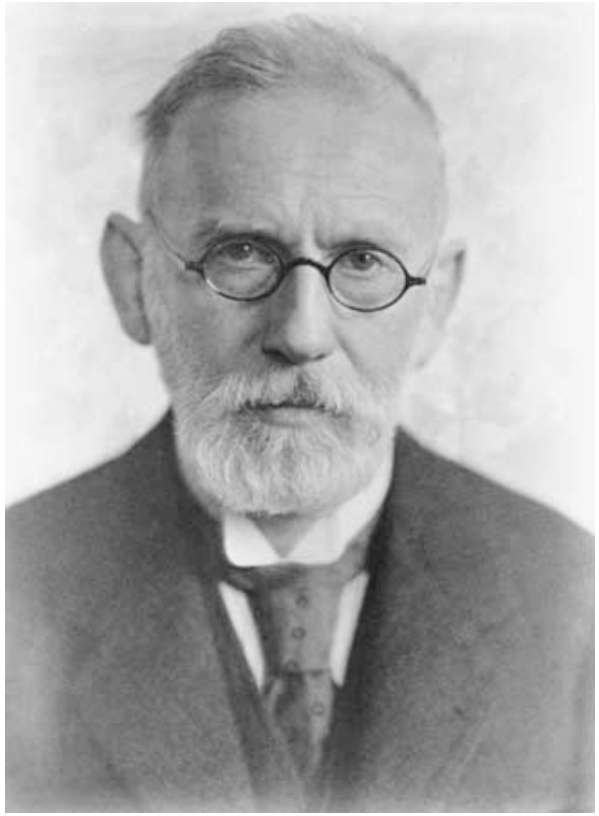
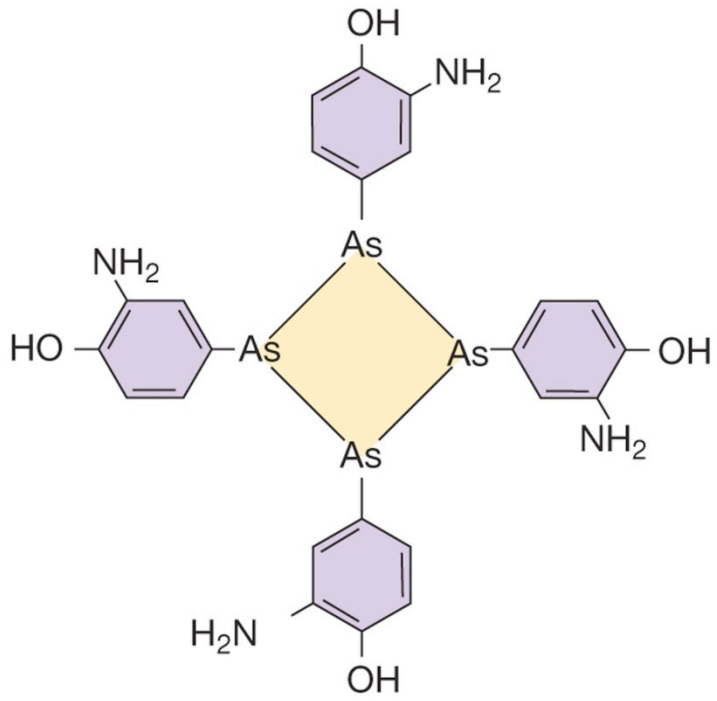
MICROBIOLOGIA GENERALE

Antibiotics, chemotherapeutic agents and resistance

The discovery of antimicrobial





M.T. Madigan, J.M. Martinko **Brock, Biologia dei Microrganismi**

Paul Ehrlich

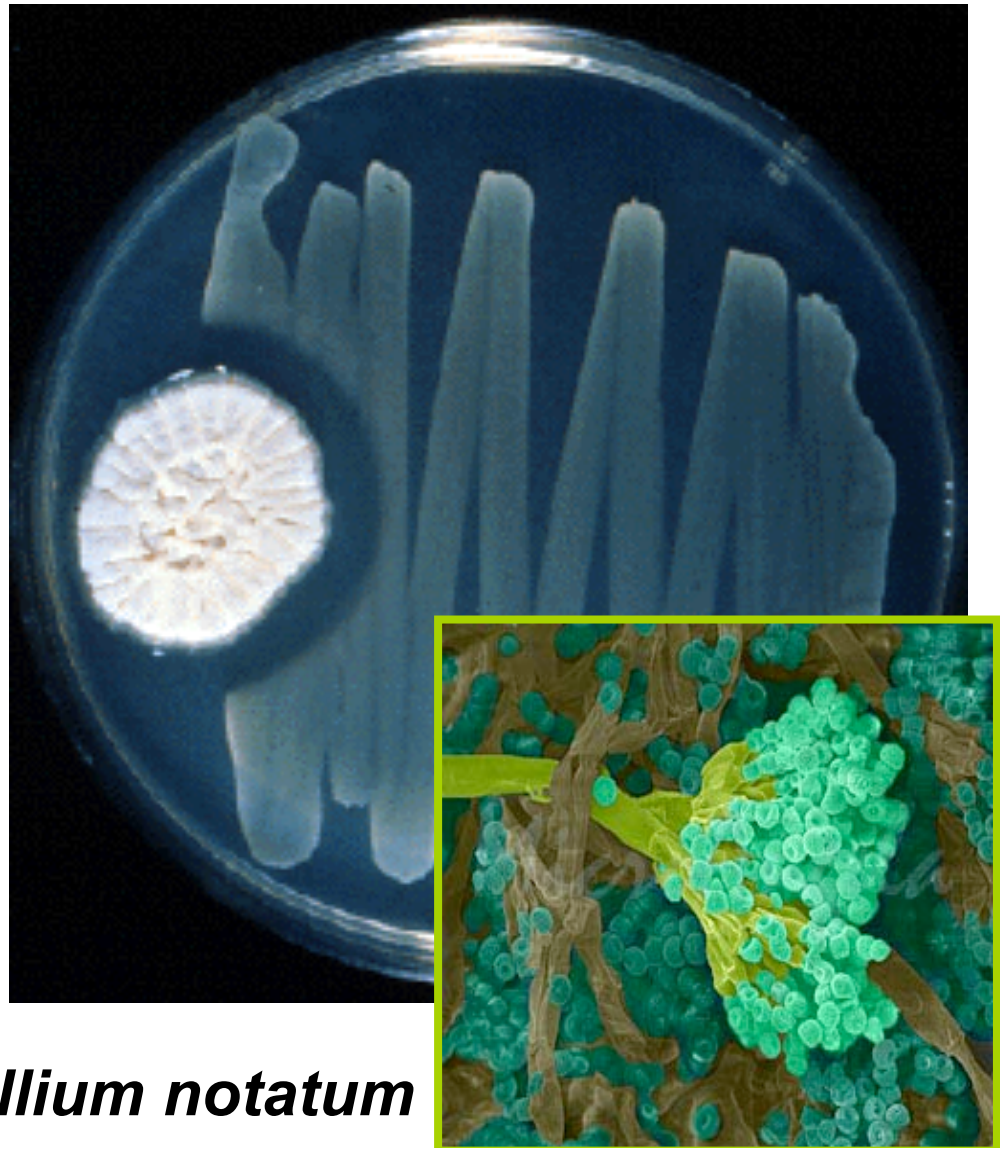
Nobel Prize for Physiology or Medicine in 1908, discovered the the first effective treatment for syphilis (Salvarsan) – selective toxicity

The discovery of antibiotics

Alexander Fleming

1881 – 1955

Nobel Prize for Physiology or Medicine in 1945



Penicillium notatum

The discovery of antibiotics: penicillin

Howard Florey,1898-1968

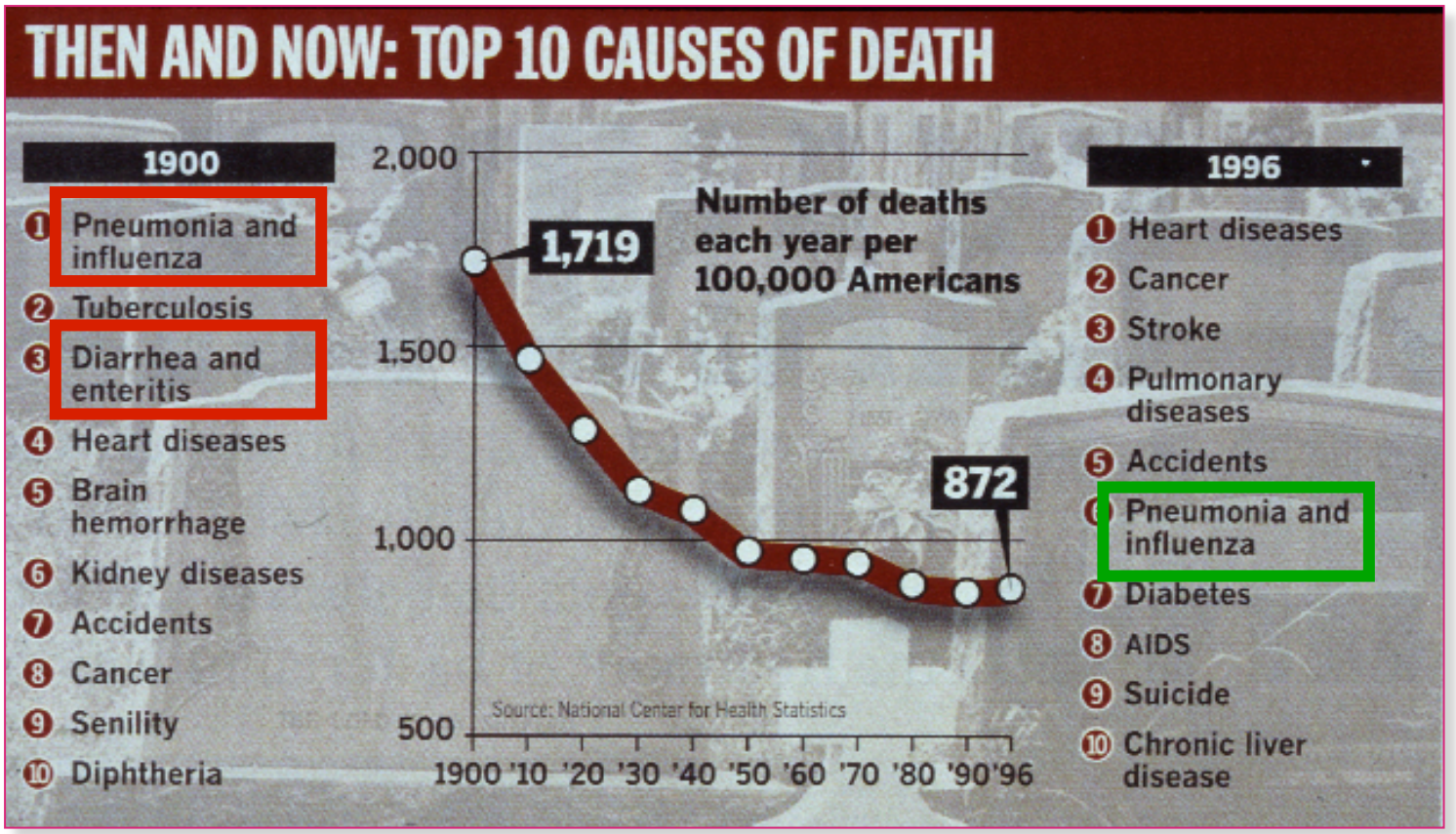
Ernst Boris Chain, 1906-1979

Nobel Prize for Physiology or Medicine in 1945

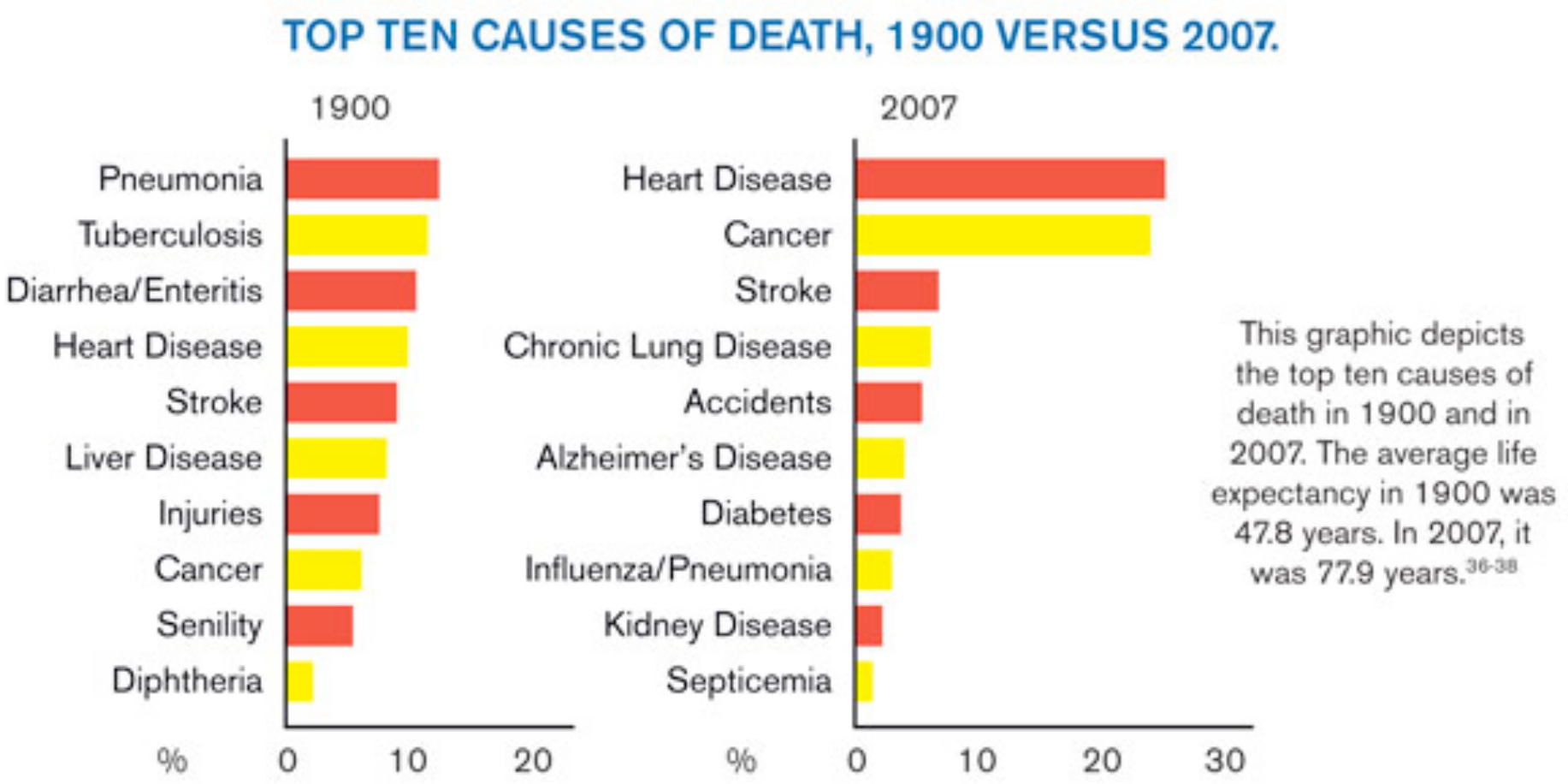
Large scale
Penicillin production
→ useful treatment

Penicillium chrysogenum

Then and Now

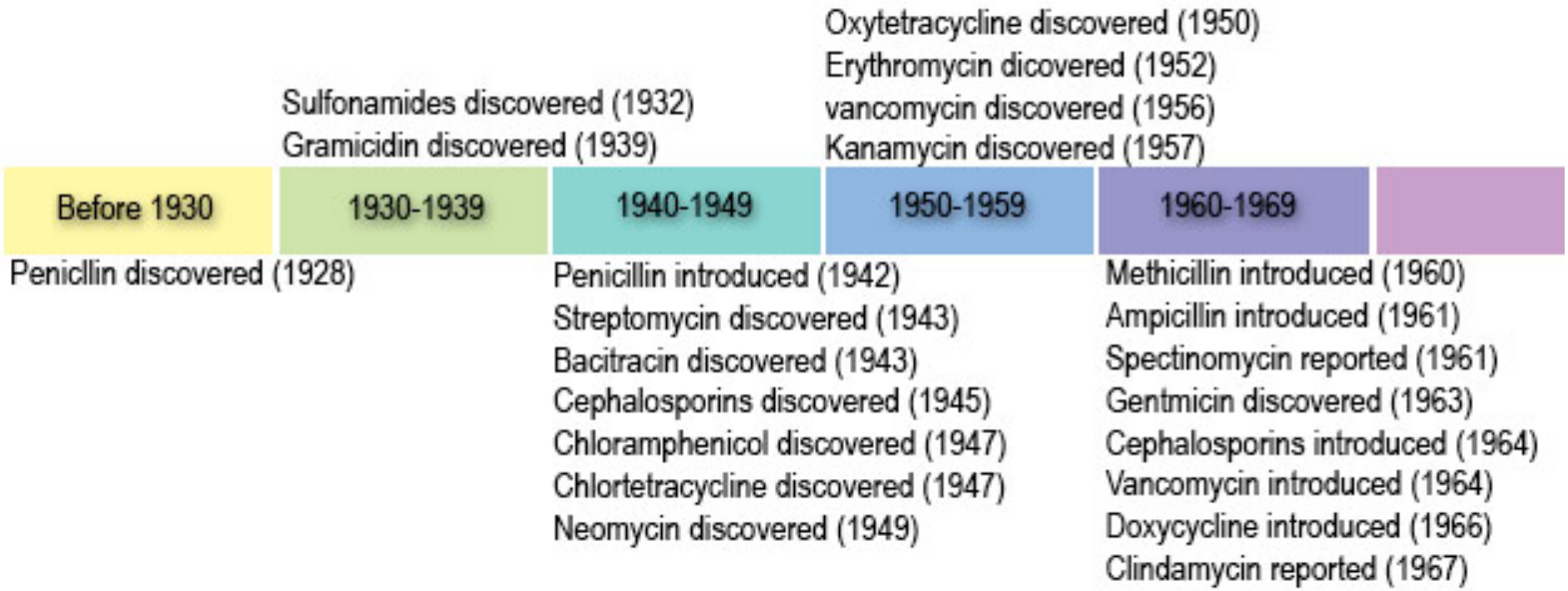

THEN AND NOW: TOP 10 CAUSES OF DEATH
1900
1 Pneumonia and influenza
2 Tuberculosis
3 Diarrhea and enteritis
4 Heart diseases
5 Brain hemorrhage
6 Kidney diseases
7 Accidents
8 Cancer
9 Senility
10 Diphtheria
2,000
1,500
1,000
500
1,719
872
Number of deaths each year per 100,000 Americans
Source: National Center for Health Statistics
1900 '10 '20 '30 '40 '50 '60 '70 '80 '90 '96
1996
1 Heart diseases
2 Cancer
3 Stroke
4 Pulmonary diseases
5 Accidents
6 Pneumonia and influenza
7 Diabetes
8 AIDS
9 Suicide
10 Chronic liver disease

Since the antibiotic discovery…

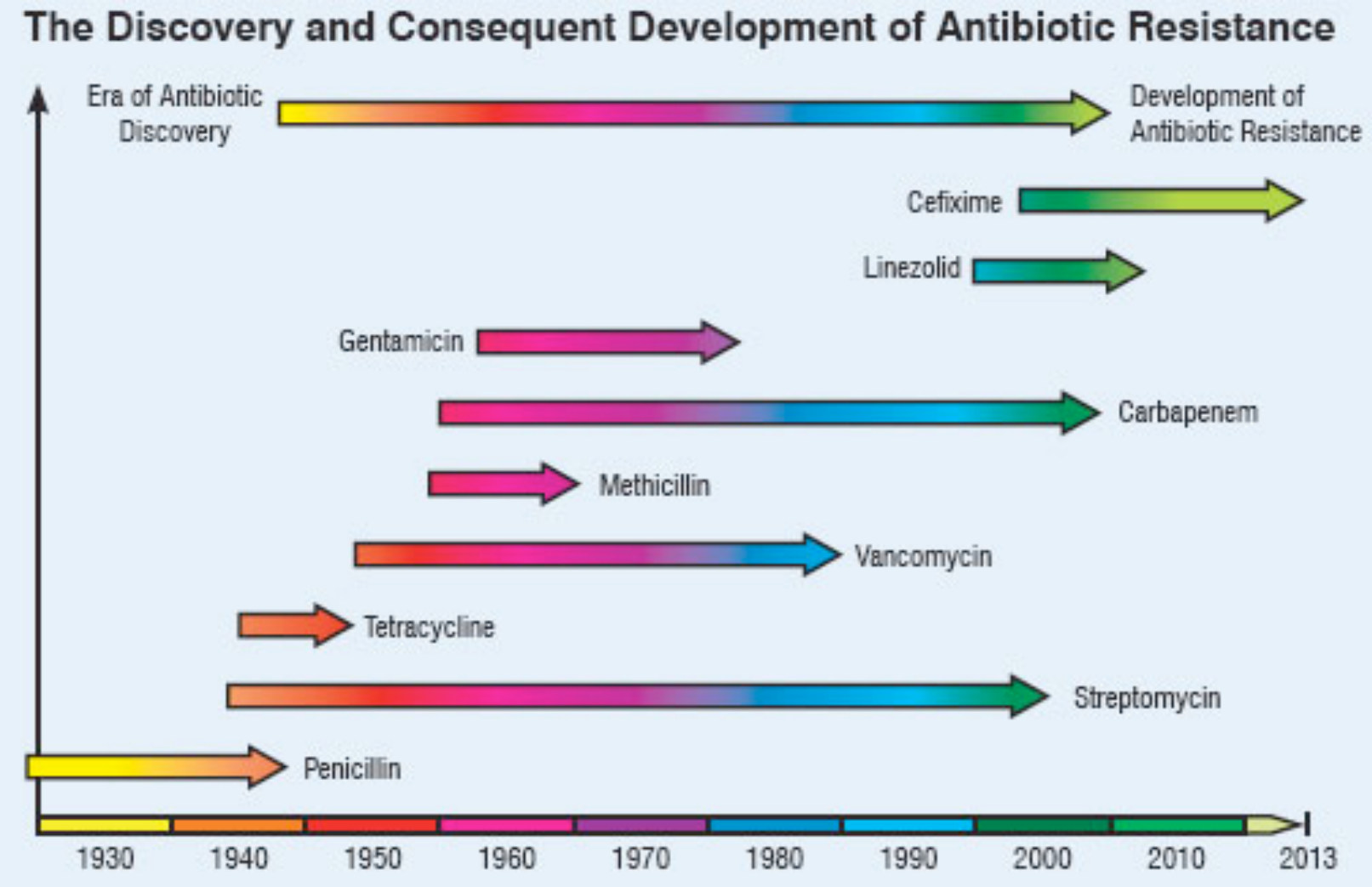


WHO

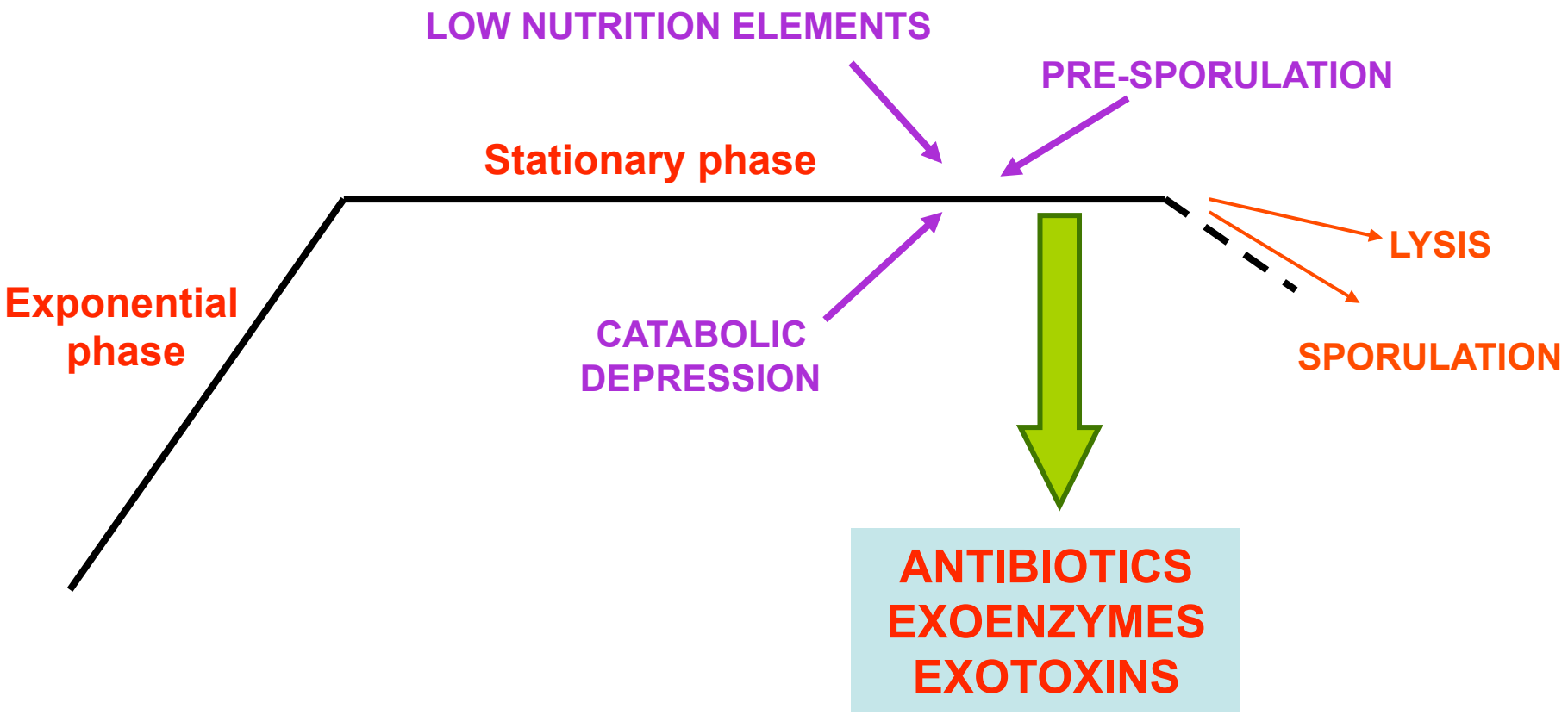
Antibiotic discovery



The race in antibiotic discovery and bacterial resistance



Streptomyces growth curve and antibiotics production



Antibiotics: low-molecular weight (>1000) molecules produced as secondary metabolites mainly by microrganisms that live in soil.

