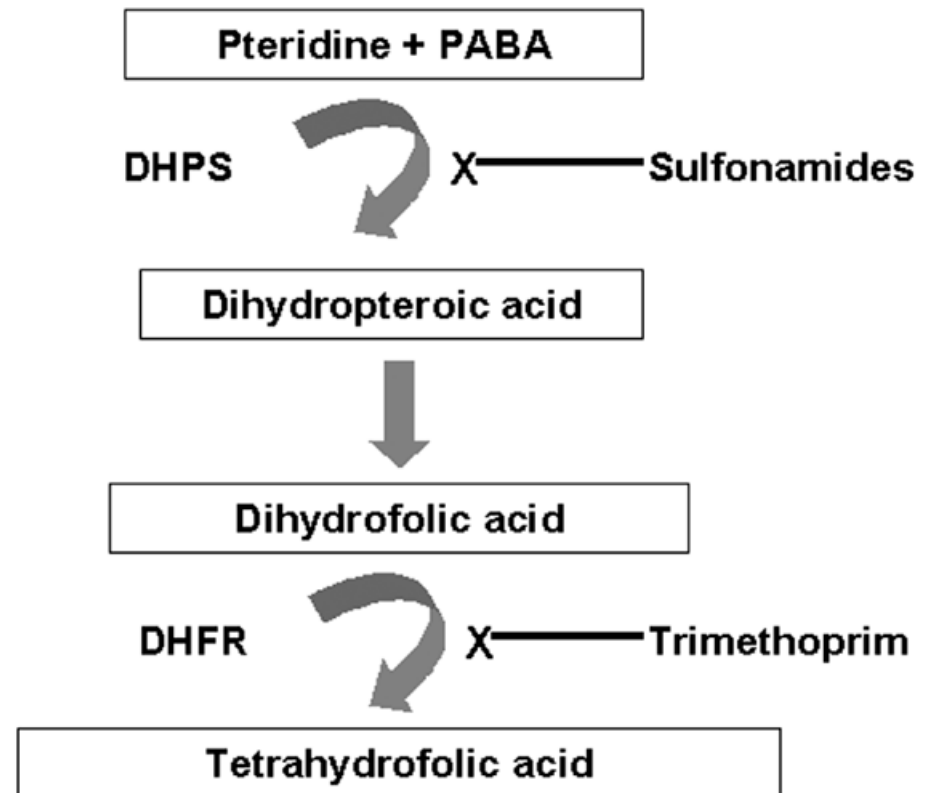


Figure from cdc.gov:

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

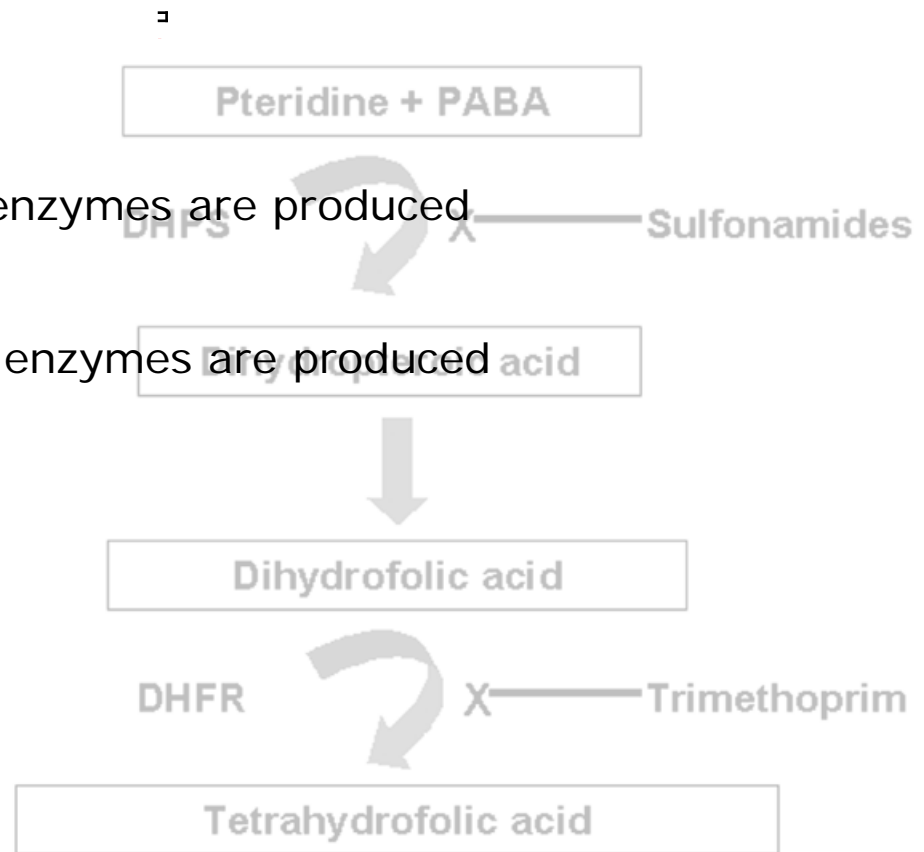


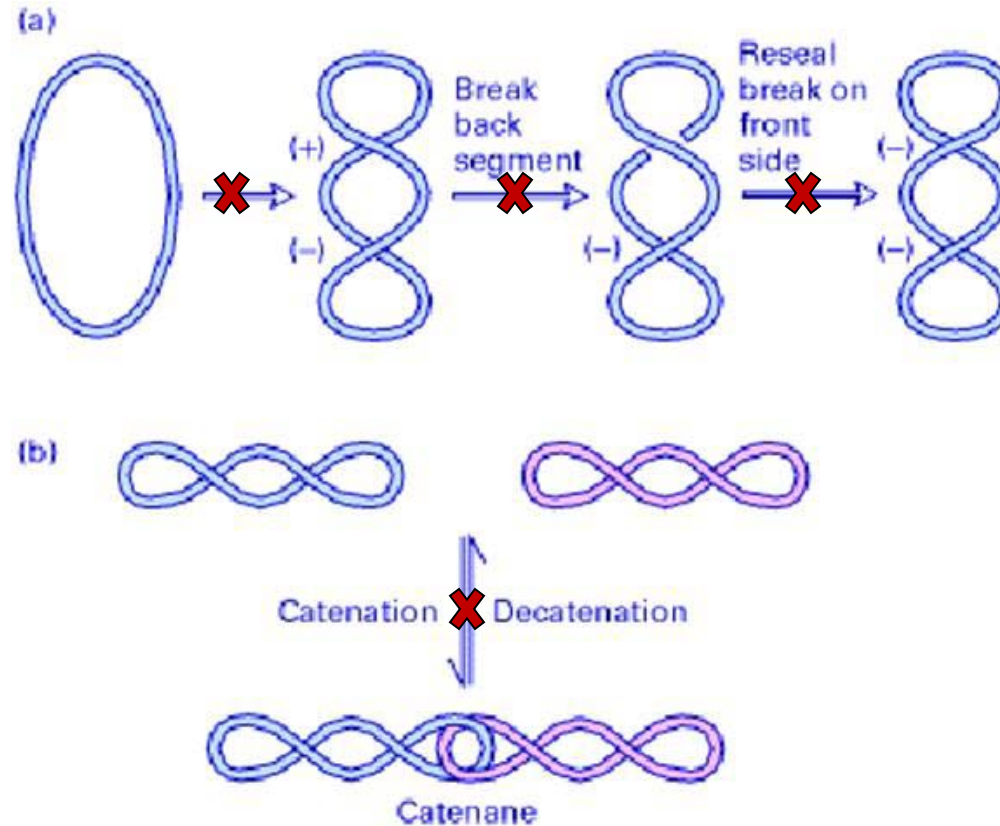
Figure from cdc.gov:

PABA paraaminobenzoic acid

DHPS, dihydropteroate synthase

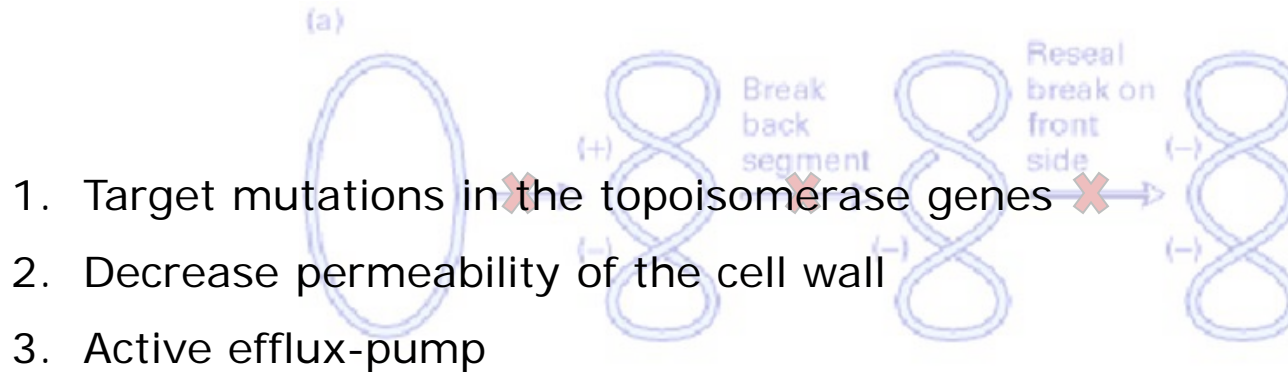
DHFR, dihydrofolate reductase

Inhibition of DNA synthesis



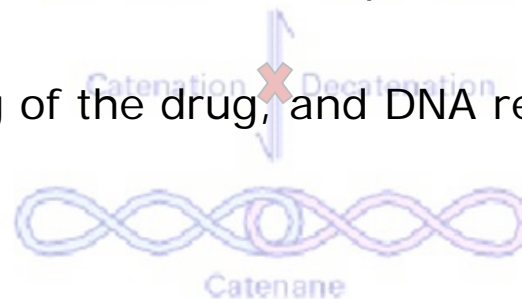
Quinolones appear to mainly target *gyrA* in G⁻ and *parC* in G⁺