Chemotherapeutic agents: chemically synthesized drugs produced in laboratory using chemical procedures

✓ Many antibiotics are now chemically modified biological products: semisynthetic antibiotics

✓ The generic terms to refer to either antibiotics or chemotherpeutic agents are antimicrobics or antimicrobial agents

- Bactericidal: kills susceptible bacteria
- Bacteriostatic: reversibly inhibits the growth of bacteria

SELECTIVE TOXICITY

Ability of antibiotics to be toxic only against microorganisms (not eukaryotic cells)

Cell structure	Prokaryotes	Eukaryotes	Principle
Cell membrane	Sterols -	Sterols +++	Different penetration
Ribosomes	70S	80S	Different target
Cell wall	Peptidoglycan	None	No target

Antibiotics: Classification

- ✓ **Origin**
- ✓ **Range of action**
- ✓ **Type of action**
- ✓ **Mechanism of action**

Antibiotics: Classification (1)

ORIGIN

Mining
by bacteria and fungi (*Penicillium, Cephalosporium, Streptomyces*)

Semisynthetic
starting from a basic structure, obtained by extraction (fermentation) and adding chains synthesis

→ **Chemoantibiotic**

Chemical synthesis
many compounds are obtained chemically synthesized (quinolones, monobactams)

→ **Chemotherapy**

Antibiotics: Classification (2)

Broad range
Activity against
G+ (+++)
G- (+++)

Intermediate range
molecule is active against
Gram+ and certain
Gram- bacteria

Limited range
Molecule is active against
some G+ or G-

Specific
Activity against one
bacterial species or
gender

RANGE OF ACTION

Antibiotics: Classification (3)

TYPE OF ACTION

Bacteriostatic: reversibly inhibits the growth of bacteria

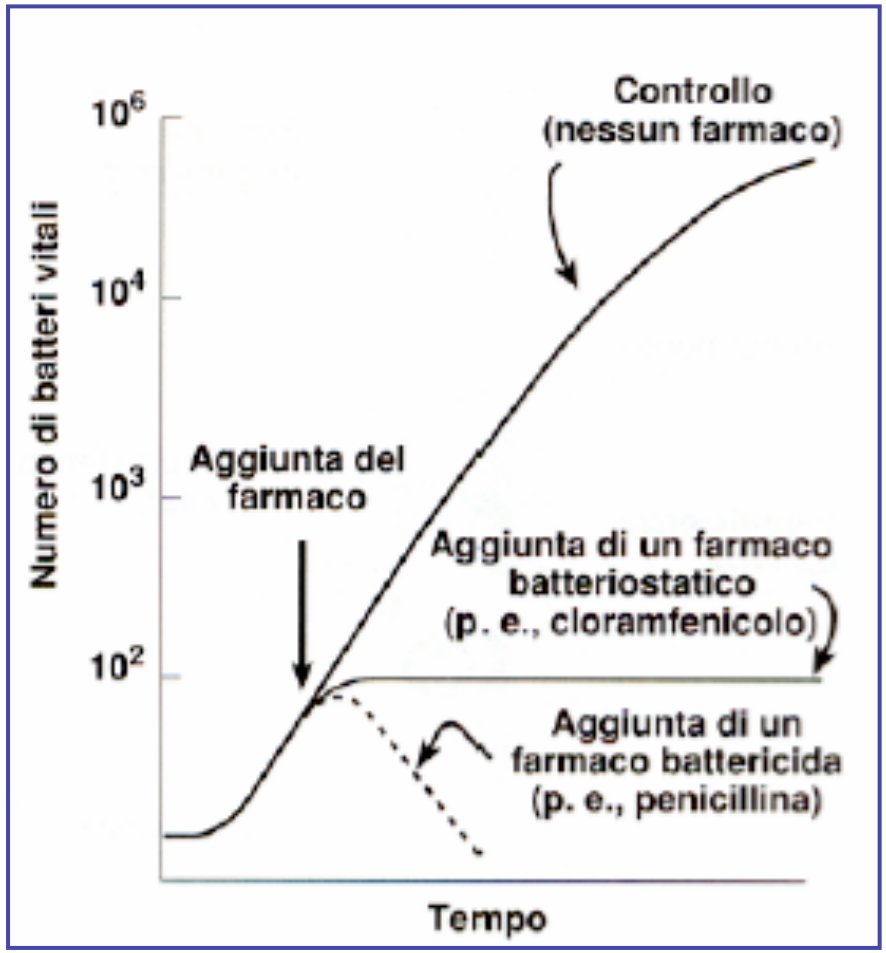
→ **M.I.C.**

Bactericidal: kills susceptible bacteria. Antibiotic is bactericidal when it determines a survival equal to or less than 0.01% (after 24 h growth *in vitro*")

→ **M.B.C.**

Antibiotics could show both bacteriostatic (low dosage) and bactericidal (high dosage) activities.

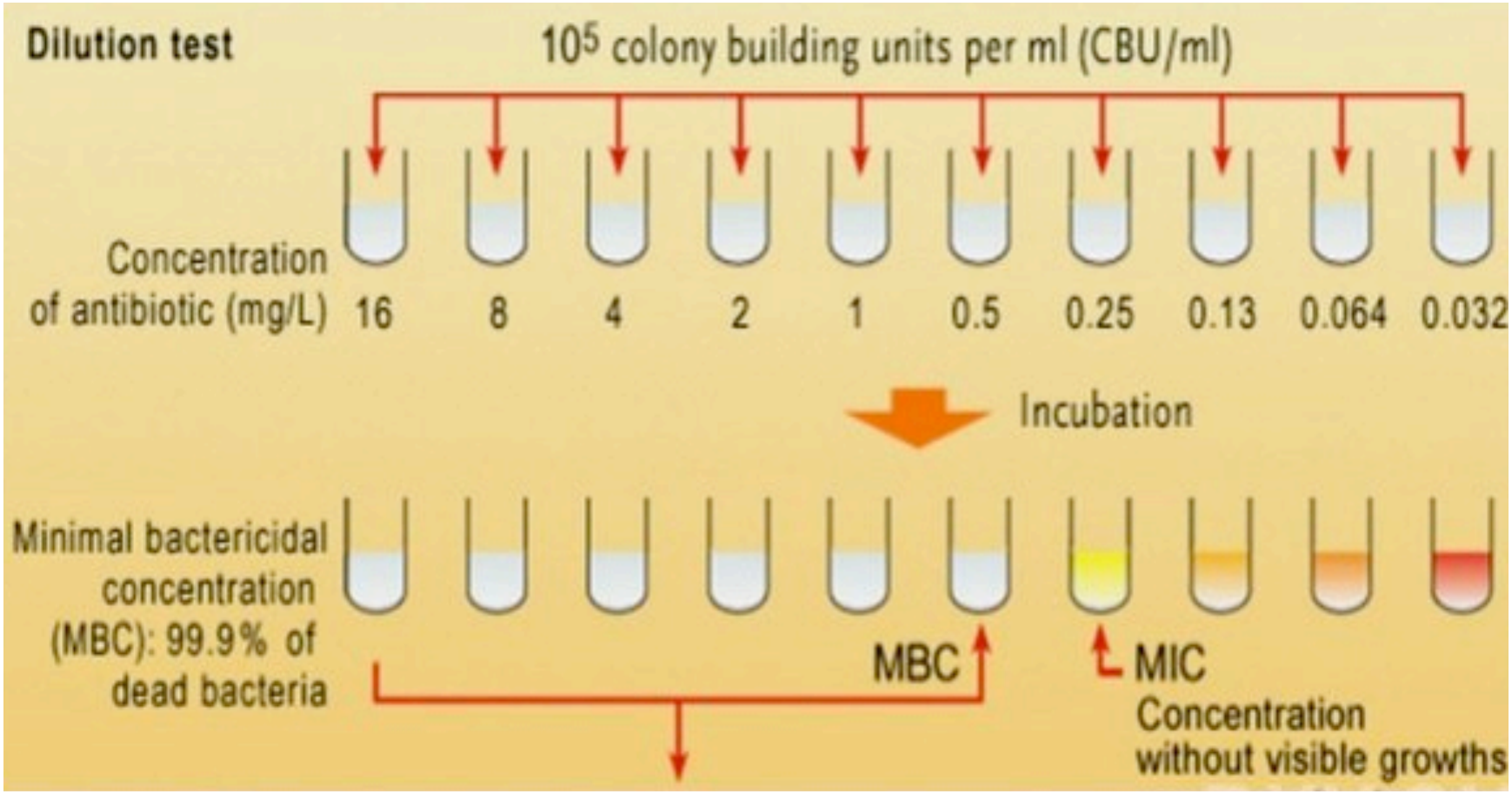
Antibiotics: MIC vs MBC



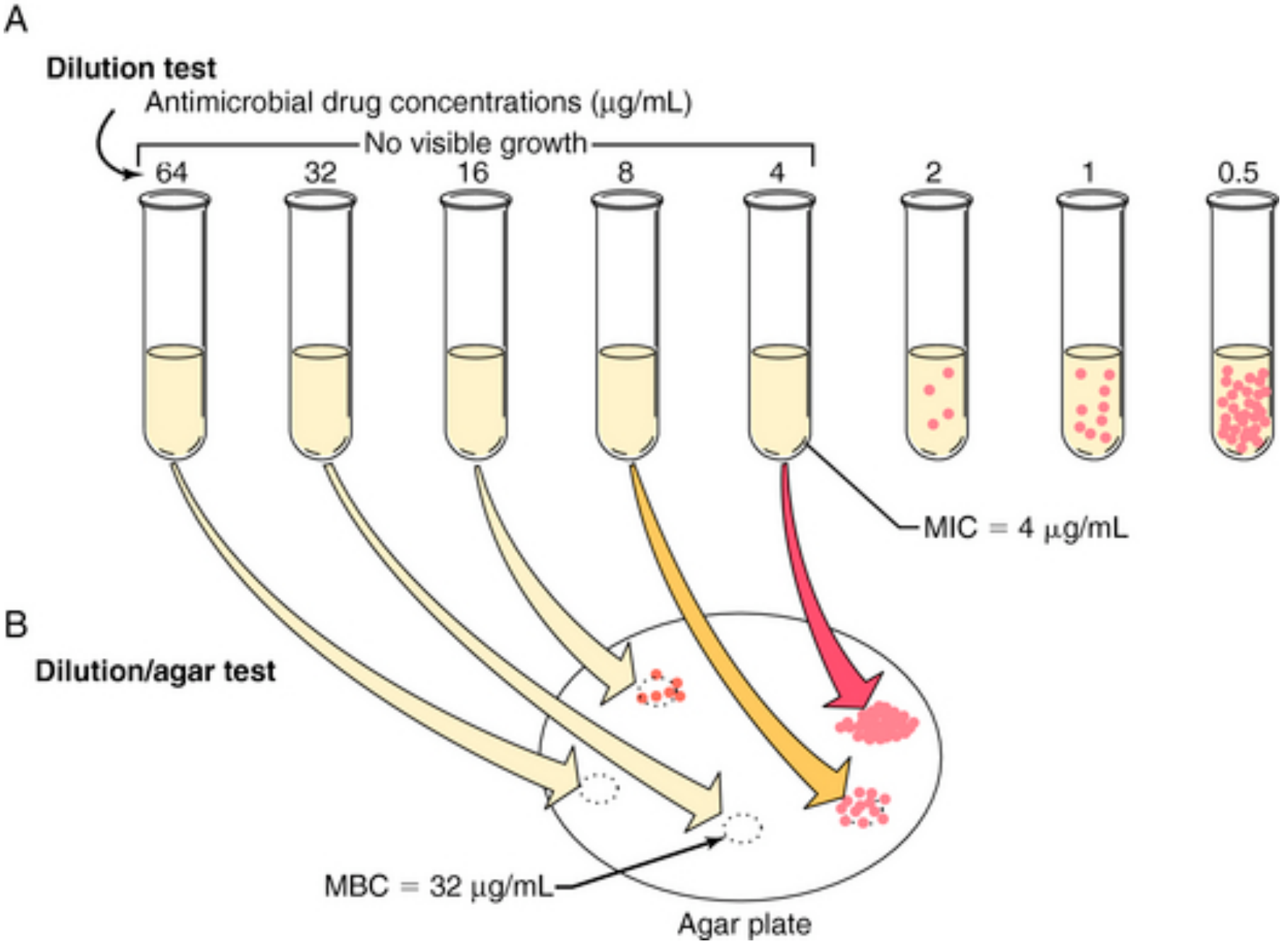
MIC: minimal inhibitory concentration is the smallest amount of drug able to inhibit the bacterial growth

MBC: minimal bactericidal concentration is the smallest amount of drug able to kill the bacterial cell

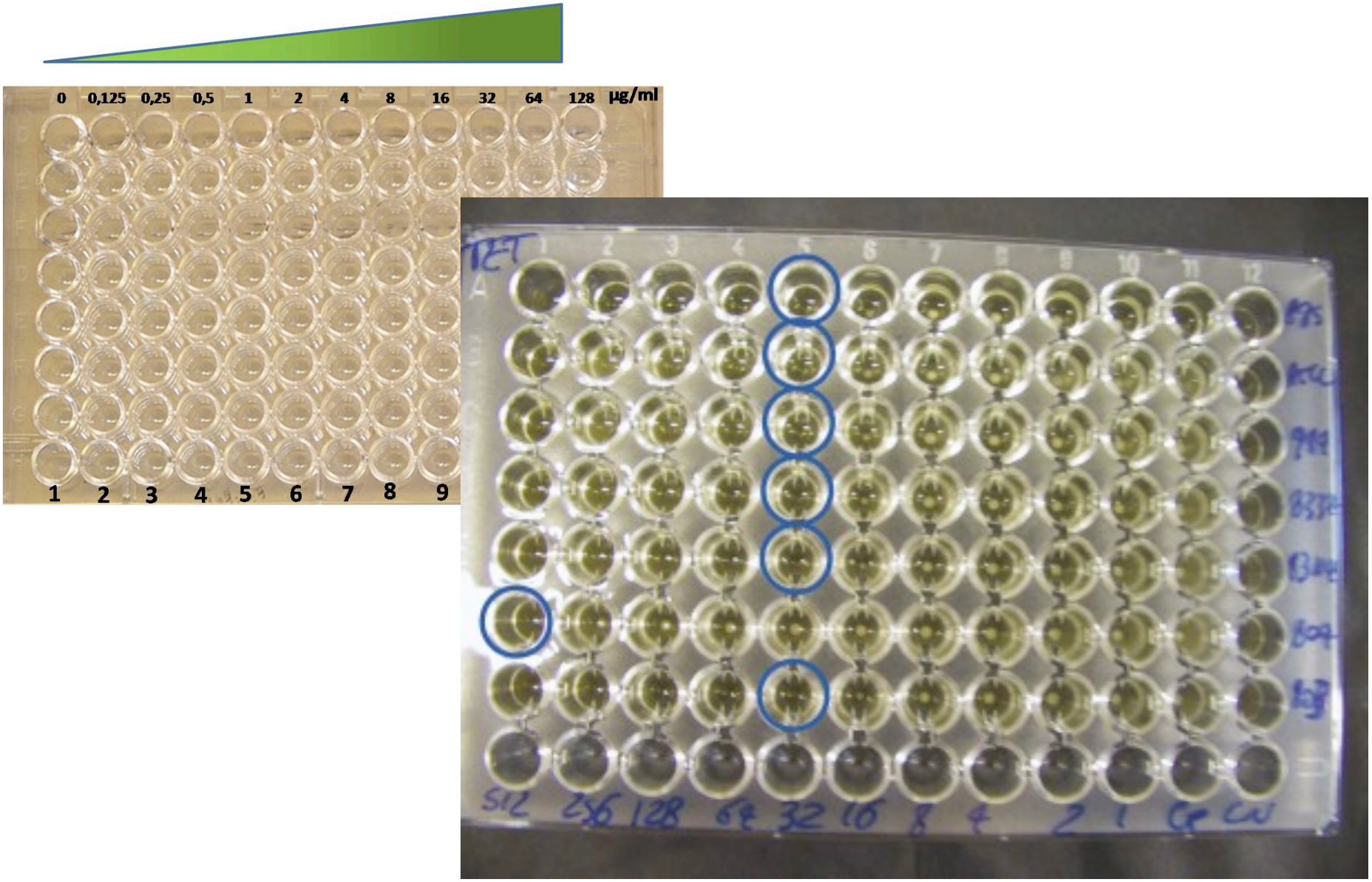
Antibiotics: MIC vs MBC



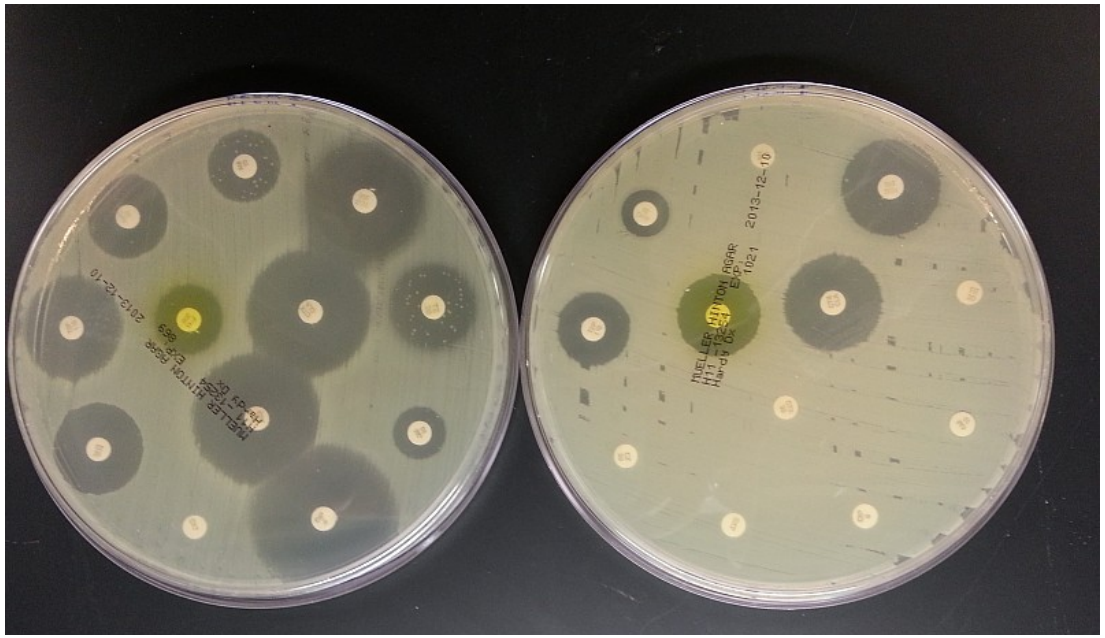
Antibiotics: MIC vs MBC

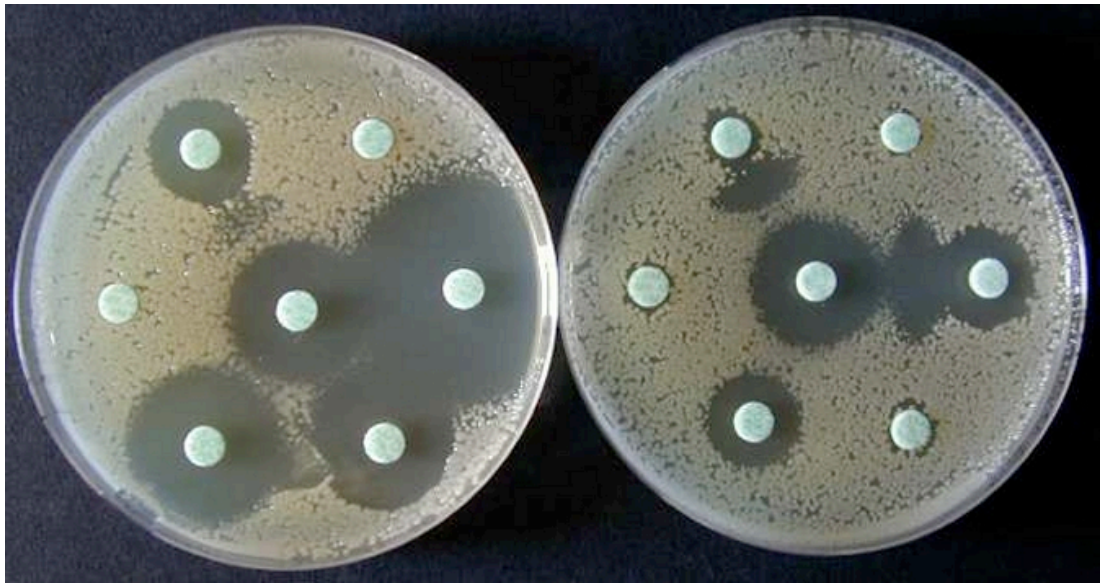


Antibiotics: MIC vs MBC



Antibiotics: antibiogram

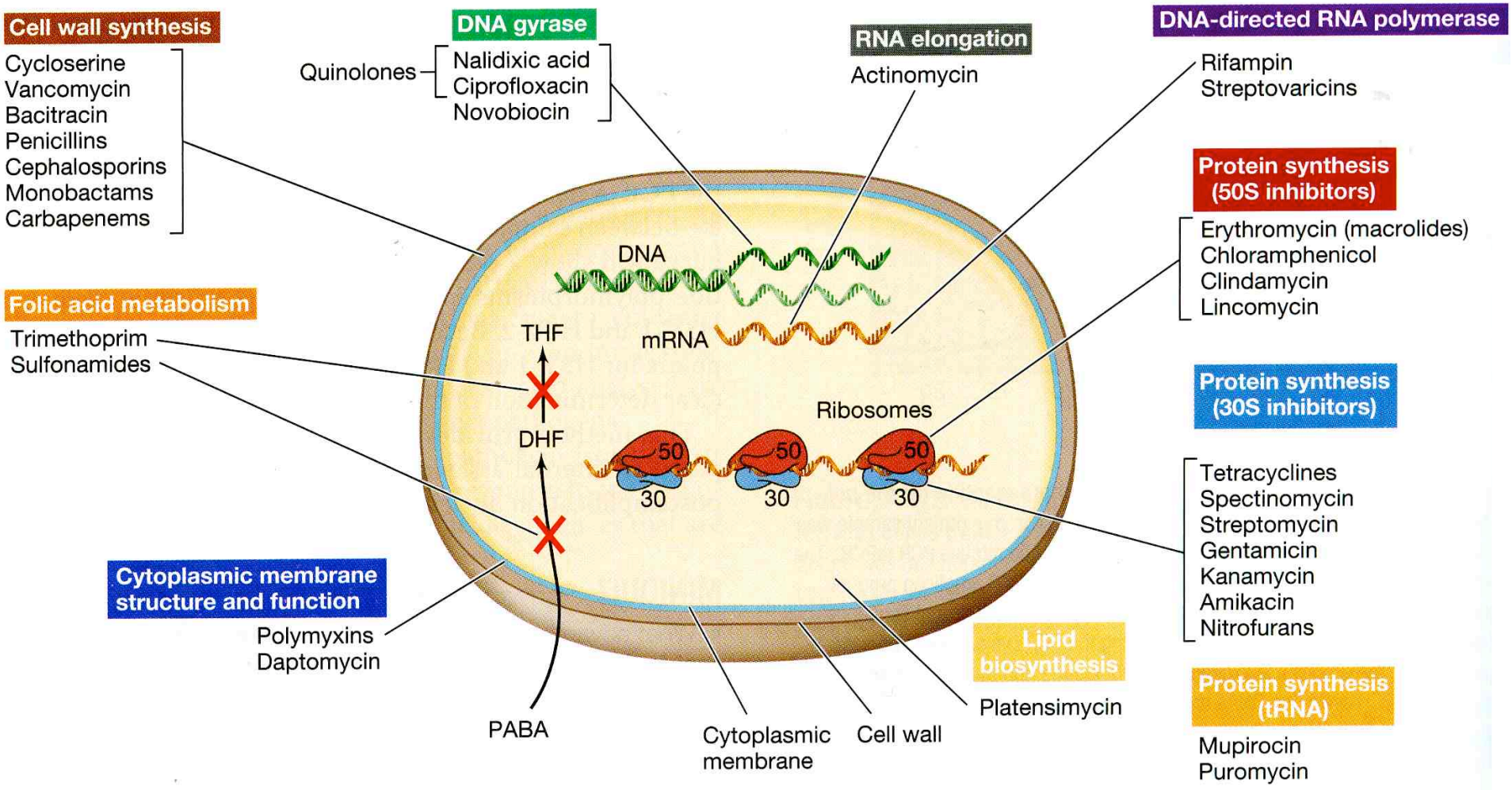


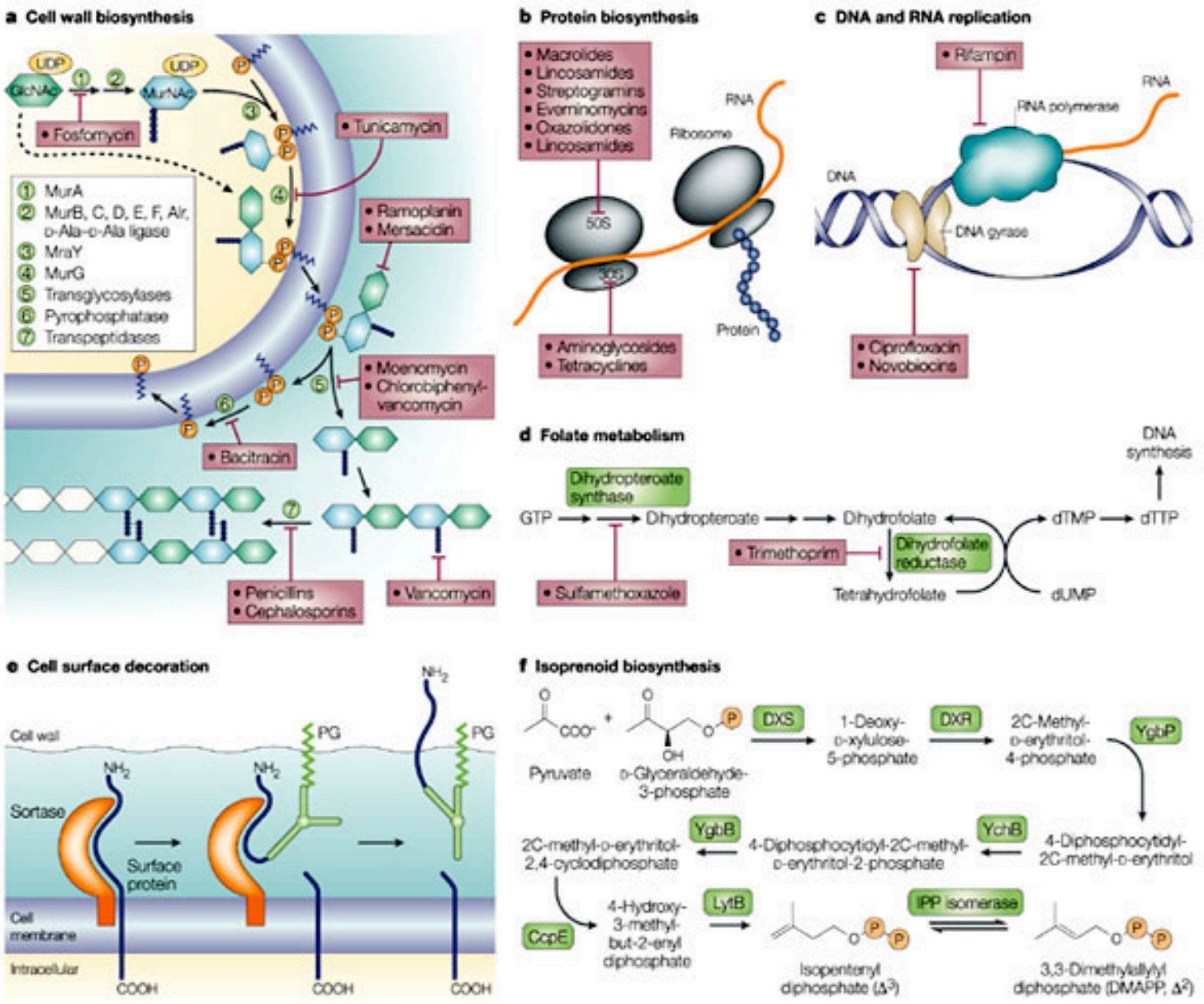


Antibiotics: Mechanisms of action

- ✓ Cell wall syntesis: β-lactam, Carbapenem, Glycopeptides
- ✓ Membrane permeability: Polymyxins
- ✓ Protein synthesis: Aminoglycosides, Macrolides, Tetracyclines
- ✓ Folic acid metabolism: Sulfonamides
- ✓ DNA replication: Quinolones
- ✓ RNA transcription: Rifamycins

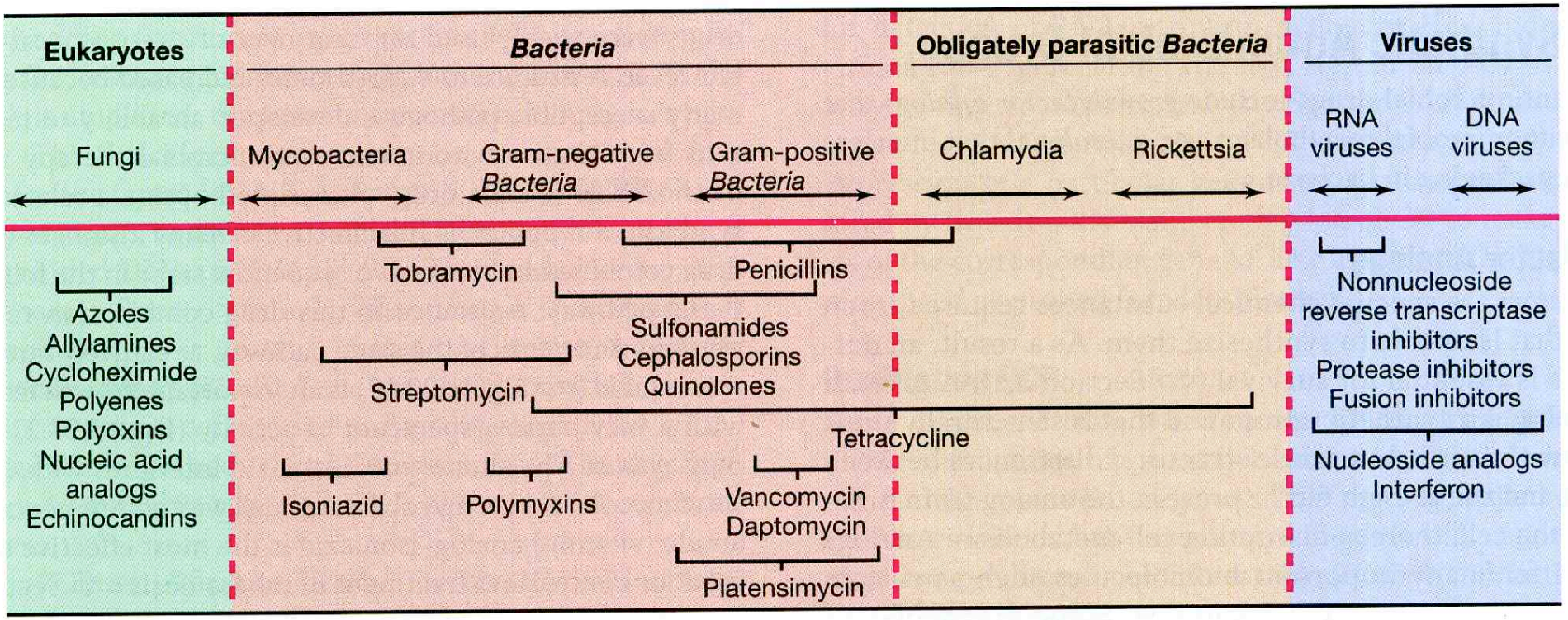
Targets of major antibacterial agents





Antibiotics: Mechanisms of action

Antimicrobial spectrum of activity

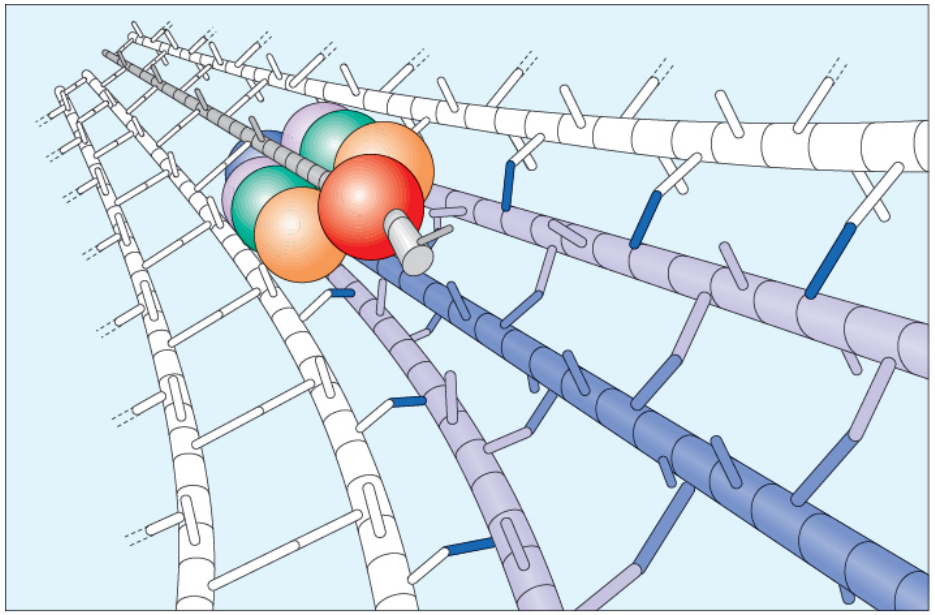


Antibiotics: Mechanisms of action

- ✓ Cell wall syntesis: β-lactam, Carbapenem, Glycopeptides
- ✓ Membrane permeability: Polymyxins
- ✓ Protein synthesis: Aminoglycosides, Macrolides, Tetracyclines
- ✓ Folic acid metabolism: Sulfonamides
- ✓ DNA replication: Quinolones
- ✓ RNA transcription: Rifamycins

Inhibition of cell wall synthesis: The Beta-Lactams

Prevent the formation of cross-linking of the cell wall



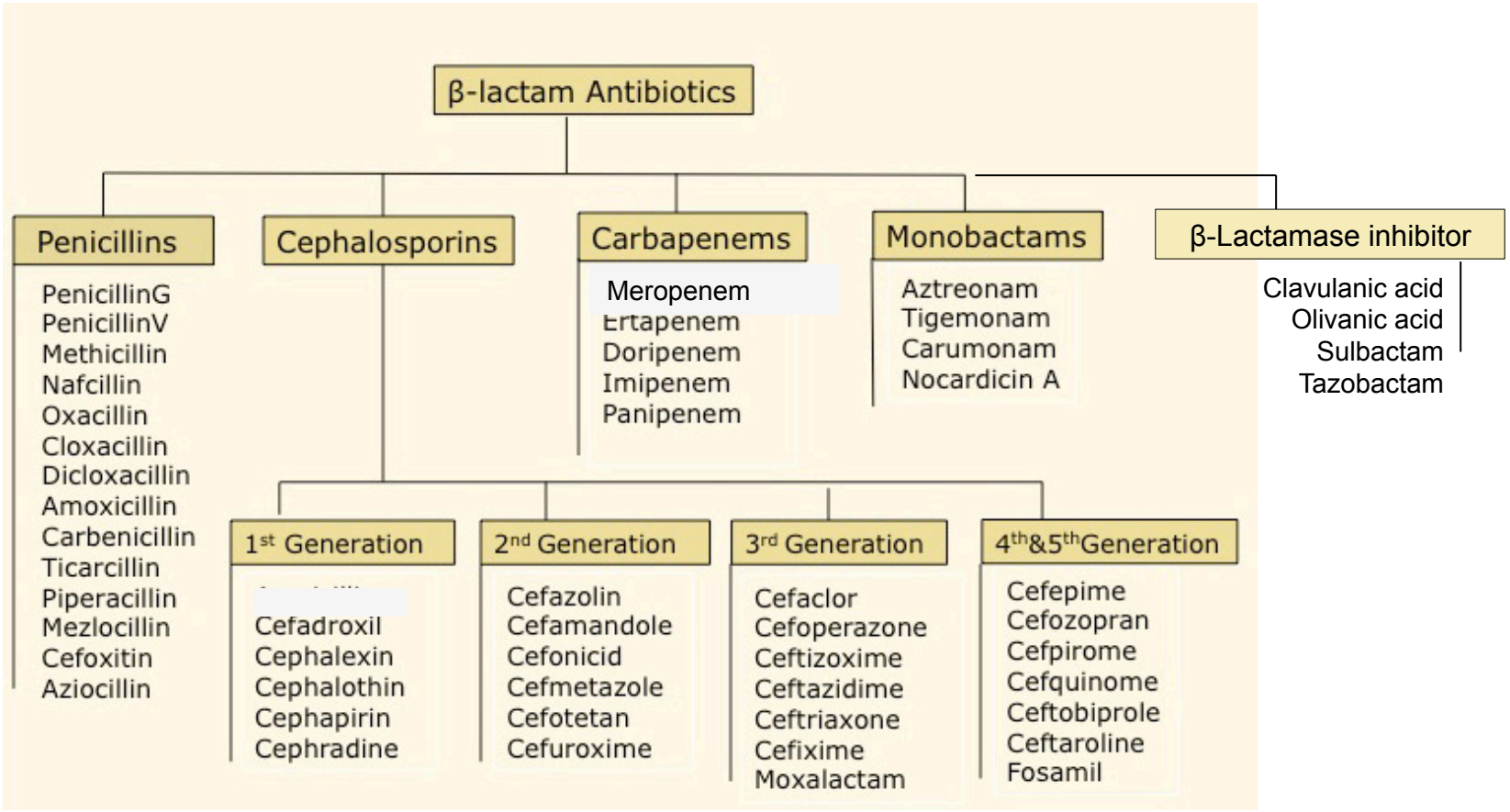
- ✓ Penicillins
- ✓ Cefalosporins
- ✓ Cephamycin
- ✓ Carbapenem
- ✓ Monobactams
- ✓ Beta lactamase inhibitors (clavulanic acid)

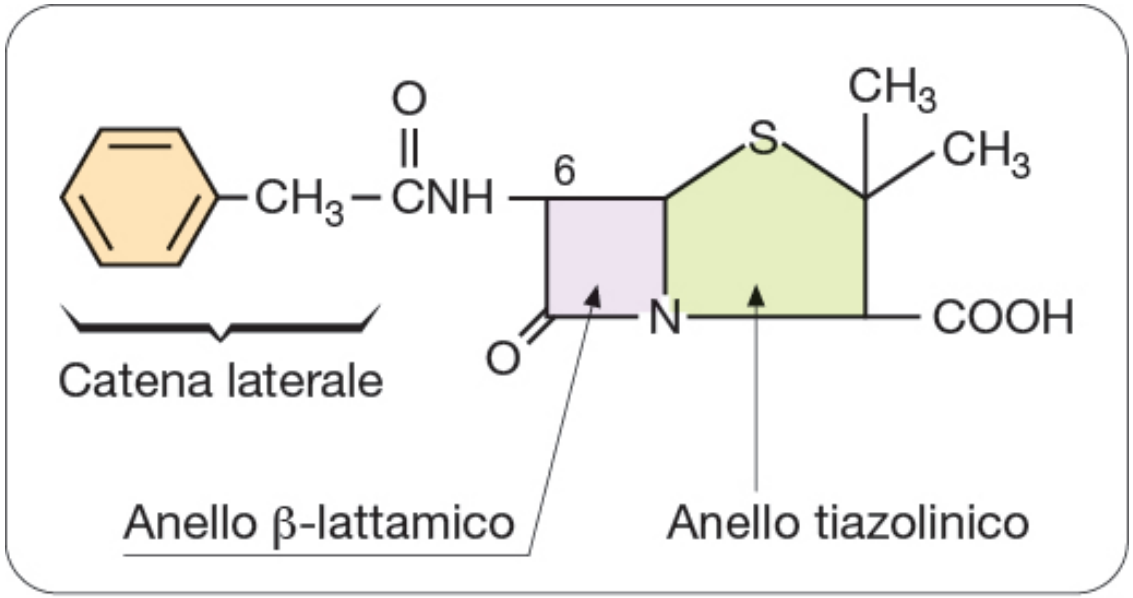
Selective toxicity:

Mycoplasma,

Eukaryotes.

Inhibition of cell wall synthesis: β-Lactams

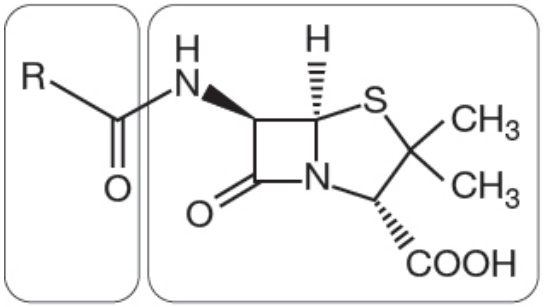




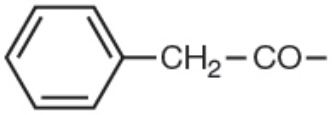
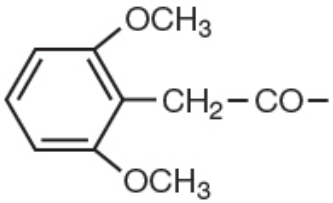
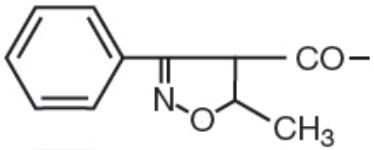
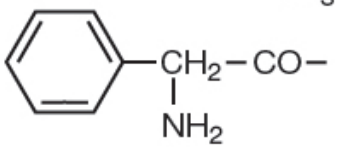
Penicillina

b) Gruppo delle penicilline

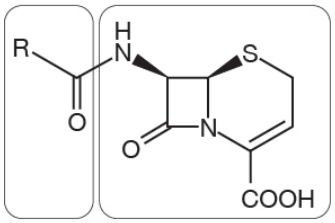
Gruppo *N*-acile



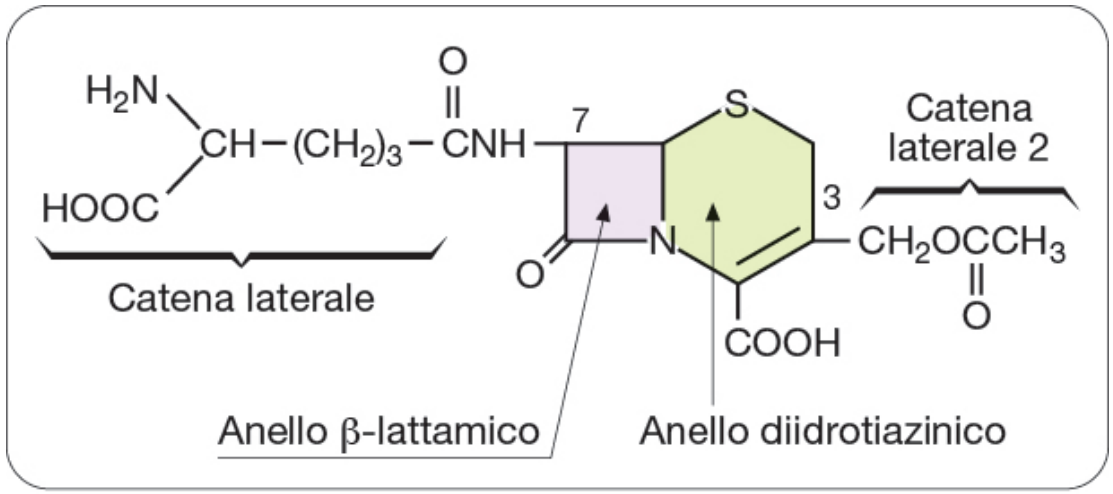
Acido 6-aminopenicillanico

Gruppo *N*-acile	Designazione
	Penicillina G
	Meticillina
	Oxacillina
	Ampicillina

c) Gruppo delle cefalosporine

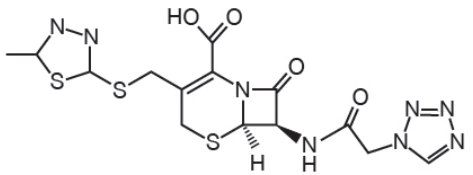


Acido 7-aminocefalosporanico

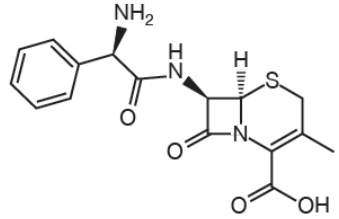


Cefalosporina

Cefalosporine di I generazione

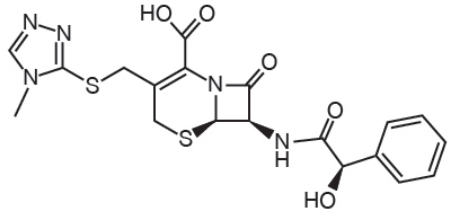


Cefazolin

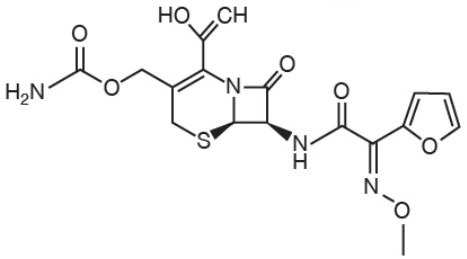


Cefalexin

Cefalosporine di II generazione

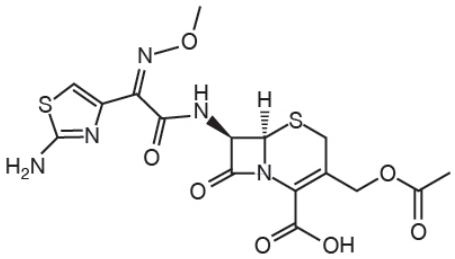


Cefamandole

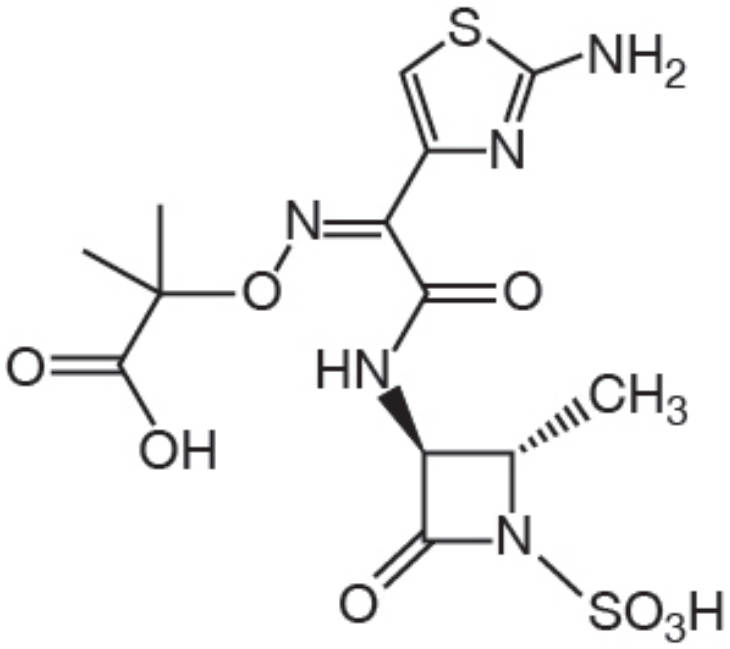


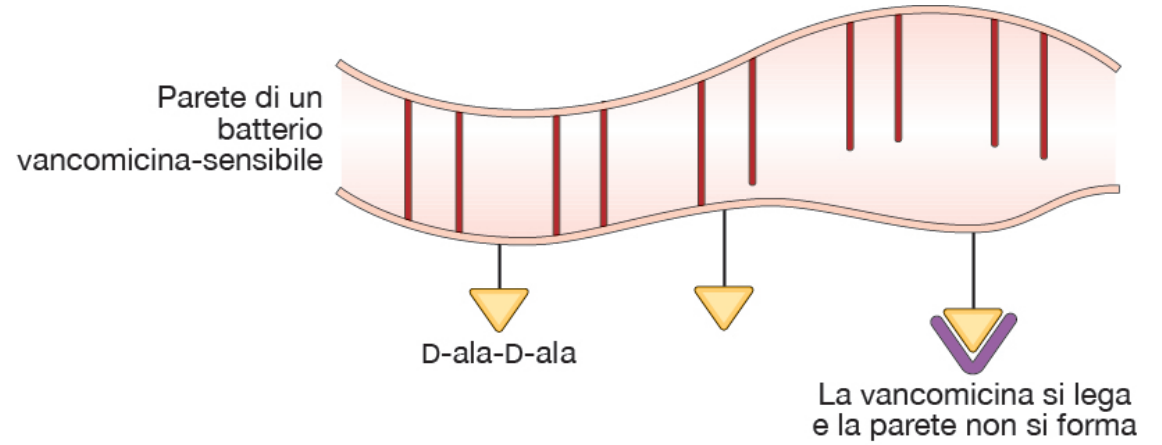
Cefuroxime

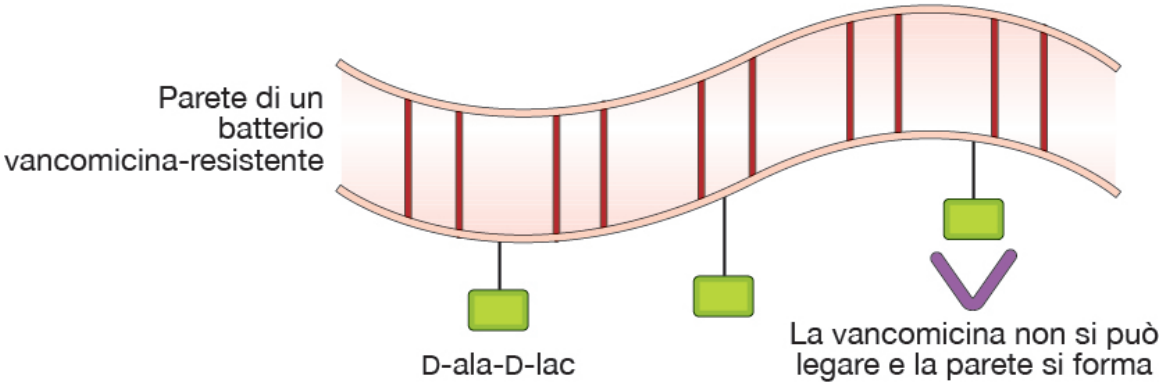
Cefalosporine di III generazione



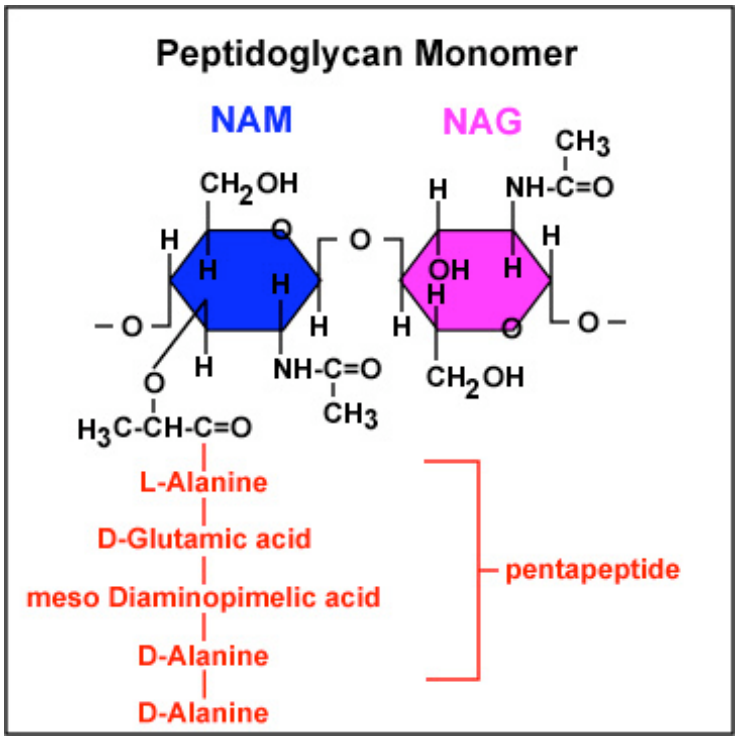
Cefotaxine

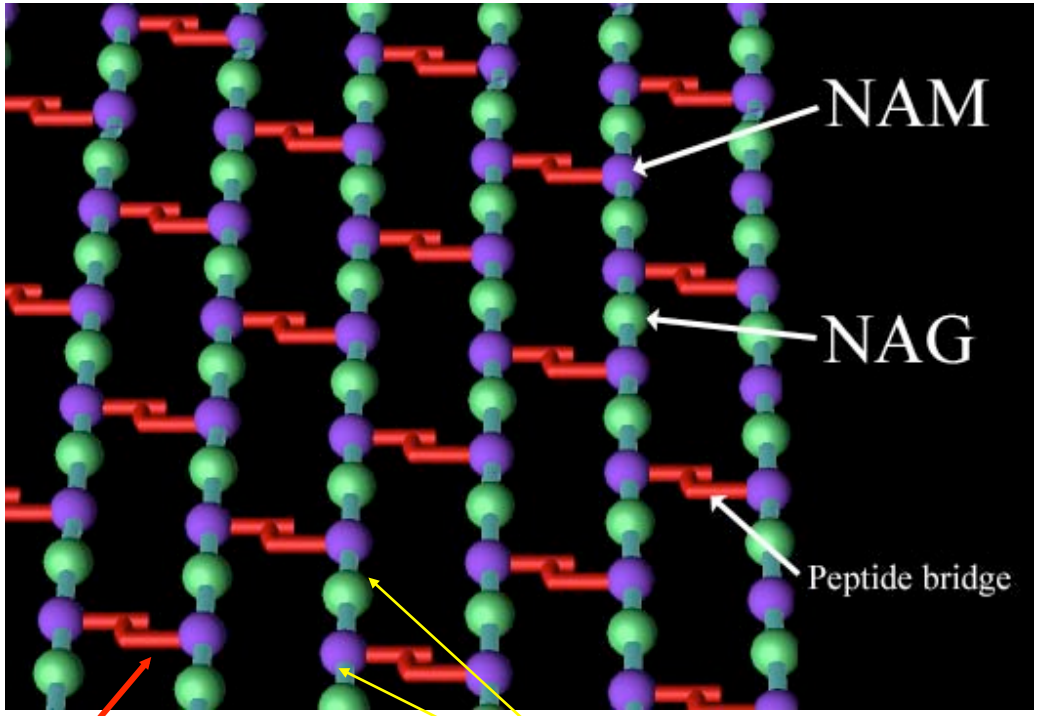

S
NH2
N
N
O
O
O
HN
CH3
OH
N
O
SO3H


Parete di un batterio vancomicina-sensibile
D-ala-D-ala
La vancomicina si lega e la parete non si forma