Resistance mechanism



(b) 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

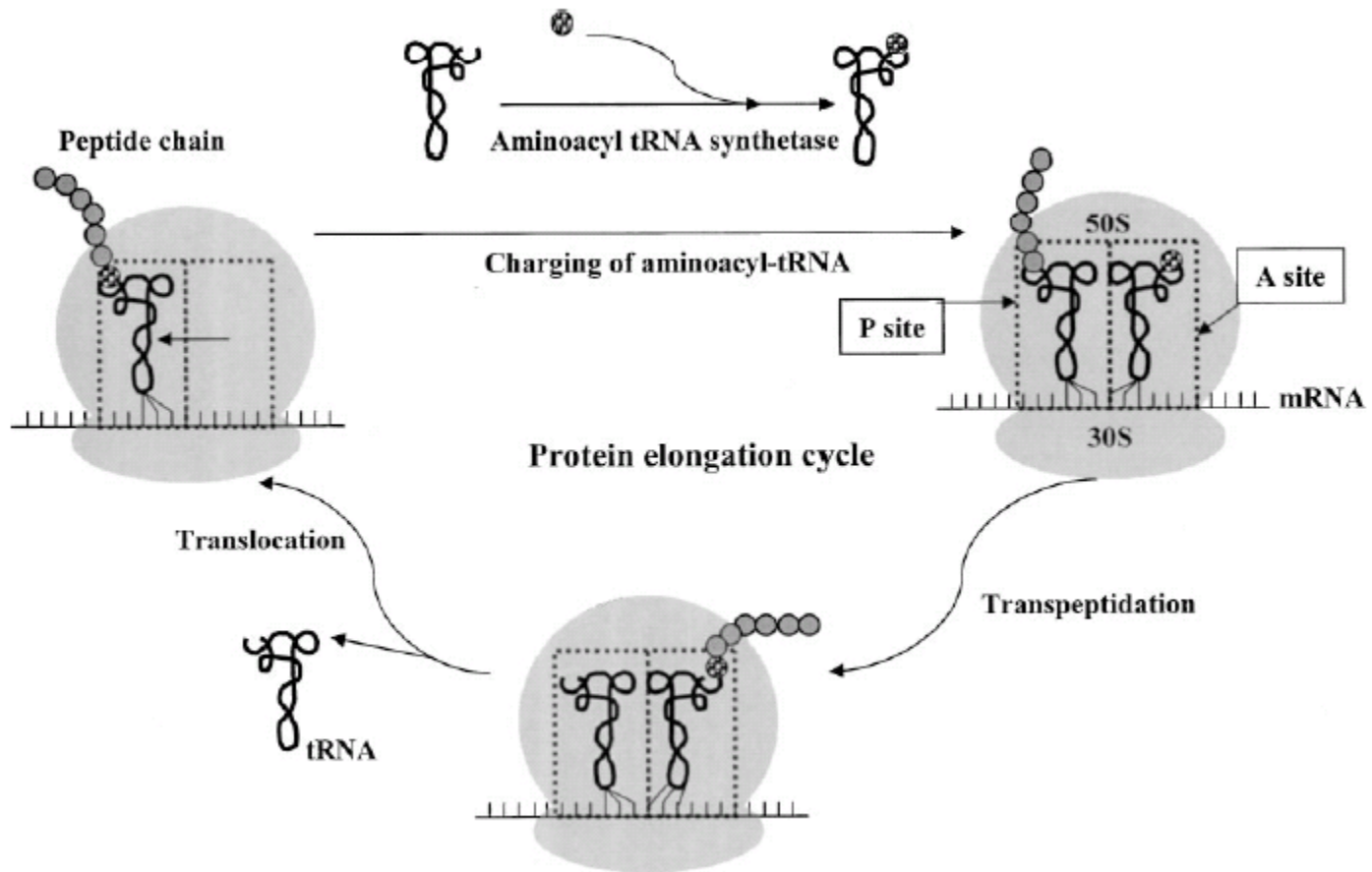


Figure from McDermott *et. al.*, 2003, International Journal of Toxicology, 22:135–143