Parete di un batterio vancomicina-resistente
D-ala-D-lac
La vancomicina non si può legare e la parete si forma

Inhibition of cell wall synthesis: The Beta-Lactams





Beta (1-6) Bound

Beta (1-4) bound

Transpeptidation reaction: PBP

Inhibition of cell wall synthesis: The Beta-Lactams

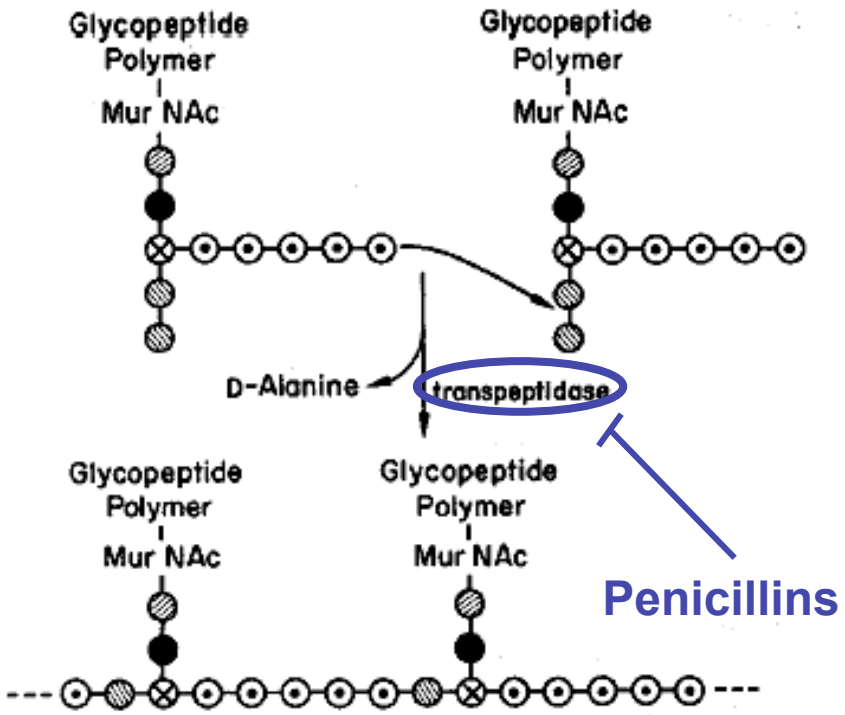


Figure 50–3. *The transpeptidase reaction in* Staphylococcus aureus *that is inhibited by penicillins and cephalosporins.*

See text for details. *Mur NAc* = N-acetylmuramic acid; ◍ = L-alanine; ● = D-glutamate; ⊗ = L-lysine; ◍ = D-alanine; ⊙ = glycine.

Penicillin-binding proteins (PBPs):

Membrane-bound enzymes

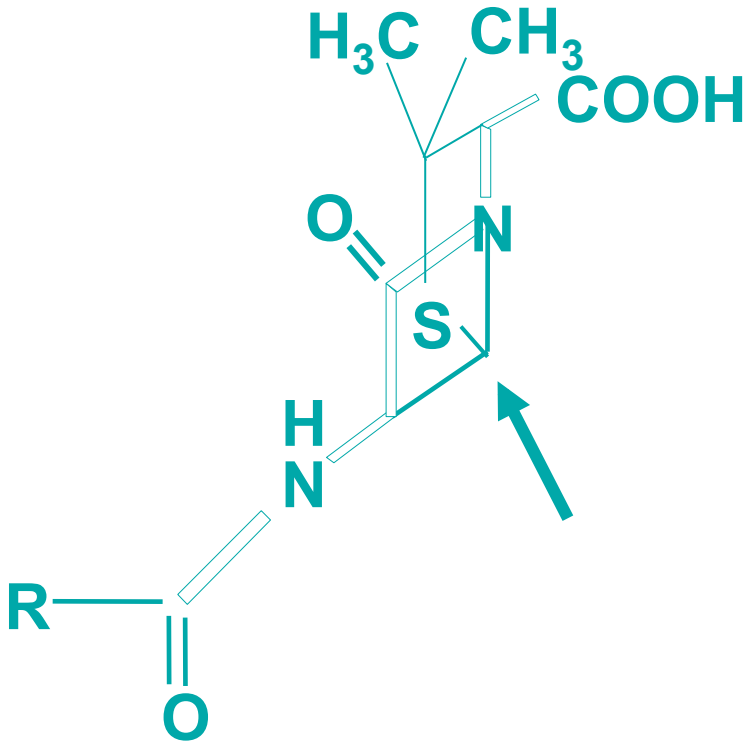
Catalyze final steps of peptidoglycan synthesis (transpeptidation)

- **β-lactams:**
  - **Act on PBPs, inhibit transpeptidation**
  - **Substrate analogues of D-Ala-D-Ala →**

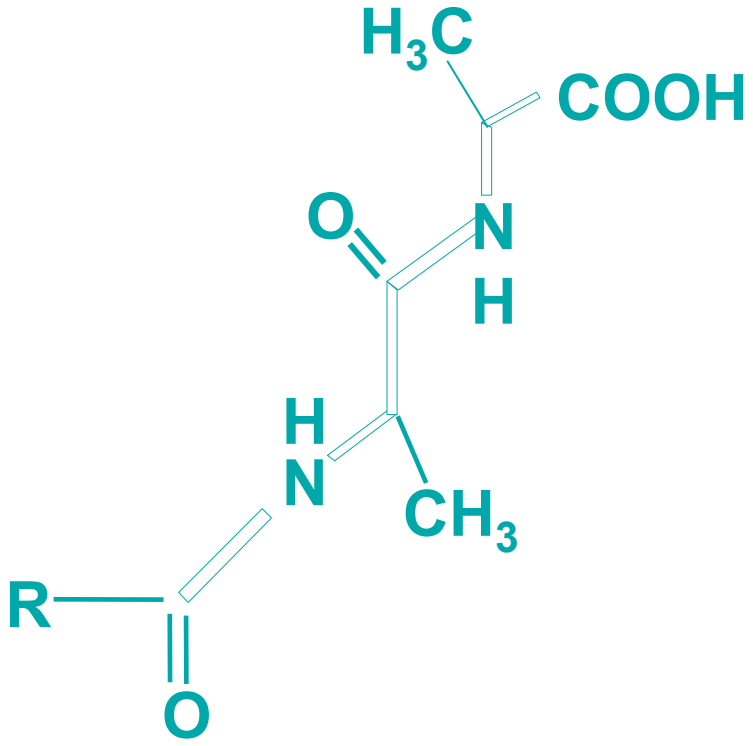
Active proliferation-Bactericidal

Inhibition of cell wall synthesis: Penicillins

Structural analogy between D-dimer ala-ala and b-lactam



B-lactam



Dala-ala

Inhibition of cell wall synthesis: Penicillins

NATURAL PENICILLINS
Benzilpenicillins (G penicillin)
Phenoxymethyl penicillin (V penicillin)

→ Not completely adsorbed because it is inactivated by gastric acids

PENICILLINASE-RESISTANT PENICILLINS
Nafcillin
Methycillin
Oxacillin
Cloxacillin
Dicloxacillin

→ Used in the treatment of infections caused by sensible staffilococci

BROAD RANGE PENICILLINS
Aminopenicillins (ampicillin, amoxicillin)
Carbossipenicillins (carbencillin e ticarcillin)
Ureidopenicillins (mezlocillin, piperacillin)

→ Ampicillin is active also on Gram- bacteria

Inhibition of cell wall synthesis: Cefalosporins

Cephalosporium achremonium

- **Chemical structure and function similar to Penicillins;**
- **Resistant to β-lactamases;**
- **Divided in 4 groups on the base of anti-bactericidal spectrum;**

	G+	G-
I	++++	+
II	+++	++
III	+	+++
IV	++	++++

Bactericidals

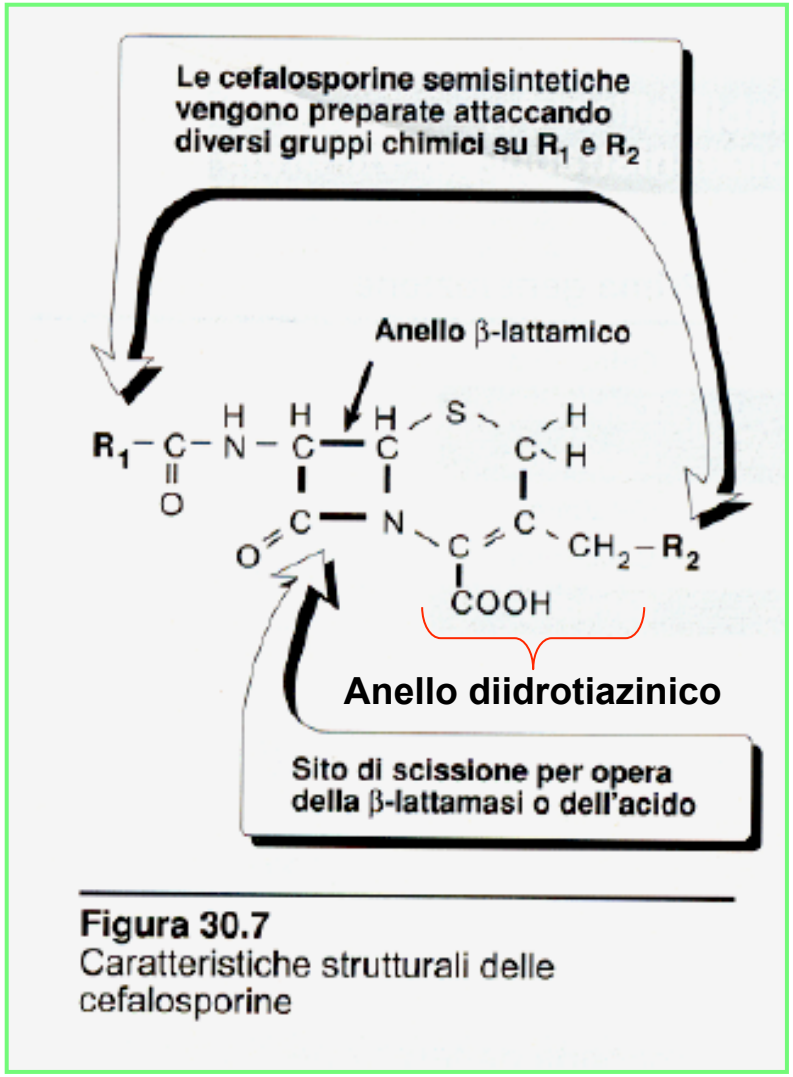
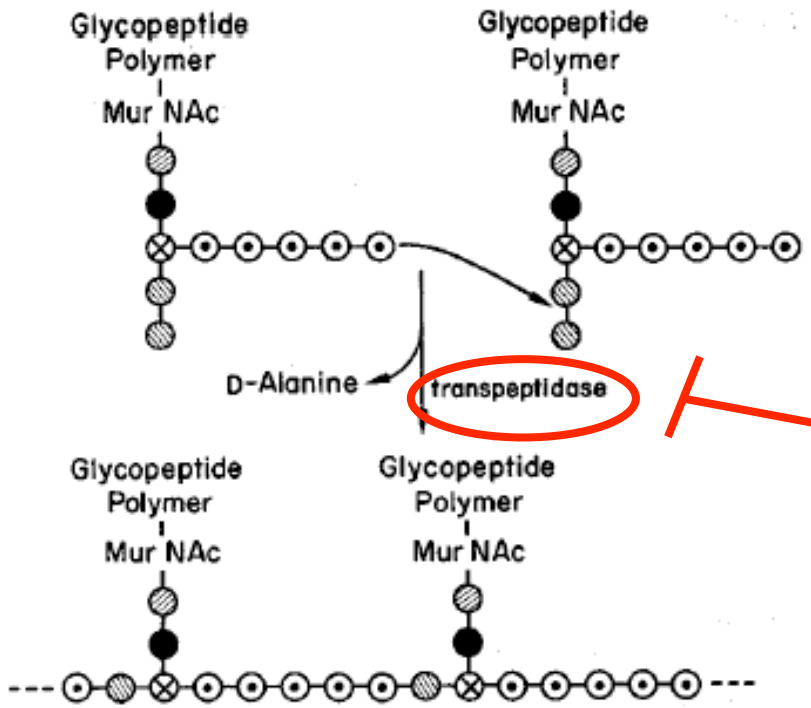


Figura 30.7
Caratteristiche strutturali delle cefalosporine

Inhibition of cell wall synthesis: Penicillins



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See text for details. *Mur NAc* = N-acetylmuramic acid; ◍ = L-alanine; ● = D-glutamate; ⊗ = L-lysine; ◍ = D-alanine; ⊙ = glycine.

cefalosporin

Mechanism of action:

They inhibit the bacterial growth by interfering with the synthesis of cell wall by binding to their receptor (PBP, penicillin binding protein)

Cephamicin

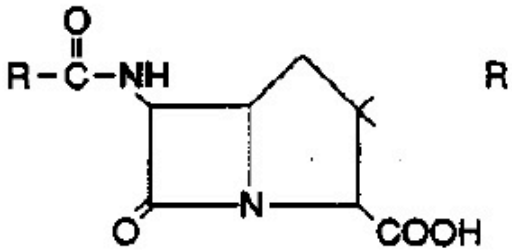
Streptomyces

Inhibition of cell wall synthesis: other β-Lactams

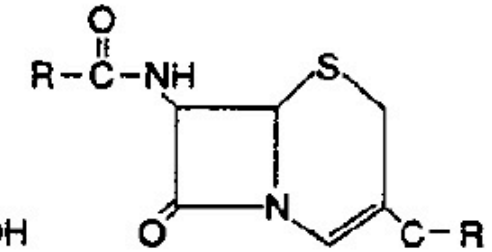
BETA-LATTAMINE NON PENICILLINE E NON CEFALOSPORINE

Sono farmaci nei quali è presente l'anello beta-lattamico, mentre sono intervenute modificazioni a carico dell'anello eterociclico (tiazolidinico o diidrotiazinico). Esistono anche derivati che hanno perso l'anello eterociclico, nei quali la struttura fondamentale è il solo anello beta-lattamico (monobattamici)

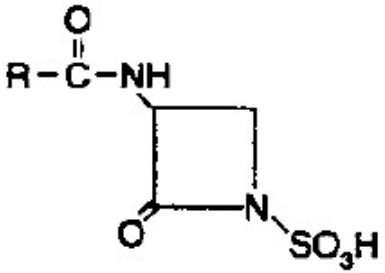
Penicillins



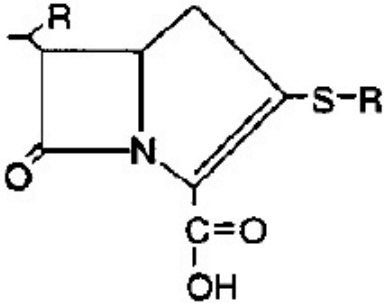
Cephalosporins



Monobactams

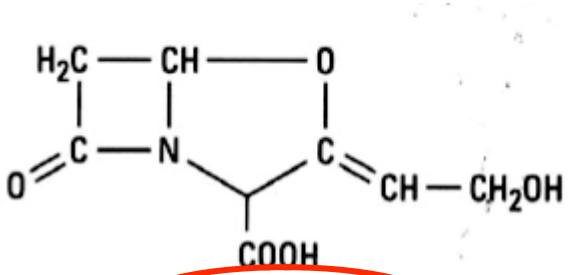


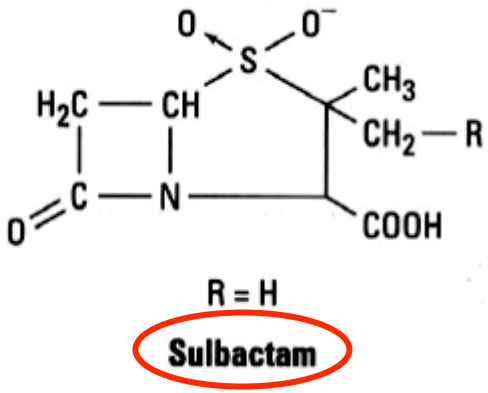
Carbapenems



Inhibition of cell wall synthesis: other β-Lactams

β-lactamase inhibitors: chemical structure similar to β-lactam antibiotics but with lower antimicrobial activity





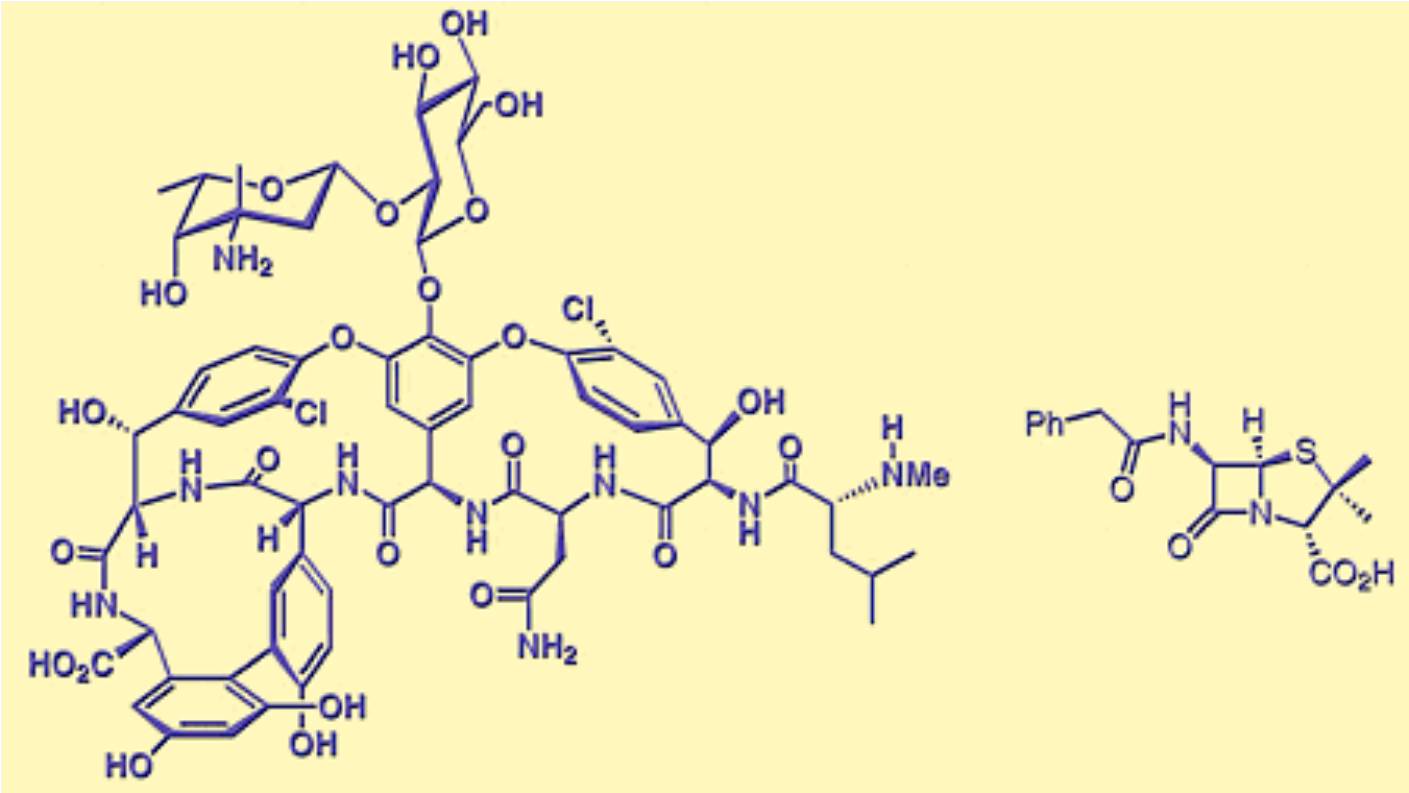
Augmentin =
A.Clavulanico +
Amoxicillina

Strong inhibitors of many β-lactamases

They can protect penicillins from β-lactamase mediated hydrolysis

Available just in fixed combinations with specific penicillins

Inhibition of cell wall synthesis: Glycopeptides



VANCOMYCIN **PENICILLIN**

Inhibition of cell wall synthesis: Glycopeptides

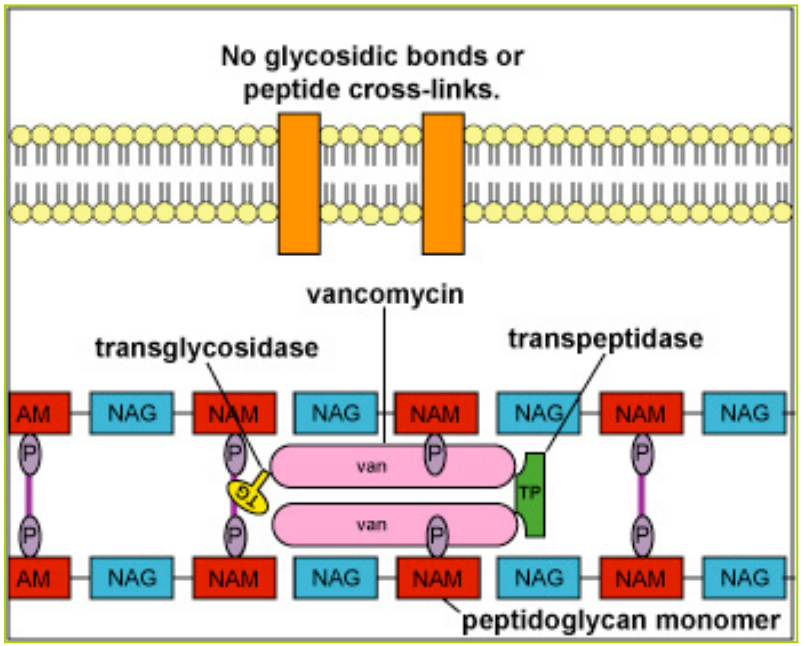
- **Bactericidal**
- **Mechanism of action**

inhibition of transglicosidases and transpeptidases

→ inhibition of peptidoglican elongation and crossed link formation

- **Spectrum of activity**
  - methicillin resistant Staphylococci
  - *Clostidrium difficile*
  - in patients allergics to penicillin

Not active against Gram- because it cannot penetrate their outer membrane



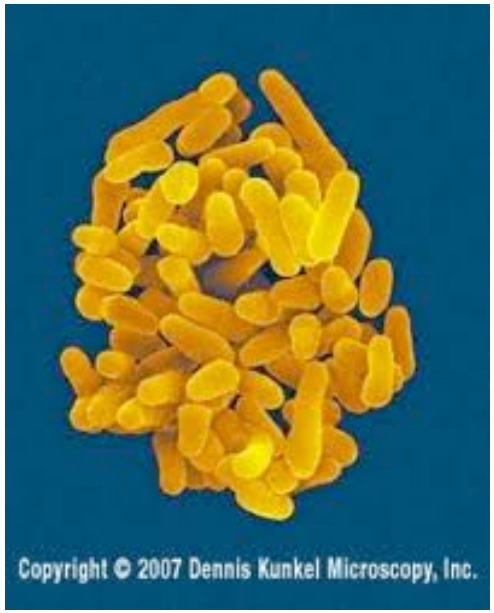
VANCOMYCIN

(Streptomyces orientalis)

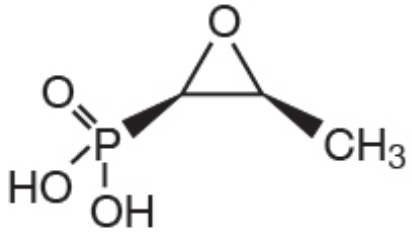
Inhibition of cell wall synthesis: not β-Lactams

ISONIAZID, ETIONAMID, ETHAMBUTOL, CYCLOSERIN

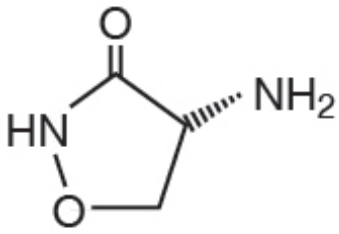
- Used to treat mycobacterial infections
- Affect the mycolic acid synthesis
- Affect the arabinogalattato synthesis in the wall
- Inhibit the D-ala-D-ala sintetase and the alanin recemase, that catalyze the cell wall synthesis

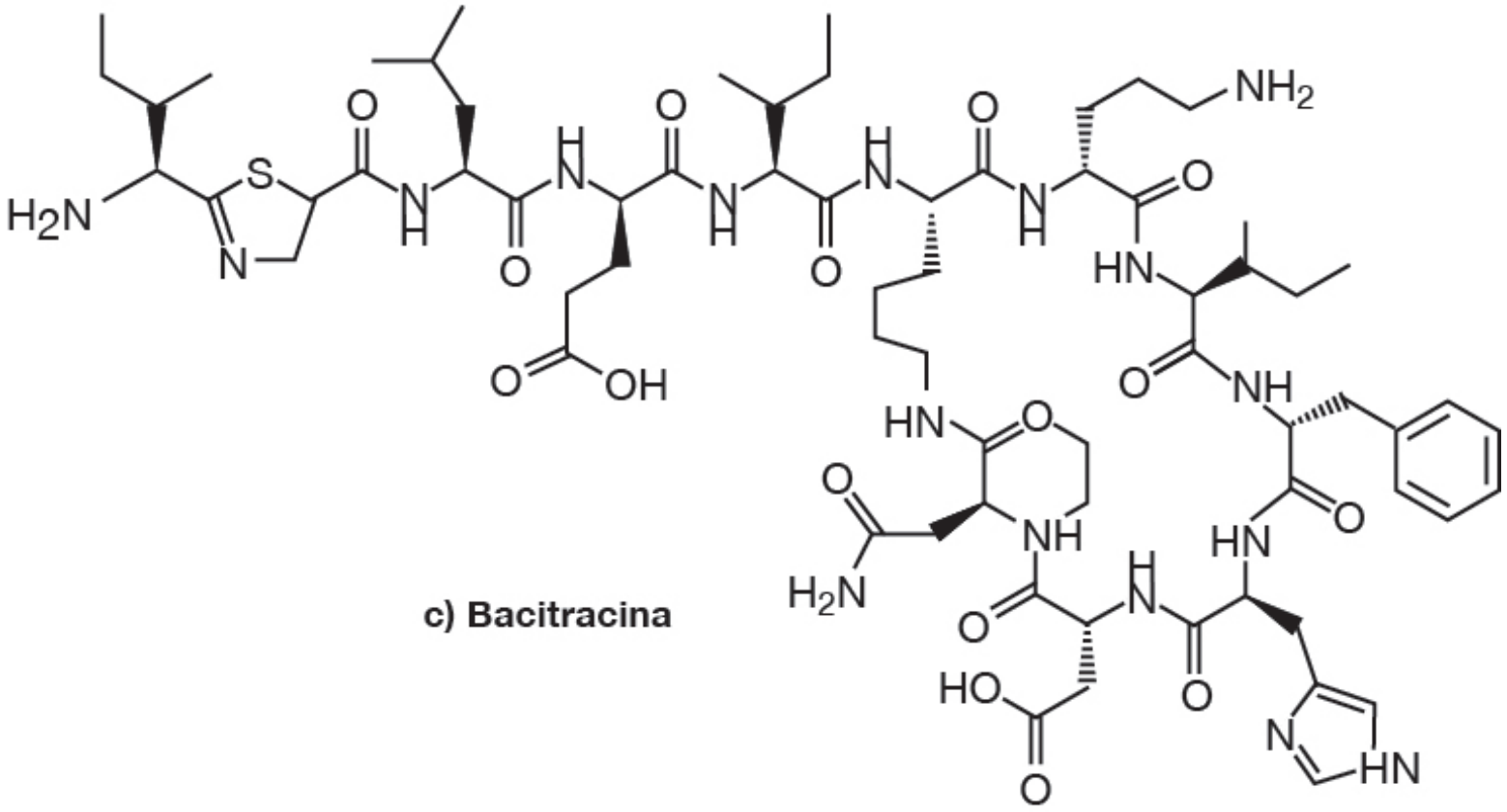


a) Fosfomicina



b) Cicloserina





c) Bacitracina

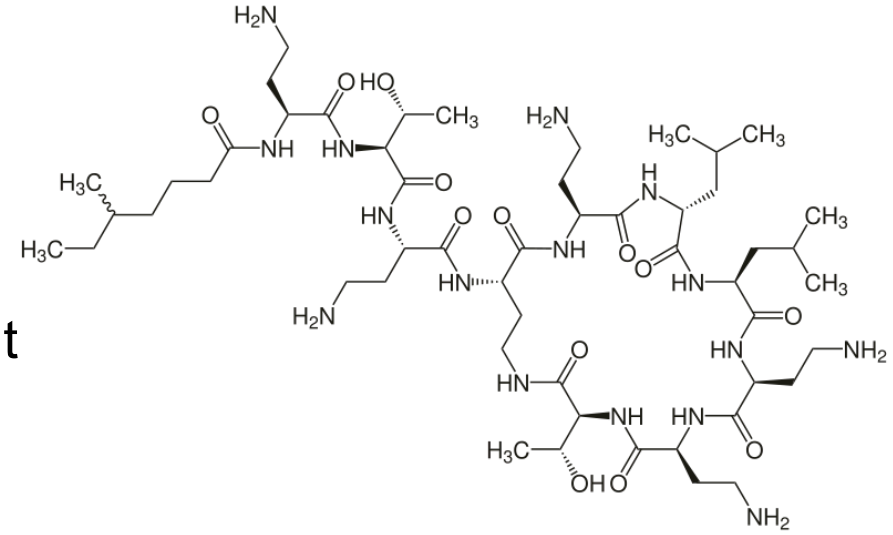
Inhibition of cell membrane functions: Polymixins

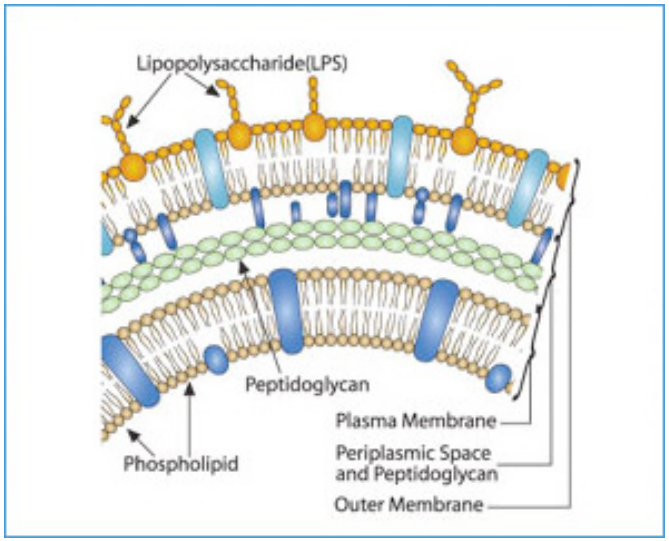
COLISTIN, (polymyxin E)

→bactericidal drug, by binding to LPS and phospholipids in the outer cell membrane of Gram-

→ competitively displacement of divalent cations from the phosphate groups of membrane lipids → disruption of the outer cell membrane

→ prevent the pathophysiologic effects of endotoxin in the circulation

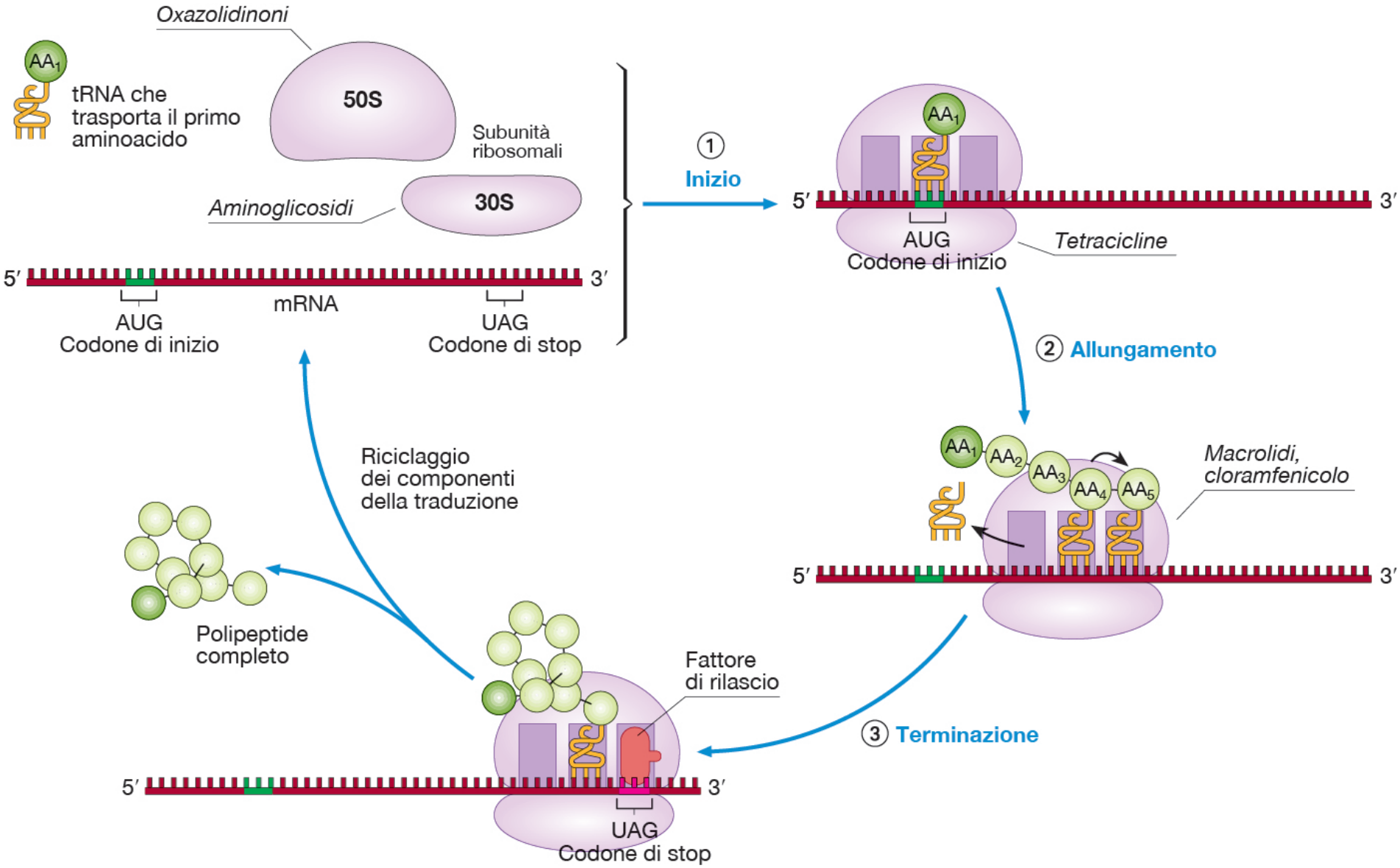




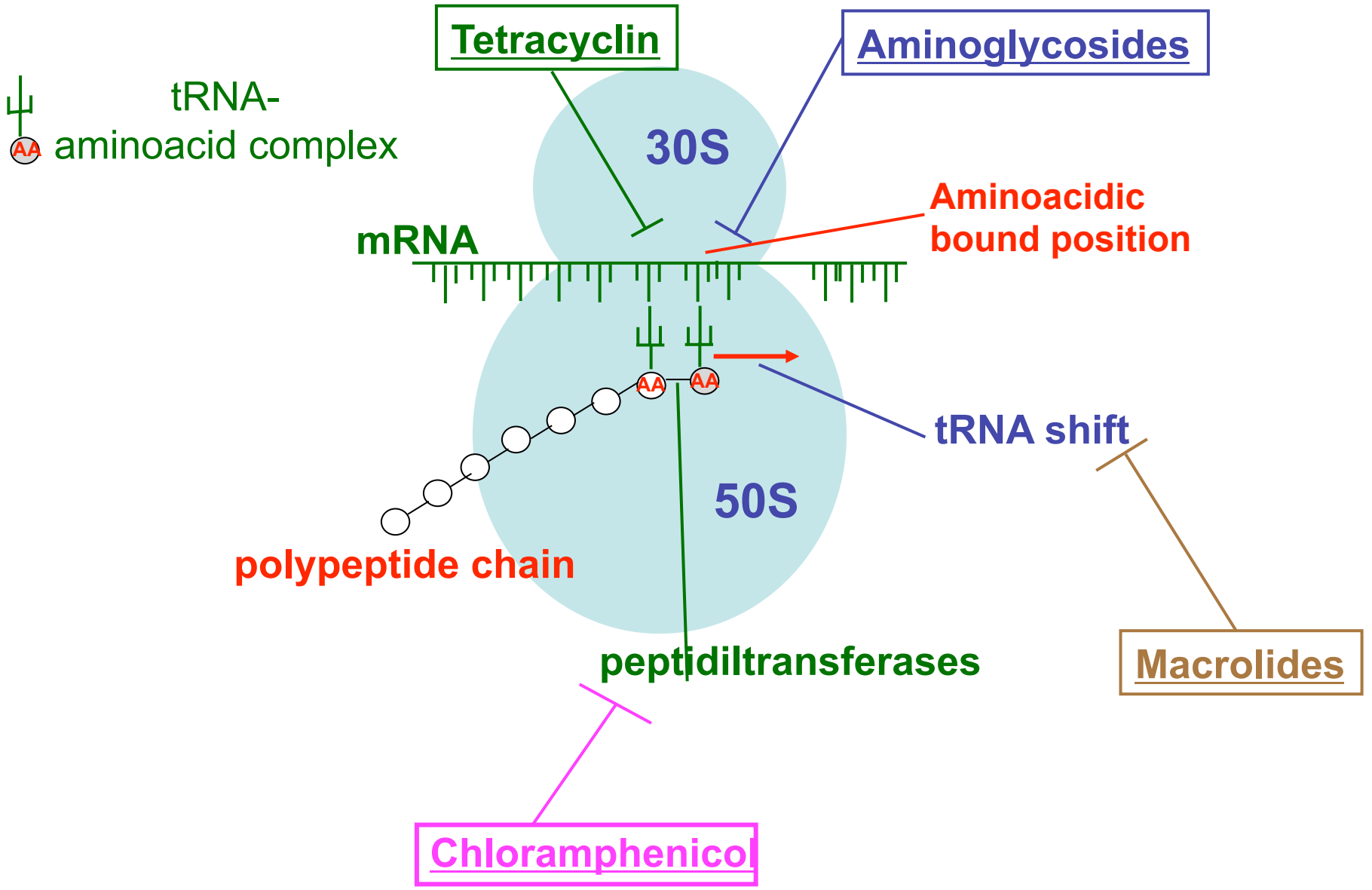
Inhibition of protein synthesis

Drug	Subunit	Bactericidal	Bacteriostatic
Aminoglycosides	30S	x	-
Tetracycline	30S	-	x
Macrolides Erythromicyn	50S	-	x
Chloramphenicol	50S	-	x

Inhibition of protein synthesis



Inhibition of protein synthesis



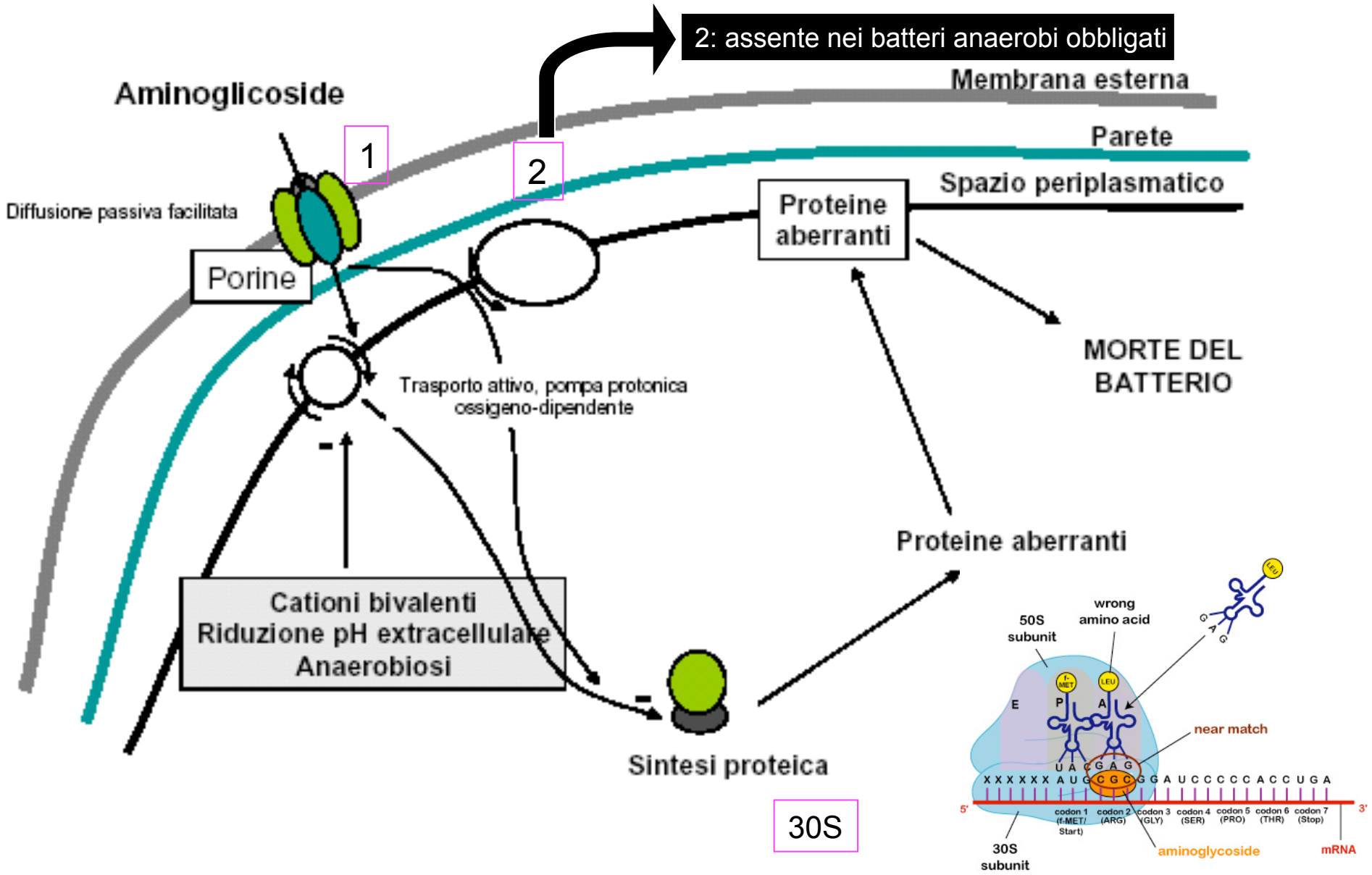
Inhibition of protein synthesis: Aminoglycosides

- ✓ Products of *Streptomyces* species
- ✓ Inhibition of the binding of t-RNA to the ribosome (30S subunit) → prevention of the formation of initiation complexes from which protein synthesis proceeds (they bind S12 protein)
- ✓ Clinical uses: wide variety of bacterial infections caused by Gram+ and Gram- bacteria (**aerobes!**)

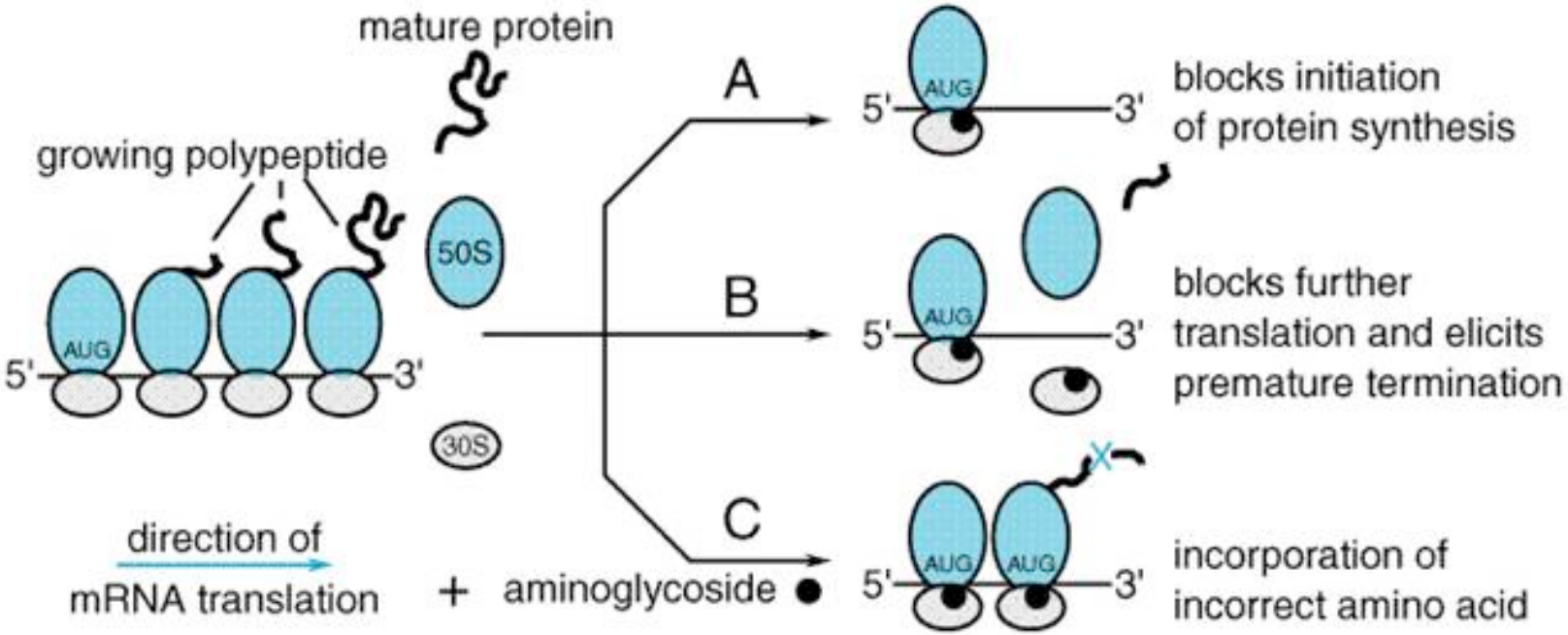
  - Streptomicina (1943)
  - *Tobramicina (n)*
  - *Kanamicina (n)*
  - *Gentamicina (n)*
  - *Amikacina*
  - *Netilmicina*
  - *…and derivatives*

Low Therapeutic index

Inhibition of protein synthesis: Aminoglycosides

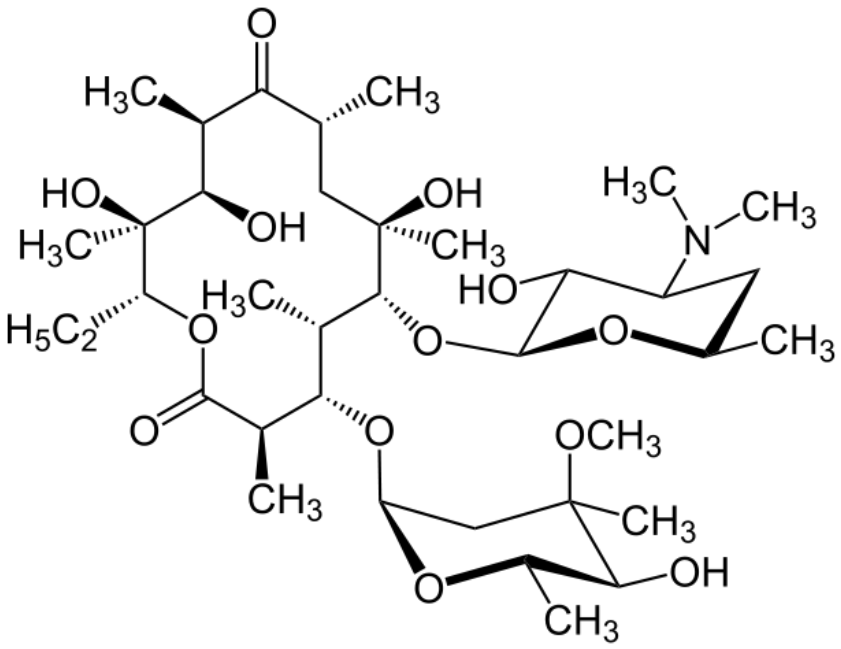


Inhibition of protein synthesis: Aminoglycosides

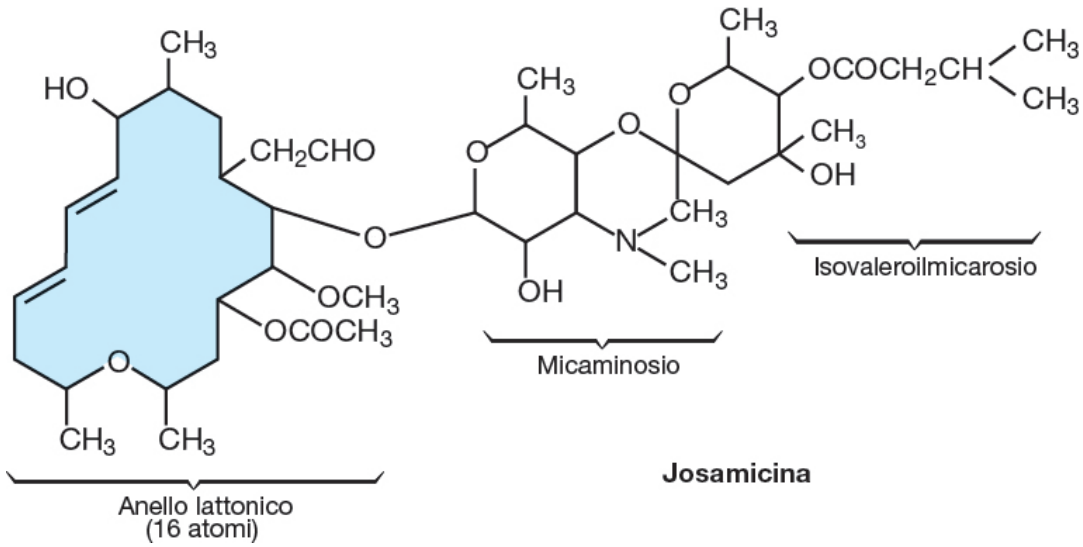


Inhibition of protein synthesis: Macrolides

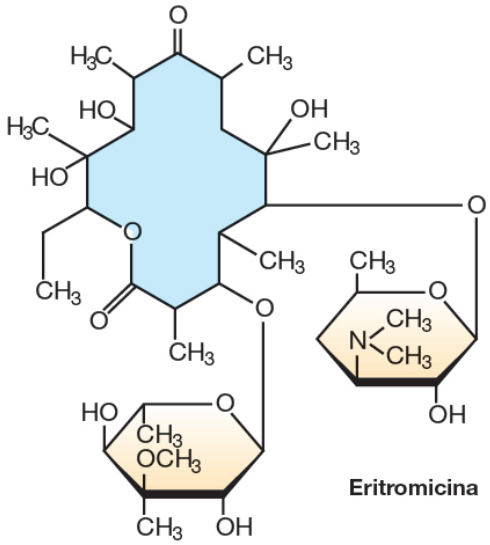
- ✓ Large lactone rings linked through glycoside bonds with amino sugars (14-15-16 atoms)
- ✓ Bacteriostatic for most bacteria but are bactericidal for a few Gram+ bacteria
- ✓ **Clinical use**: Gram+ bacteria, Neisseria, Legionella and Haemophilus, but not Enterobacteriaceae
- ✓ **Mechanism of action**: inhibit bacterial protein synthesis by binding to the 50S ribosomal subunit → inhibition of elongation of the protein by peptidyl transferase or prevention of translocation of the ribosome