Inhibition of protein synthesis II

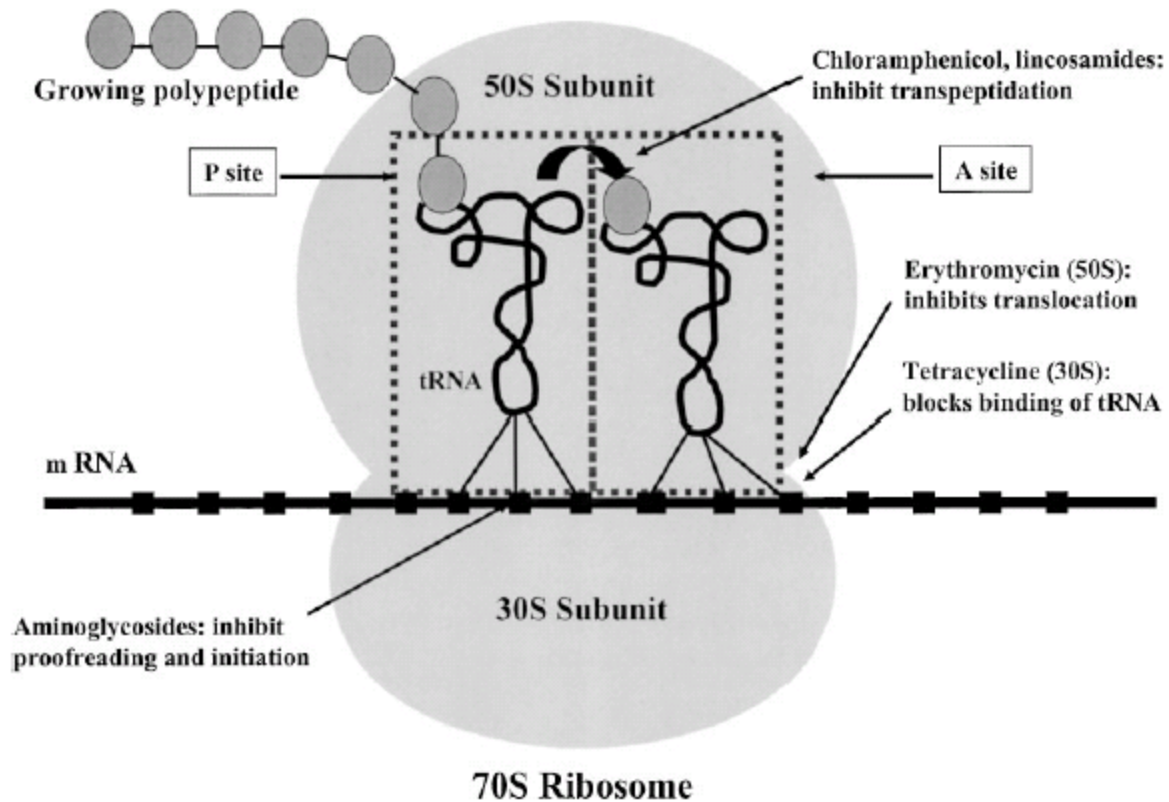


Figure from McDermott *et. al.*, 2003, International Journal of Toxicology, 22:135–143

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 tetracycline:

Against macrolides (e.g. ery):

1. G- are intrinsically resistant

1. Modifications of the ribosome

2. Efflux-pump

Against streptogramins:

2. Mutations or modifications (methylation) of the 23S ribosomal RNA subunit

1. Inactivation by acetylation

3. Efflux-pump

2. Ribosomal mutations

Against linezolid:

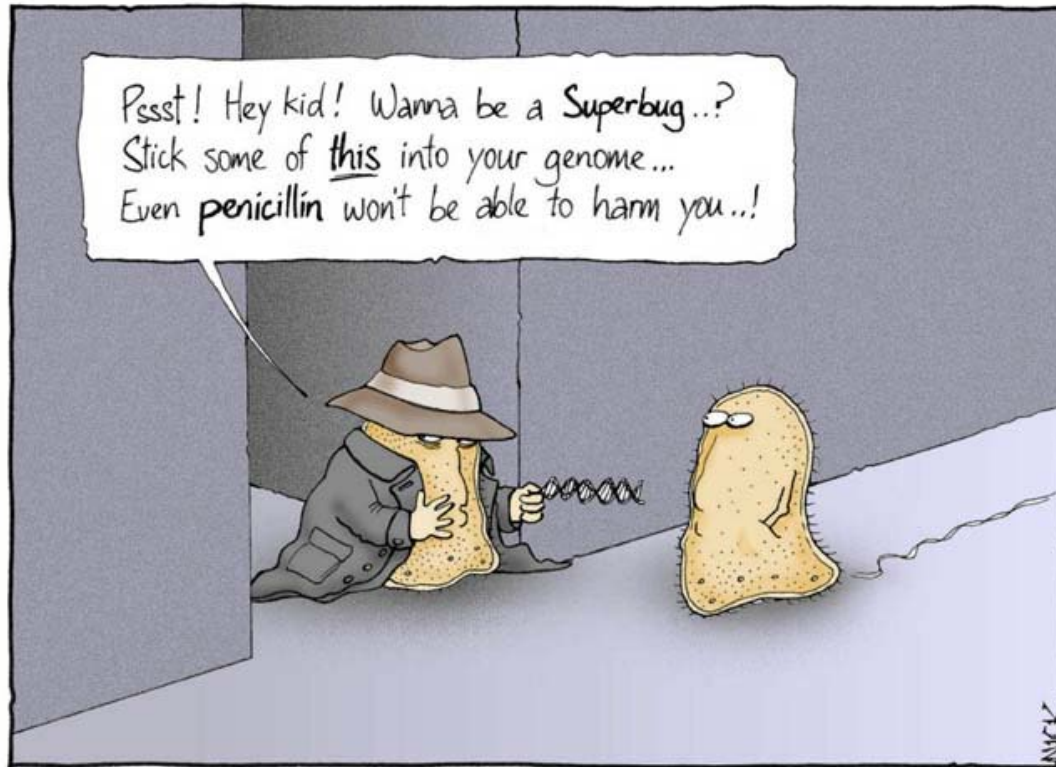
1. Mutations in the 23S rRNA subunit

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 <ul style="list-style-type: none"> - 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!