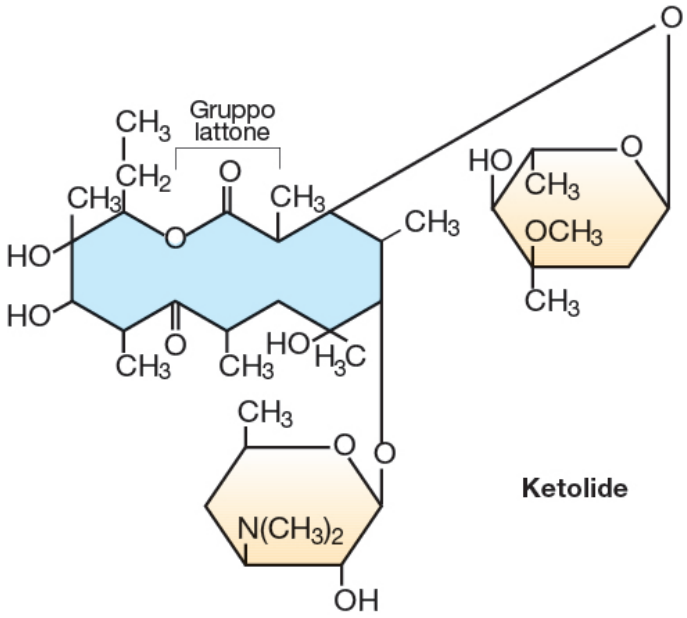
Erythromycin A



Josamicina

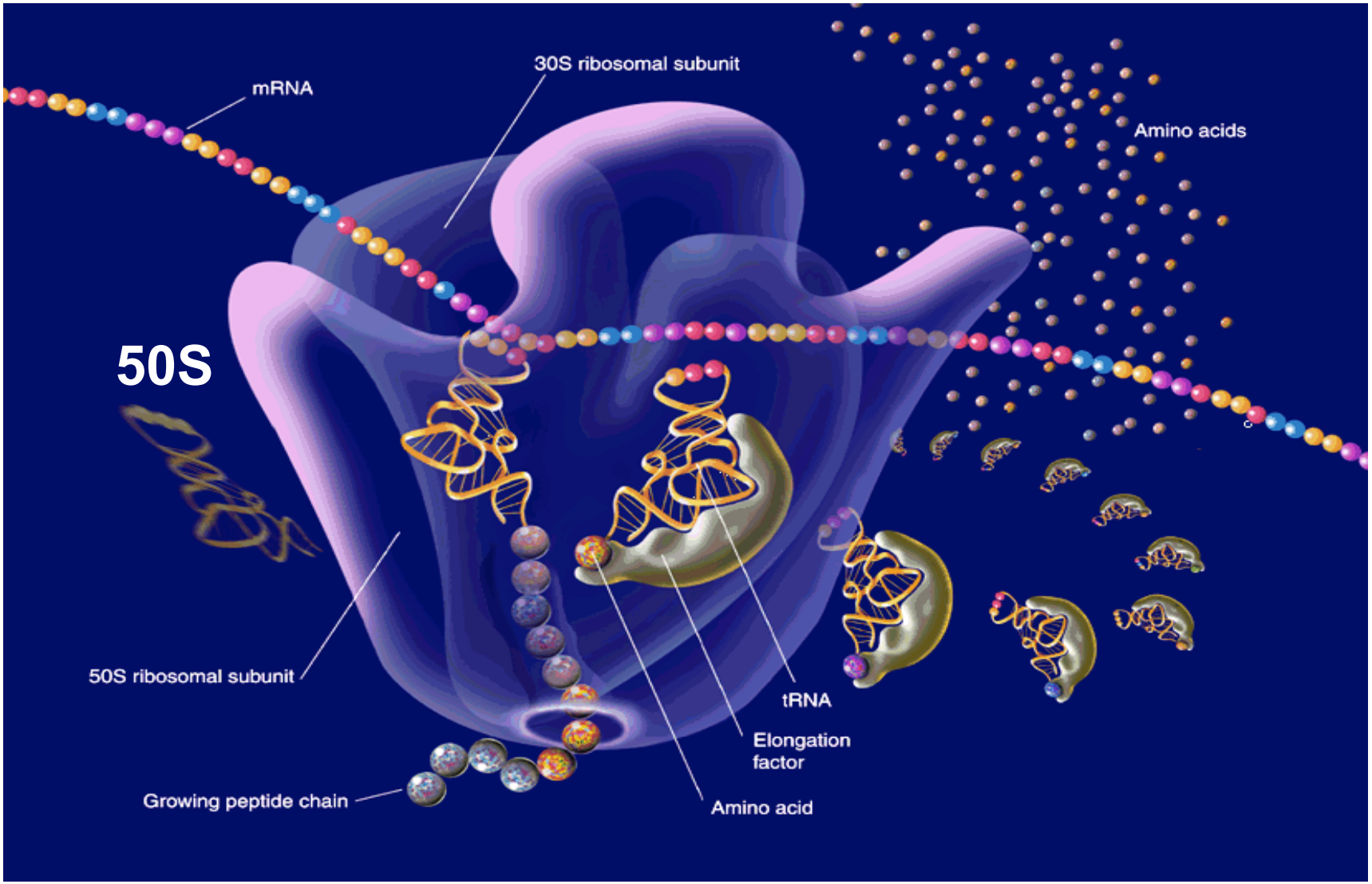


Eritromicina

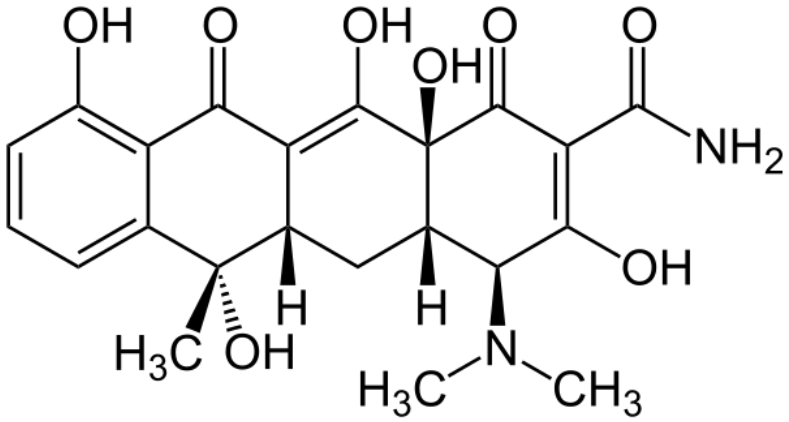


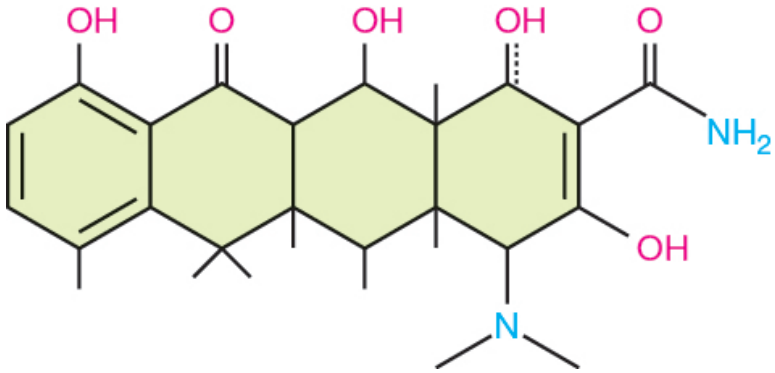
Ketolide

Inhibition of protein synthesis: Macrolides



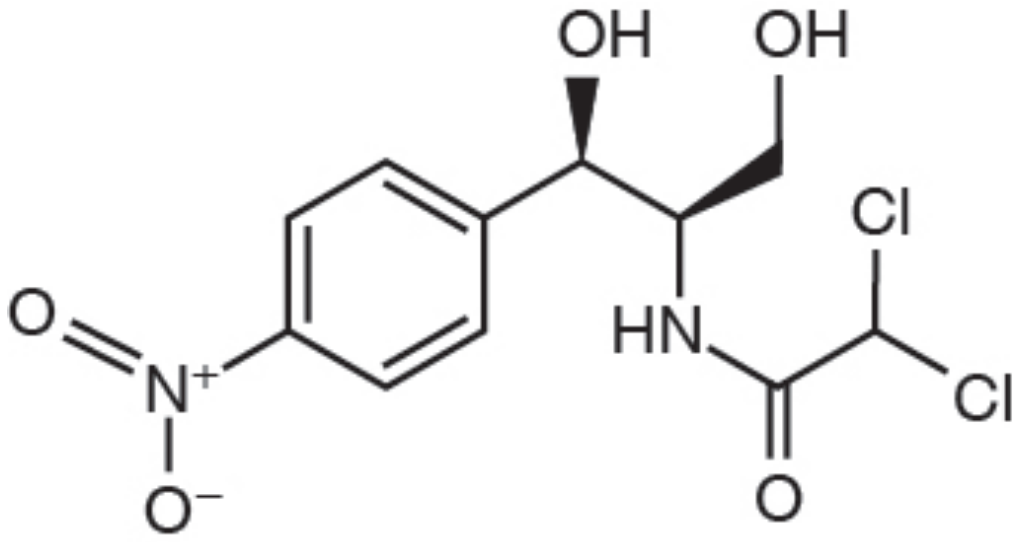
Inhibition of protein synthesis: Tetracyclines



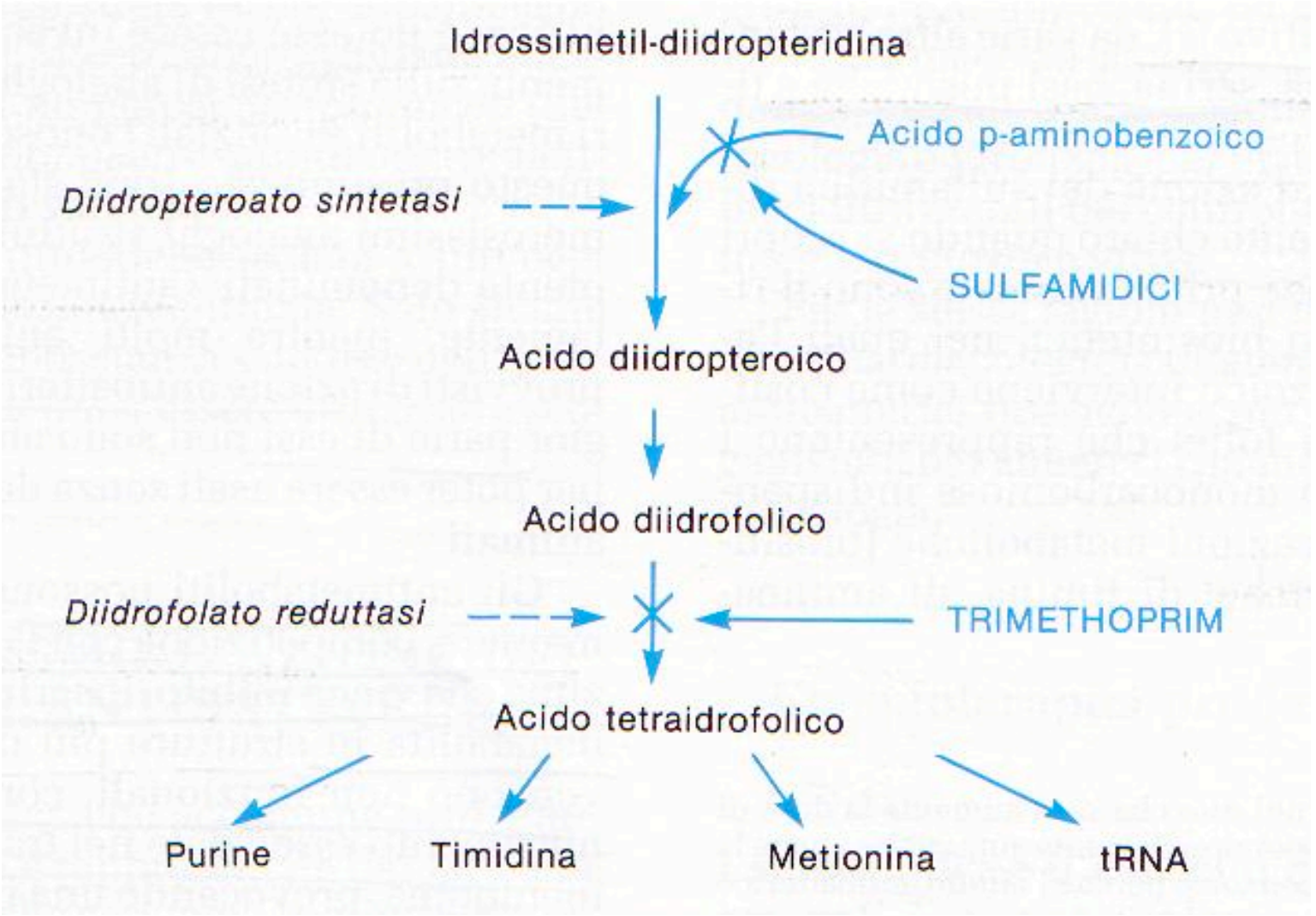


- ✓ Wide range bacteriostatics
- ✓ → Natural products of *Streptomyces* species (can actually be produced semisynthetically or synthetically)
- ✓ Mechanism of action:
  - → blocking the binding of aminoacyl tRNA to the A site on the ribosome (30S)
  - → Misreading of mRNA codon
- ✓ Absorption is altered by food, by bivalent cations and Al3 +, antacids and alkaline pH (insoluble complex)

Inhibition of protein synthesis: Chloramphenicol



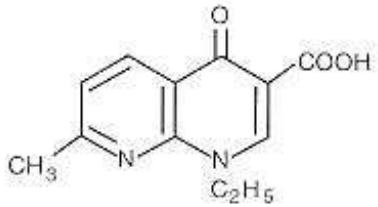
Inhibition of Folic Acid synthesis: Sulphonamides



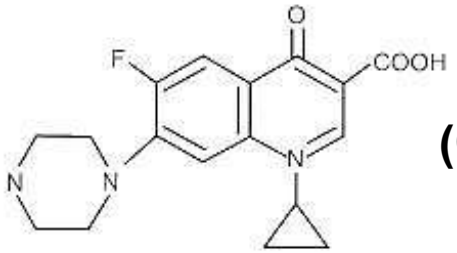
Inhibition of Nucleic Acids replication: Quinolones

DNA inhibitor: *Quinolones*

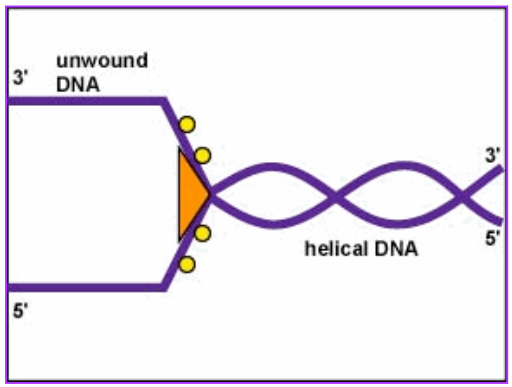
Nalidixic Acid



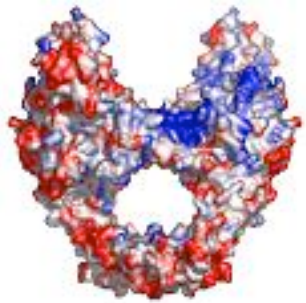
Ciprofloxacin



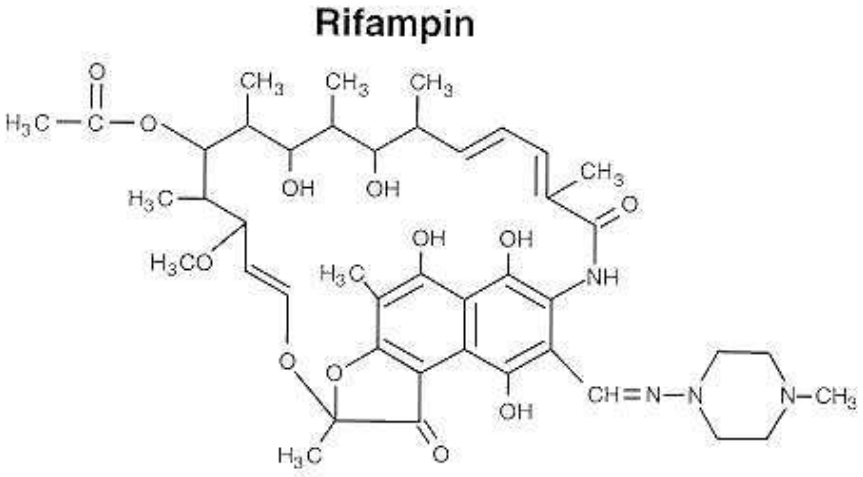
(Chemotherapy)

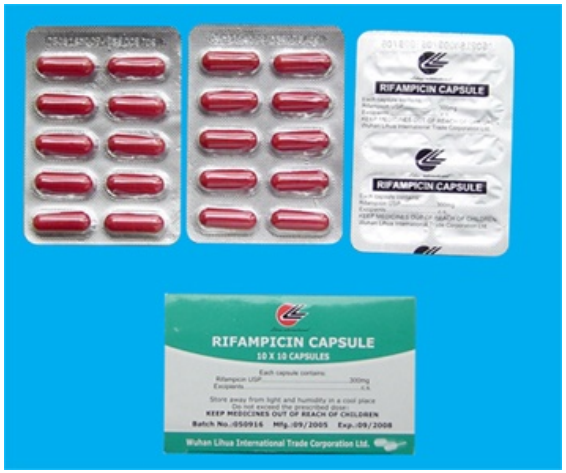


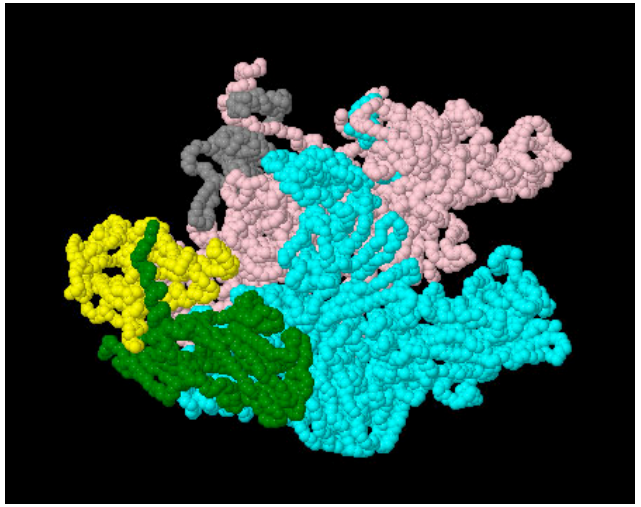
Inhibit DNA gyrase (α subunit), causing permanent DNA cleavage



Inhibition of RNA transcription: Rifampicin





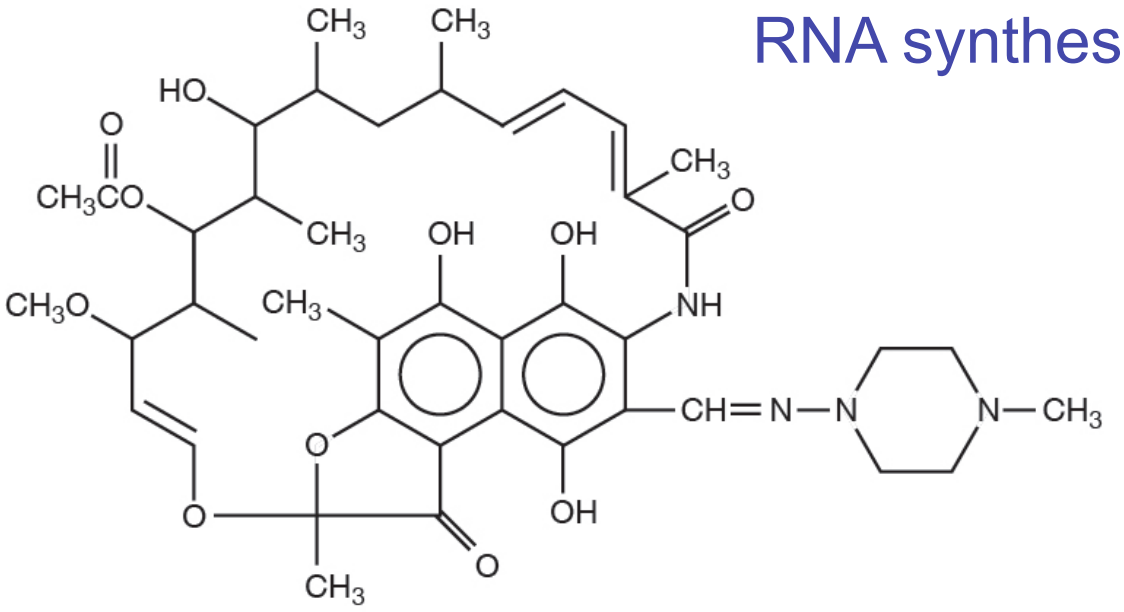


Interacts with the bacterial DNA-dependent RNA polymerase

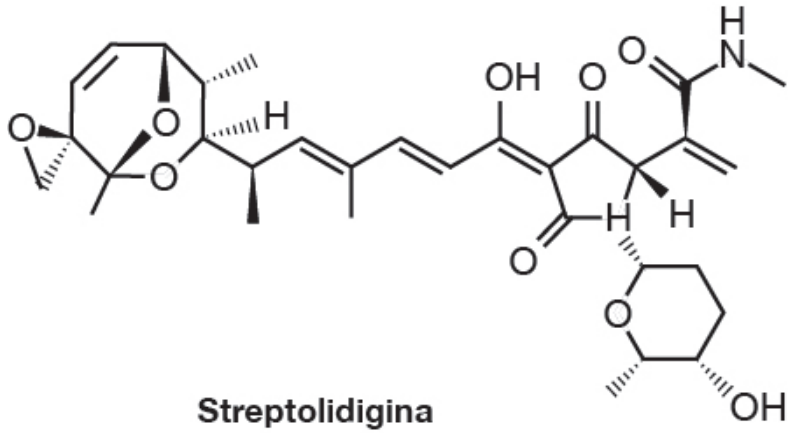
(β subunit), inhibiting RNA synthesis

Gram$^+$ (Mycobacterium tubercolosis)

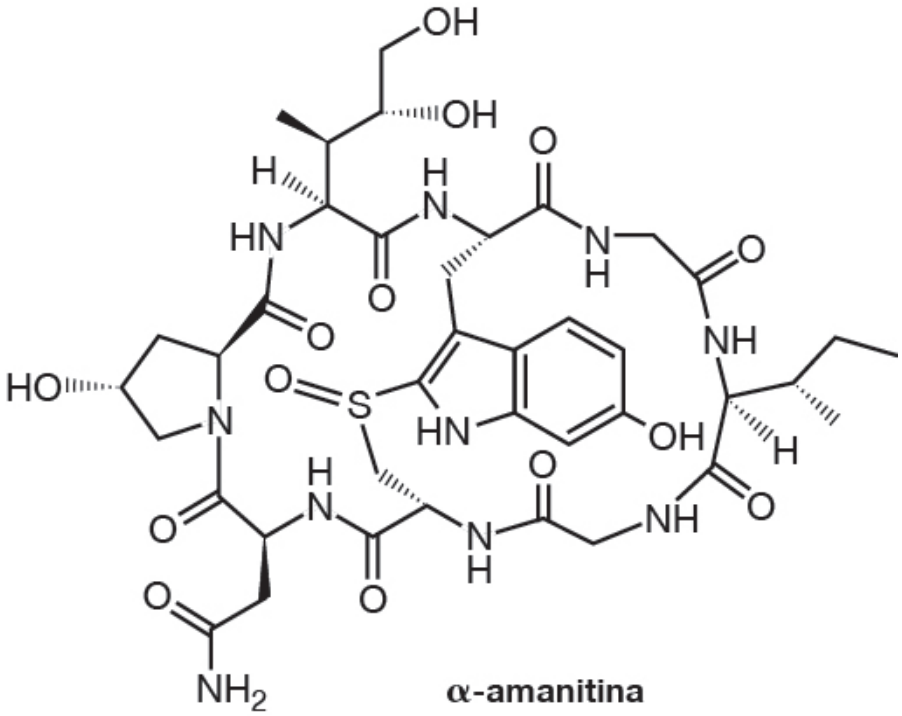
RNA synthesis inhibitor: Rifampicin



Rifampicina

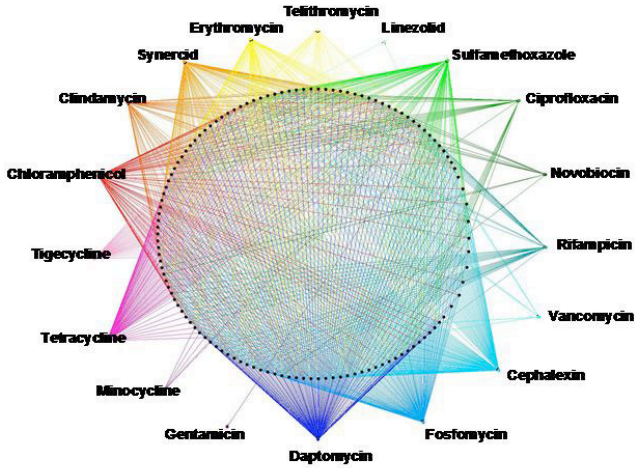


Streptolidigina

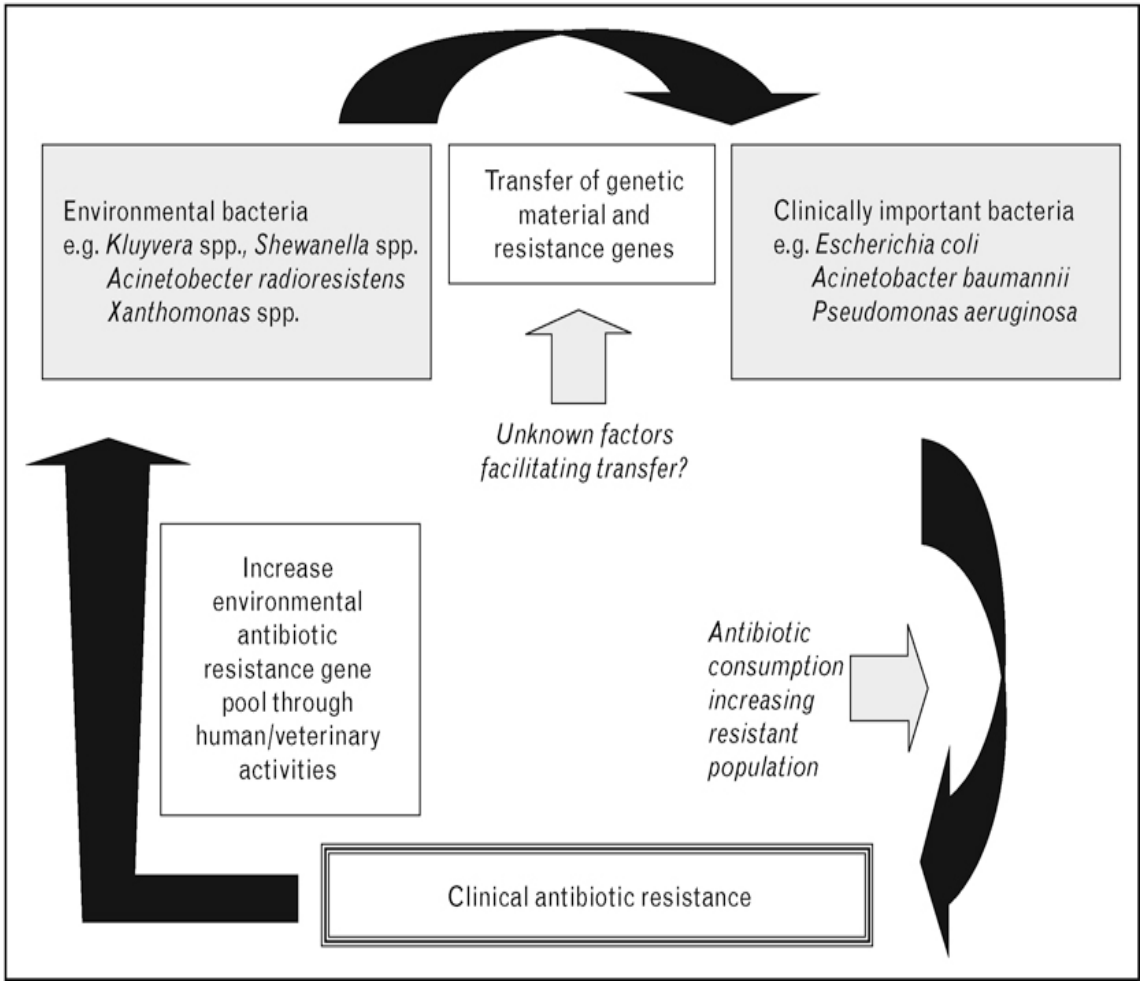


α-amanitina

Antimicrobial Resistance



The mechanism of transfer of genetic material (DNA) into clinical isolates, for the better part, also still remains an enigma. However, once established, antibiotic usage will augment either the propagation of the resistant population and/or the genes carrying the carbapenemase gene. This amplification invariably is recycled back into the environment through human/animal activities and waste.

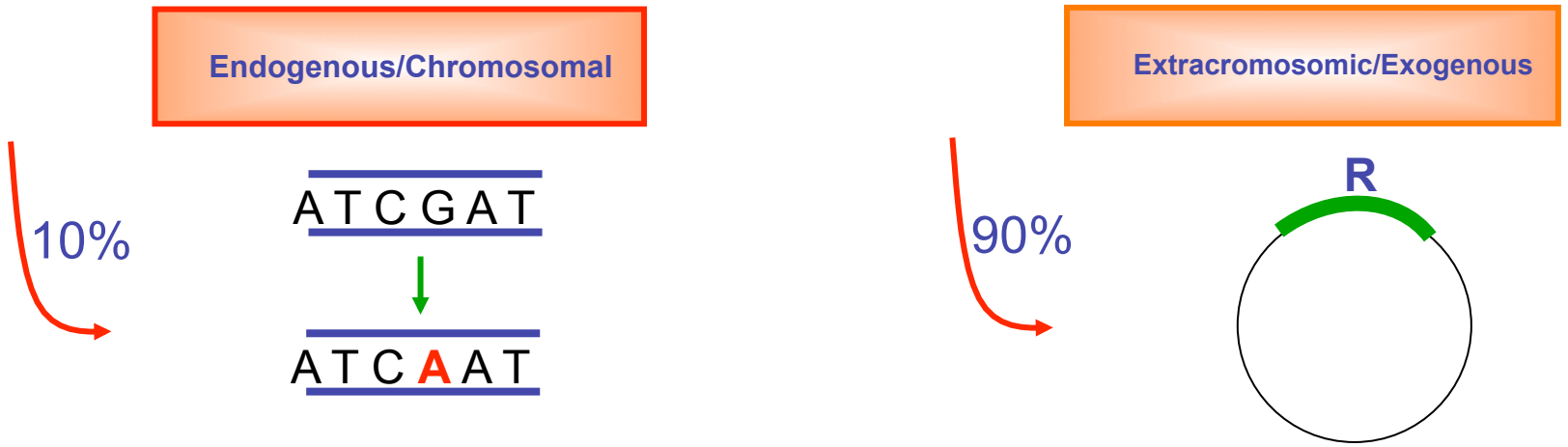


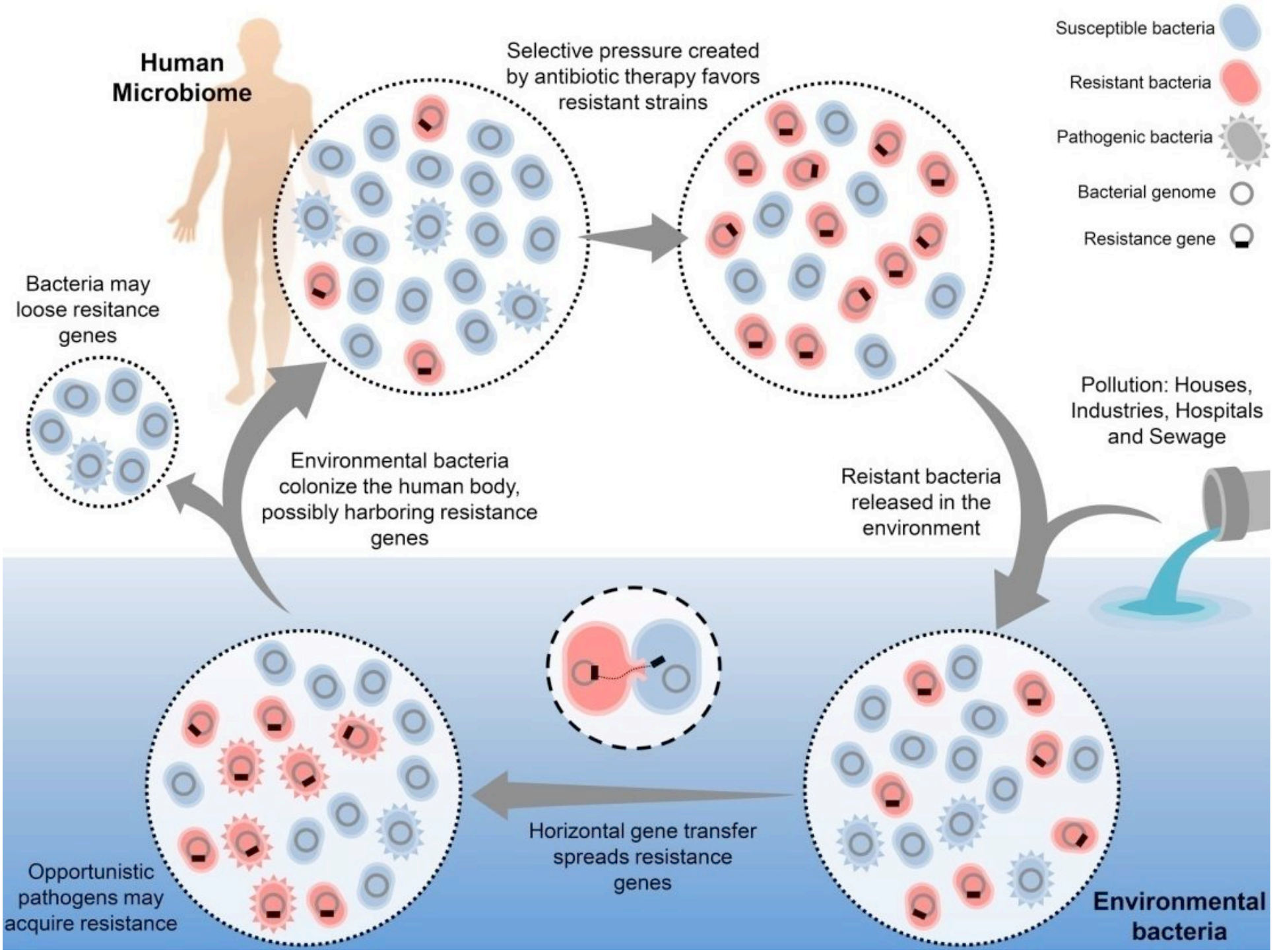
Antimicrobial Resistance: definition and general features

Clinical resistance to an antimicrobial agent occurs when the minimum inhibitory concentration of the drug for a particular strain of bacteria exceeds that which is capable of being achieved with safety *in vivo*

INHERENT (NATURAL) RESISTENCE (*Mycoplasma* vs penicillins)

ACQUIRED RESISTENCE




Human Microbiome
Selective pressure created by antibiotic therapy favors resistant strains
Susceptible bacteria
Resistant bacteria
Pathogenic bacteria
Bacterial genome
Resistance gene
Bacteria may loose resitance genes
Environmental bacteria colonize the human body, possibly harboring resistance genes
Reistant bacteria released in the environment
Pollution: Houses, Industries, Hospitals and Sewage
Horizontal gene transfer spreads resistance genes
Opportunistic pathogens may acquire resistance
Environmental bacteria

Antimicrobial Resistance: mechanisms

1) Alteration of permeability (efflux or lower permeability)

→ **Active transport mechanism (ATP required);**
(Found in bacterial plasma membrane and outer layer of gram-negative organisms)
Rationale: pumping keeps antibiotic concentration below toxic levels.

→ **Reduction of membrane permeability;**
(Turn off production of porin and other membrane channel proteins).
E.g. Resistance to streptomycin, tetracycline, and sulfam.

2) Inactivation enzimes

- Production of enzymes that modify or inactivate antibacterial compound
E.g. β-lactamase, carbapenemase (more than 190 forms of β-lactamase)
- Usually secreted into bacterial periplasmic space.

3) Target modification

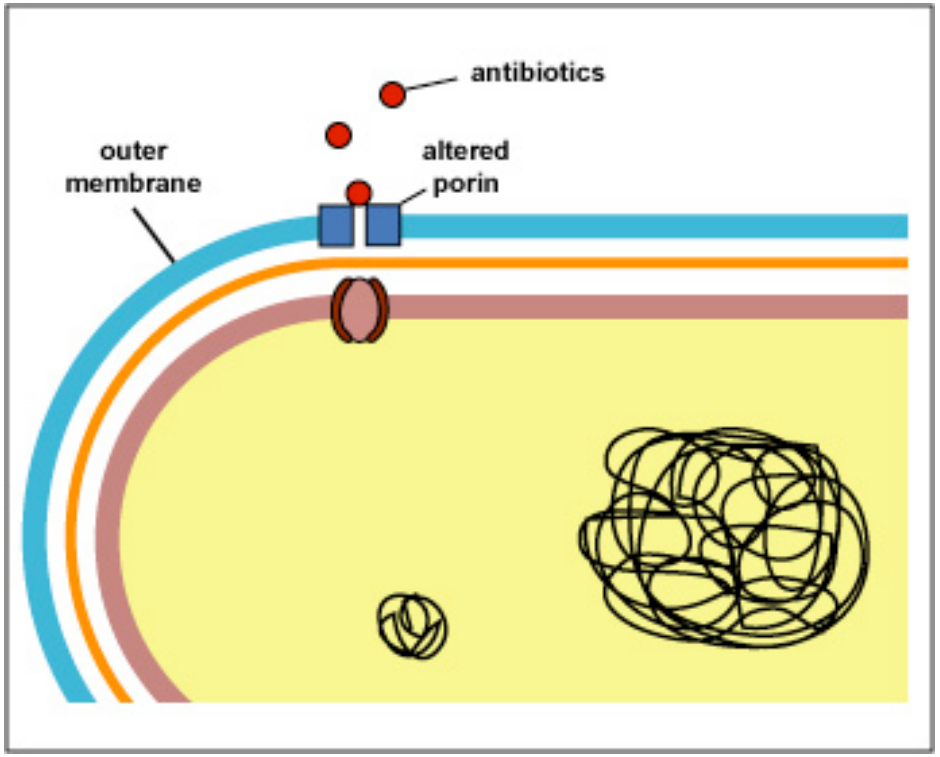
E.g. MRSA: similar PBP (penicillin- binding- protein). *mec A* gene that codes for a different PBP.

4) Loss of a pathway involved in drug activation

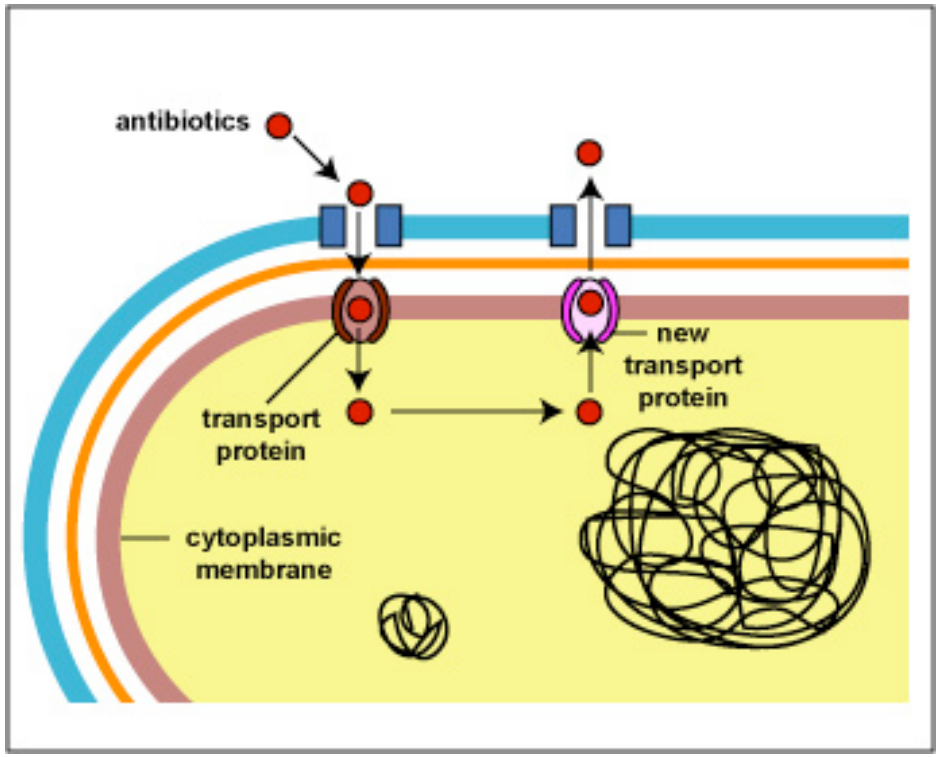
Mechanisms of Resistance: Summary

ANTIBIOTICS	METHODS OF RESISTANCE
Chloramphenicol	reduced uptake into cell
Tetracycline	active efflux from the cell
β-lactams, Erythromycin, Lincomycin	eliminates or reduces binding of antibiotic to cell target
β-lactams, Aminoglycosides, Chloramphenicol	Enzymatic cleavage or modification to inactivate antibiotic molecule
Sulfonamides, Trimethoprim	metabolic bypass of inhibited reaction overproduction of antibiotic target (titration)
Vancomycin	D-Ala-D-lactate instead of D-Ala-D-Ala

Mechanisms of Resistance: Alteration of Permeability



Porine reduction or alteration

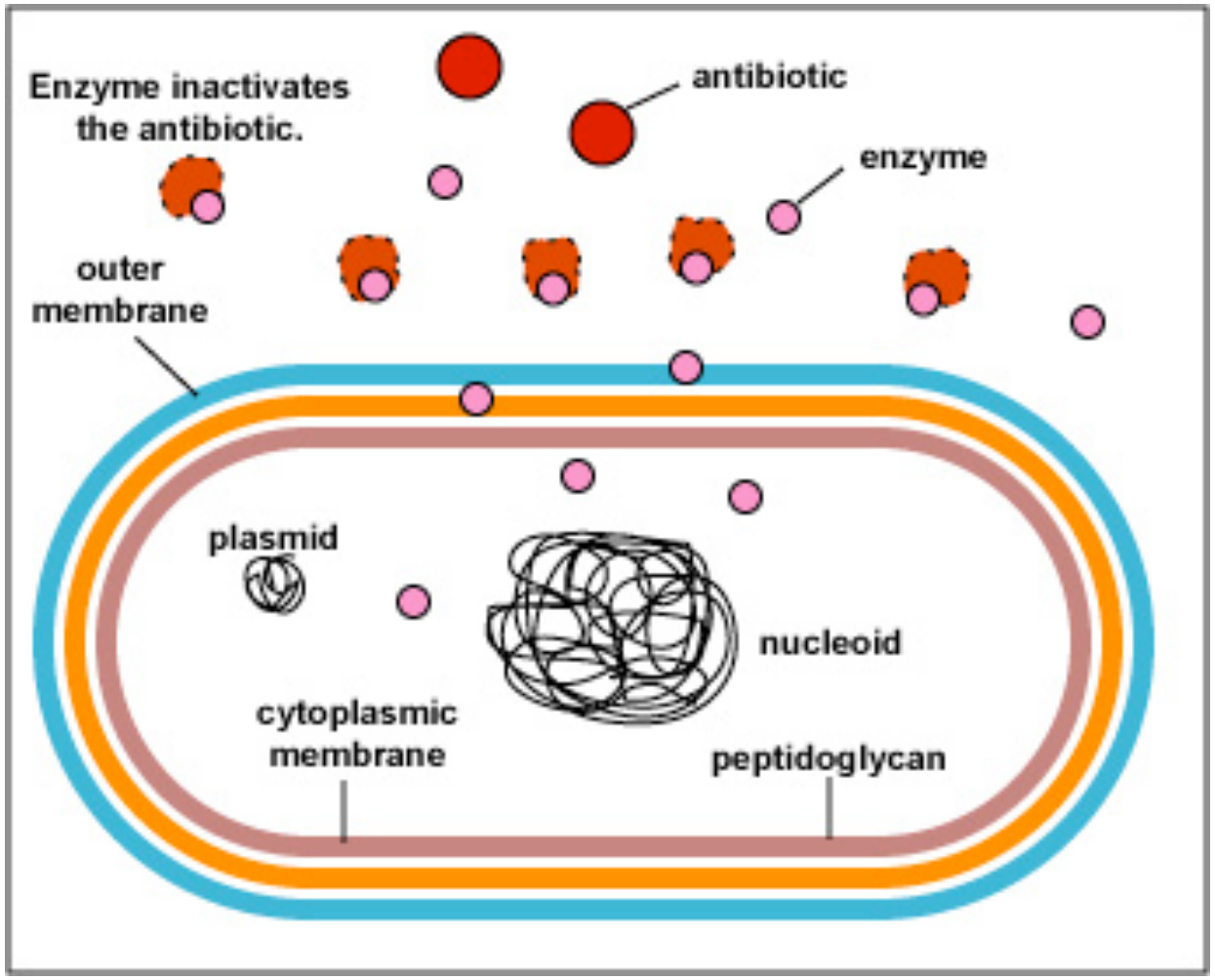


Efflux

Alteration of permeability: Carbapenem resistance

- Porin protein OprD forms transmembrane channels, normally accessible only to carbapenems, not to other ß-lactams
- Strategy: loss or inactivation of OprD
  - Decrement in carbapenems permeability →
    increased carbapenem MICs
- Upregulation of MexAB-OprM efflux system
  - Increased MICs of meropenem, not imipenem
- Coregulation of MexE-MexF-OprN efflux system with OprD porin in *P. aeruginosa*
  - –upregulation of efflux associated with OprD
  - –associated with increased MICs of fluoroquinolones as well as carbapenems
  - –mechanism sometimes selected by fluoroquinolones, rarely by carbapenems

Mechanisms of Resistance: Inactivation Enzimes



Enzyme production

- Aminoglycoside modifying enzymes
- β-lactamases:
  - Four structural classes

Ambler class	Bush-Jacoby Medeiros group	Active site	Enzyme type	Host organisms	Substrates
A plasmid	2b, 2be, 2br, 2c, 2e, 2f	Serine	Broad-spectrum β-lactamases (TEM, SHV) ESBL (TEM, SHV, CTX-M)	Enterobacteriaceae and nonfermenters	Ampicillin, cephalothin Penicillins, 3rd-generation cephalosporins
			Carbapenemases (KPC, GES, SME)		All β-lactams
B chromosomal	3	Zinc-binding thiol group	Carbapenemases (VIM, IMP)	Enterobacteriaceae and nonfermenters	All β-lactams
C chromosomal	1	Serine	AmpC cephamycinases (AmpC)	*Enterobacter* species *Citrobacter* species	Cephamycins, 3rd-generation cephalosporins
			AmpC cephamycinases (CMY, DHA, MOX FOX, ACC)	Enterobacteriaceae	Cephamycins, 3rd-generation cephalosporins
D plasmid	2d	Serine	Broad-spectrum β-lactamases (OXA) ESBL (OXA)	Enterobacteriaceae and nonfermenters	Oxacillin, ampicillin, cephalothin Penicillins, 3rd-generation cephalosporins All β-lactams
			Carbapenemases (OXA)		

Table 1. Selected β-Lactamases of Gram-Negative Bacteria.

β-Lactamase	Examples	Substrates	Inhibition by Clavulanic Acid*	Molecular Class
Broad-spectrum	TEM-1, TEM-2, SHV-1	Benzylpenicillin (penicillin G), aminopenicillins (amoxicillin and ampicillin), carboxypenicillins (carbenicillin and ticarcillin), ureidopenicillin (piperacillin), narrow-spectrum cephalosporins (cefazolin, cephalothin, cefamandole, cefuroxime, and others)	+++	A
	OXA family	Substrates of the broad-spectrum group plus cloxacillin, methicillin, and oxacillin	+	D
Expanded-spectrum	TEM family and SHV family	Substrates of the broad-spectrum group plus oxyimino-cephalosporins (cefotaxime, cefpodoxime, ceftazidime, and ceftriaxone) and monobactam (aztreonam)	++++	A
	Others (BES-1, GES/IBC family, PER-1, PER-2, SFO-1, TLA-1, VEB-1, and VEB-2)	Same as for TEM family and SHV family	++++	A
	CTX-M family	Substrates of the expanded-spectrum group plus, for some enzymes, cefepime	++++	A
	OXA family	Same as for CTX-M family	+	D
AmpC	ACC-1, ACT-1, CFE-1, CMY family, DHA-1, DHA-2, FOX family, LAT family, MIR-1, MOX-1, and MOX-2	Substrates of expanded-spectrum group plus cephamycins (cefotetan, cefoxitin, and others)	0	C
Carbapenemase	IMP family, VIM family, GIM-1, and SPM-1	Substrates of the expanded-spectrum group plus cephamycins and carbapenems (ertapenem, imipenem, and meropenem)	0	B
	KPC-1, KPC-2, and KPC-3	Same as for IMP family, VIM family, GIM-1, and SPM-1	+++	A
	OXA-23, OXA-24, OXA-25, OXA-26, OXA-27, OXA-40, and OXA-48	Same as for IMP family, VIM family, GIM-1, and SPM-1	+	D

* Plus signs denote relative sensitivity to inhibition.

ESBL-mediated resistance

- Hydrolyze expanded-spectrum β-lactam antibiotics
- Derived from older antibiotic-hydrolyzing β-lactamase enzymes (TEM-1, TEM-2, SHV-1)
- Not efficient against cephamycins (cefoxitin, cefotetan) and carbapenems

  - single amino acid substitution → can give rise to new ESBLs
  - Inhibited by β-lactamase inhibitors
  - 10% - 40% of *K. pneumoniae, E. coli* express ESBLs

- **ESBL *K. pneumoniae*, *E. coli*** : Derived from chromosomal genes for inducible *ampC* transferred onto plasmids

Carbapenemases

β-lactamases able to hydrolyze penicillins, cephalosporins, monobactams, and carbapenems. Two major groups:

- **Metallo-β-lactamases (MBLs)**
- **Serine β-lactamases**

1) Class D:
Oxacillinases or D β-lactamases (OxaA)
2) Class A:
carbapenemases

Classification	Enzyme	Most Common Bacteria
Class A	KPC, SME, IMI, NMC, GES	Enterobacteriaceae (rare reports in *P. aeruginosa*)
Class B (metallo-β-lactamse)	IMP, VIM, GIM, SPM	*P. aeruginosa* Enterobacteriacea *Acinetobacter* spp.
Class D	OXA	*Acinetobacter* spp.

Mechanism in Gram negative resistance to antibiotics

Antibiotic Class	Mechanism of Resistance
Cephalosporins	> ESBLs > chromosomal cephalosporinases
β-Lactamase inhibitors	> hyperproducers of β-lactamases > new β-lactamases resistant to inhibitors > chromosomal cephalosporinases
Carbapenems	> porin mutations > efflux pump overproduction (excluding imipenem) > zinc metalloenzymes and other β-lactamases
Fluoroquinolones	> alterations in DNA topoisomerase > efflux mechanisms > permeability changes

Mechanisms of Resistance: Target modification

- PBPs: in cell membrane
  - (*S. pneumoniae*, *MRSA*)

  Involved in the final stages of the synthesis of peptidoglycan, which is the major component of bacterial cell walls (more common R mechanism for gram positive organisms, Gram negative access to PBP is limited by outer membrane)

  - D-Ala-D-Ala target: VRE (*VanA*, *VanB*, *VanC*, *VanD*)

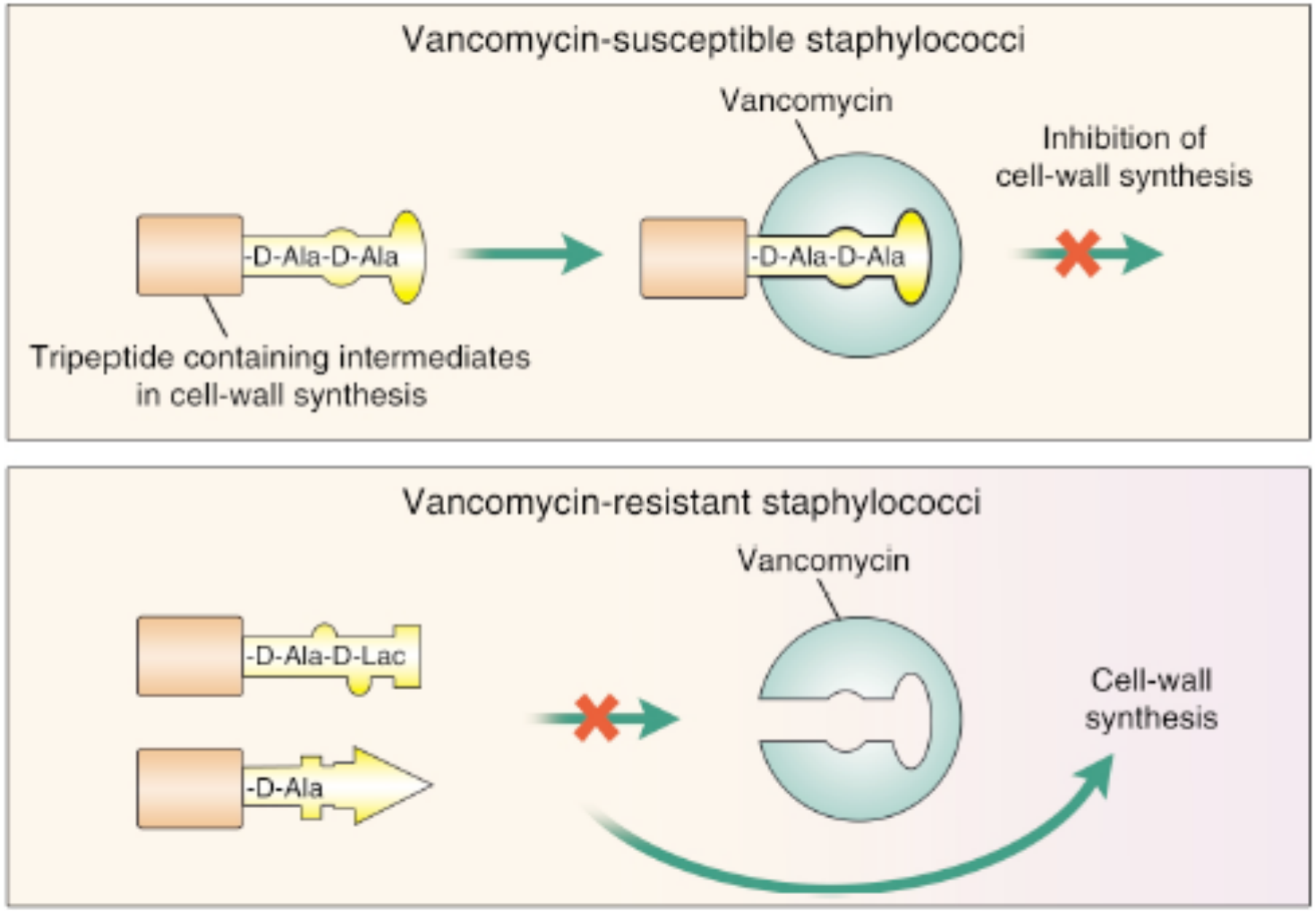
- Alterations in ribosomes
- Cell membrane changes

MRSA: target modification

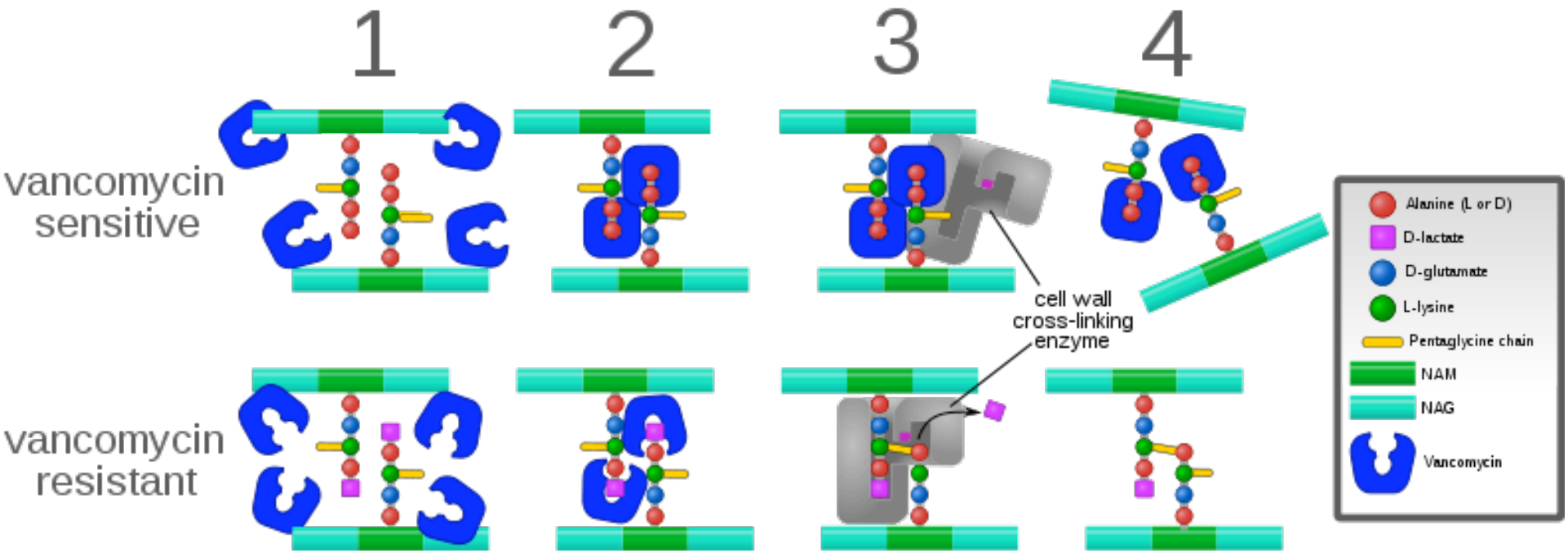
MRSA= **M**ethicillin **R**esistance **S**. **A**ureus

- Acquisition of *mecA* (into the mobile chromosomal element called staphylococcal cassette chromosome –SCCmec-)
  - → SCCmec types I, II, and III and are multidrug resistant-large cassettes
    - – Health-care associated
  - → SCCmec type IV and type V not multidrug resistant
    - – Community associated
- *mecA*: encodes PBP2a
  - →Weak affinity for methicillin and all beta-lactams

Mechanisms of Resistance: Target modification



Mechanisms of Resistance: Target modification



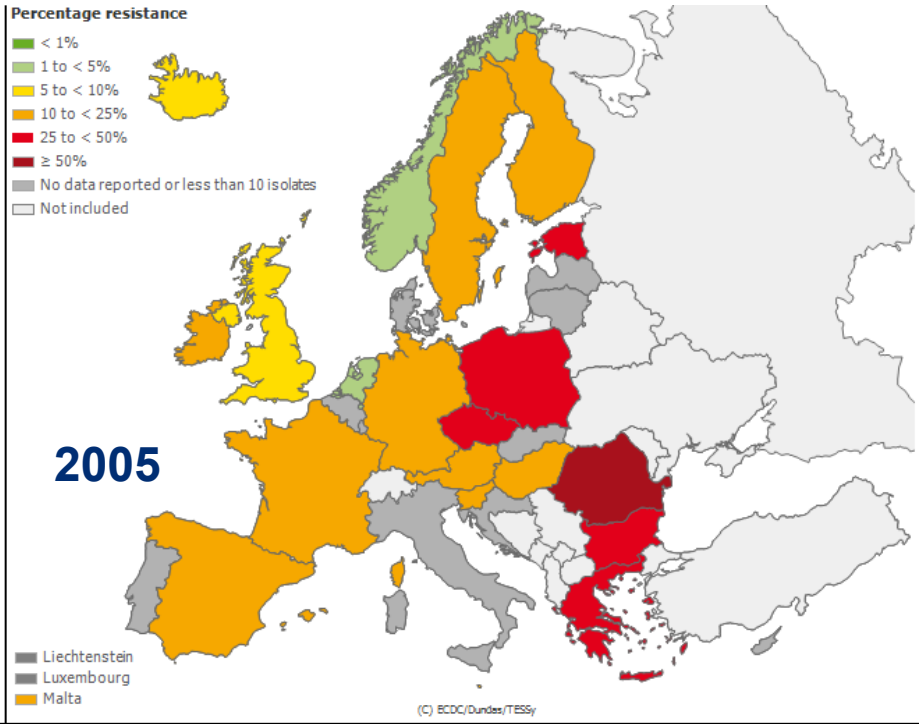
Superbugs* are visible manifestations of our prolonged failure to preserve antibiotics

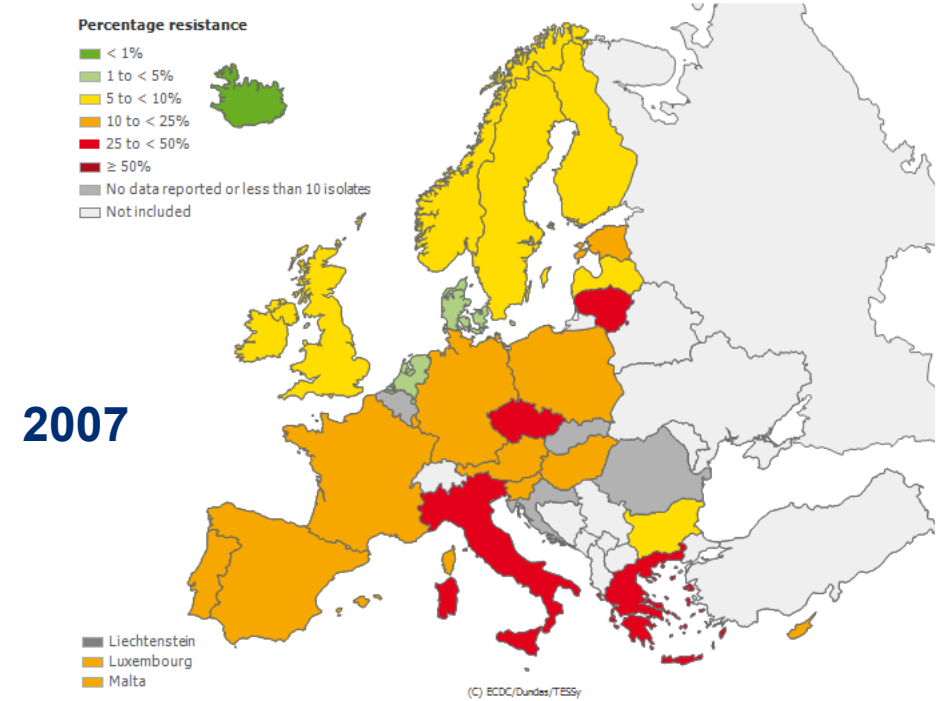
** Methicillin resistant *Staph aureus*, MDR-and XDR Mycobacteria, ESBL producing Gram negative bacteria and NDM-1 producing enterobacteriaceae bacteria are few examples of superbugs because these fail to respond to large number of commonly used antibiotics

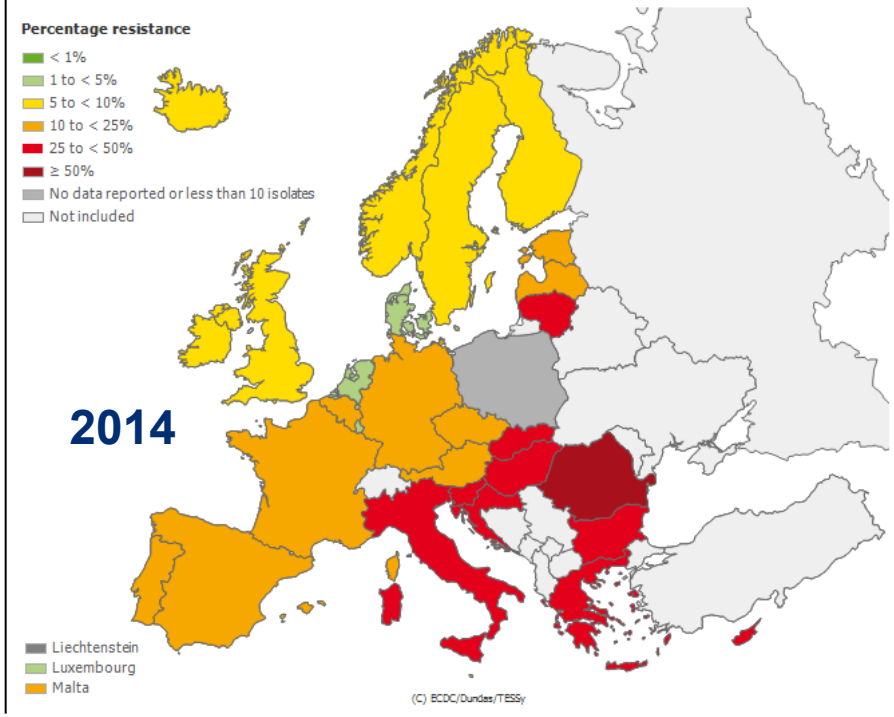
Pseudomonas aeruginosa
Carbapenem resistant

Invasive infection

http://ecdc.europa.eu/en/healthtopics/antimicrobial_resistance/database/Pages/map_reports.aspx

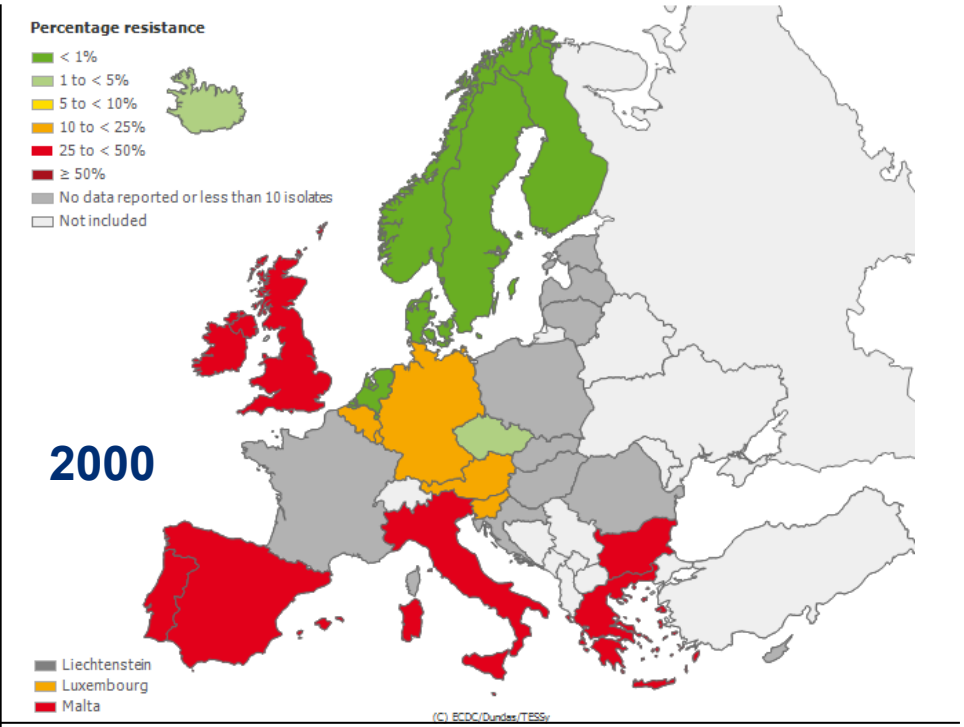


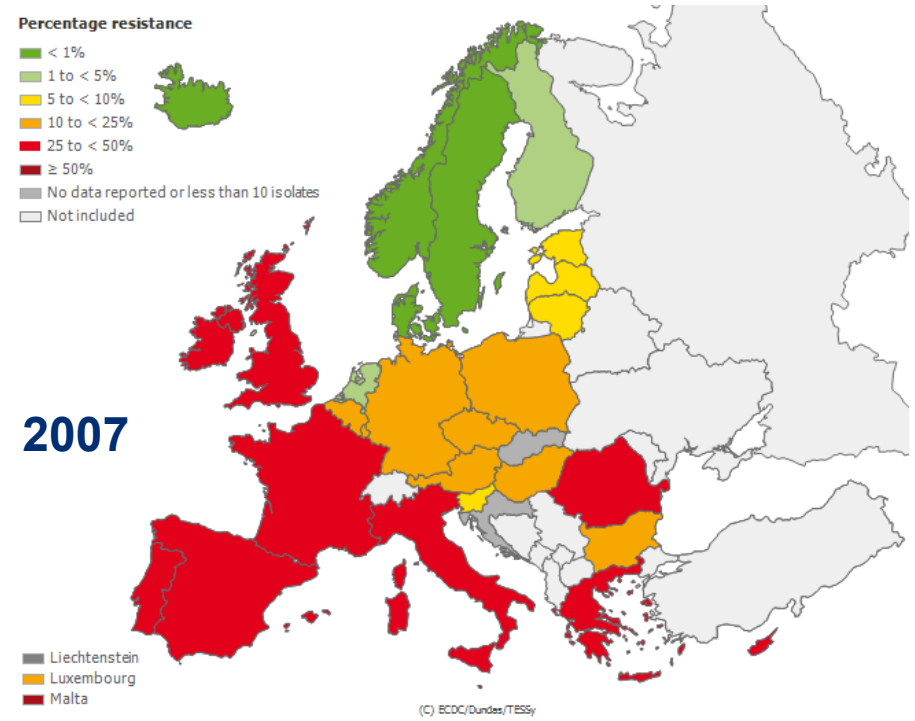


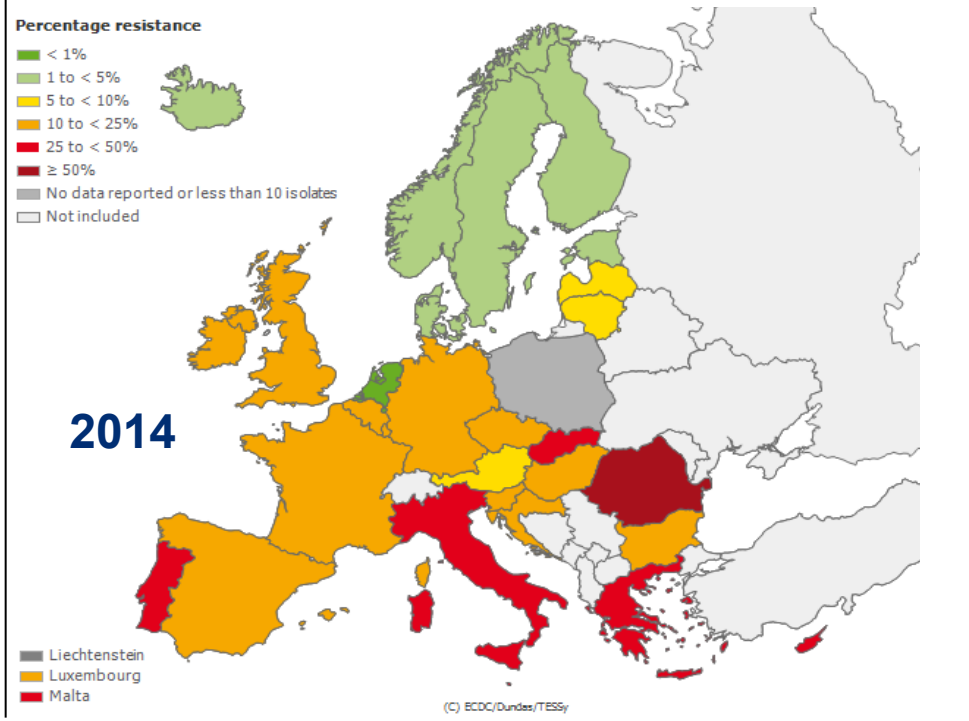


Staphylococcus aureus MRSA

Invasive infection

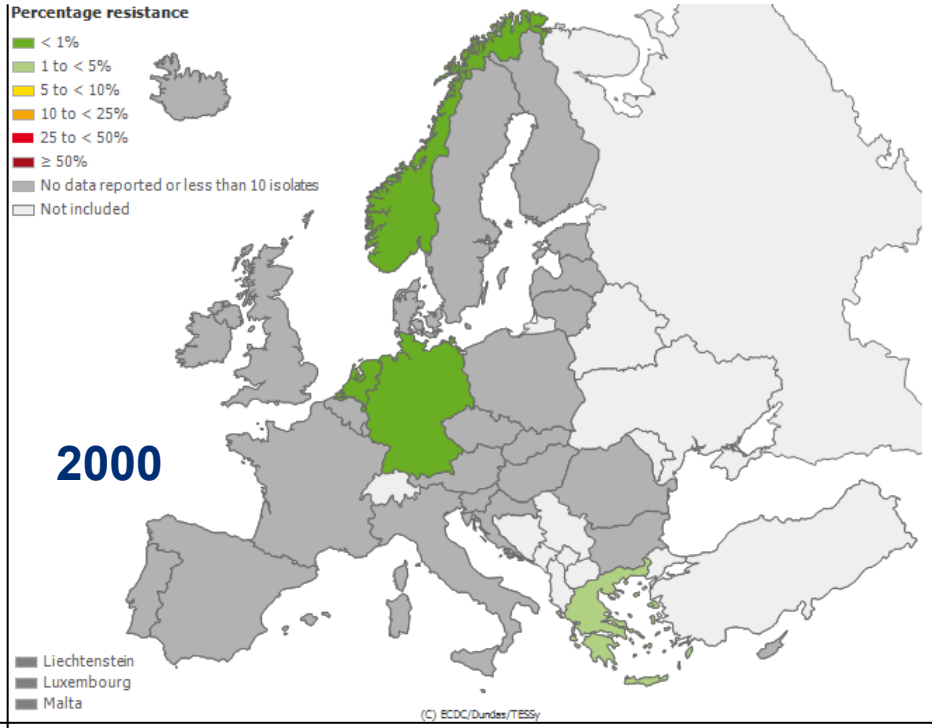


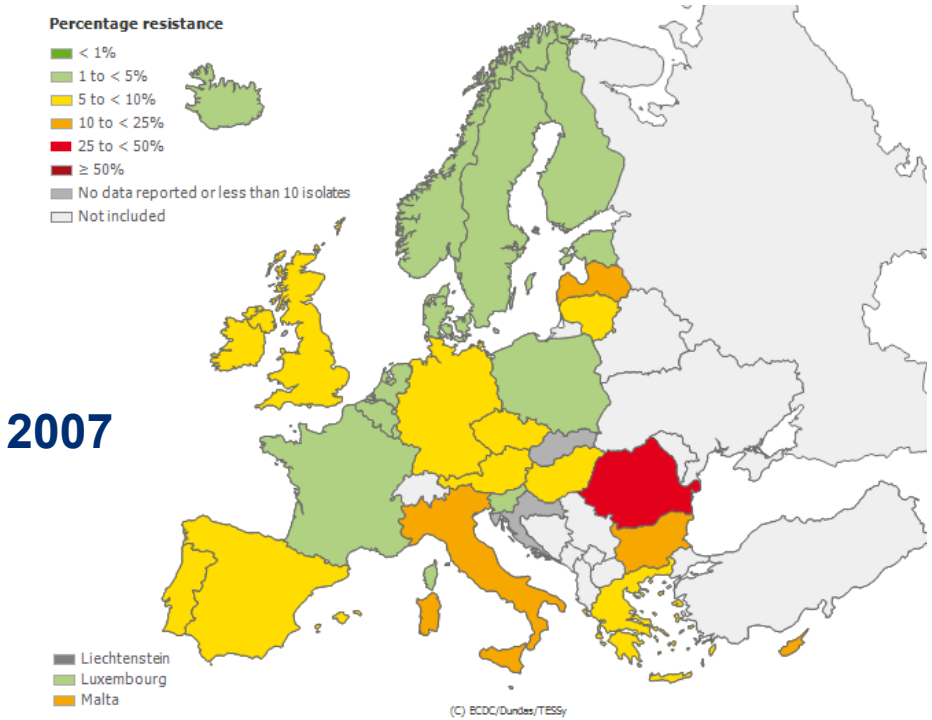


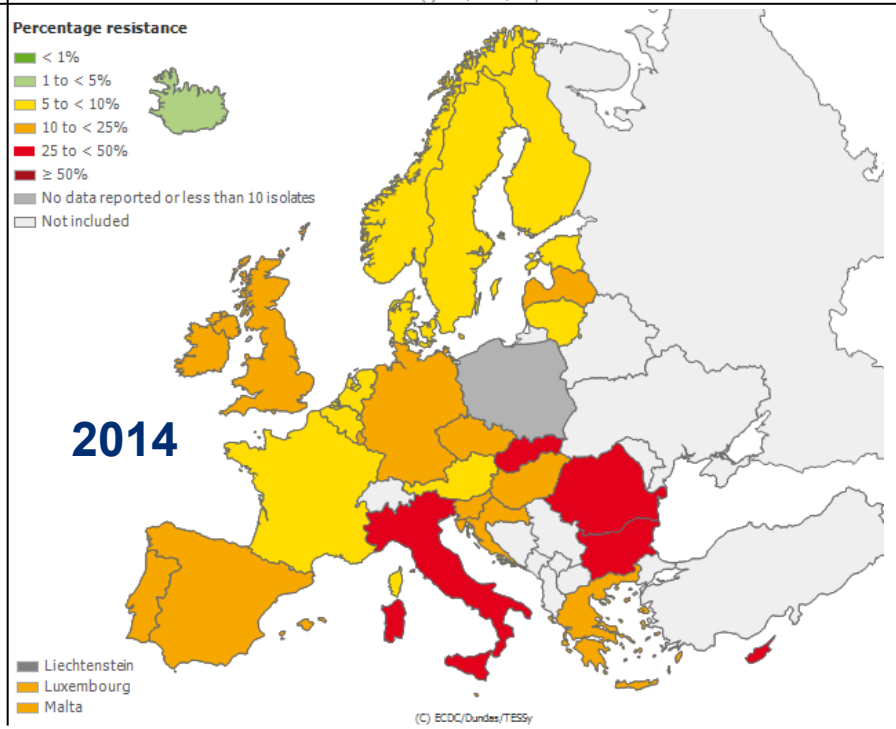


Escherichia coli
3rd gen. cephalosporins resistant

Invasive infection

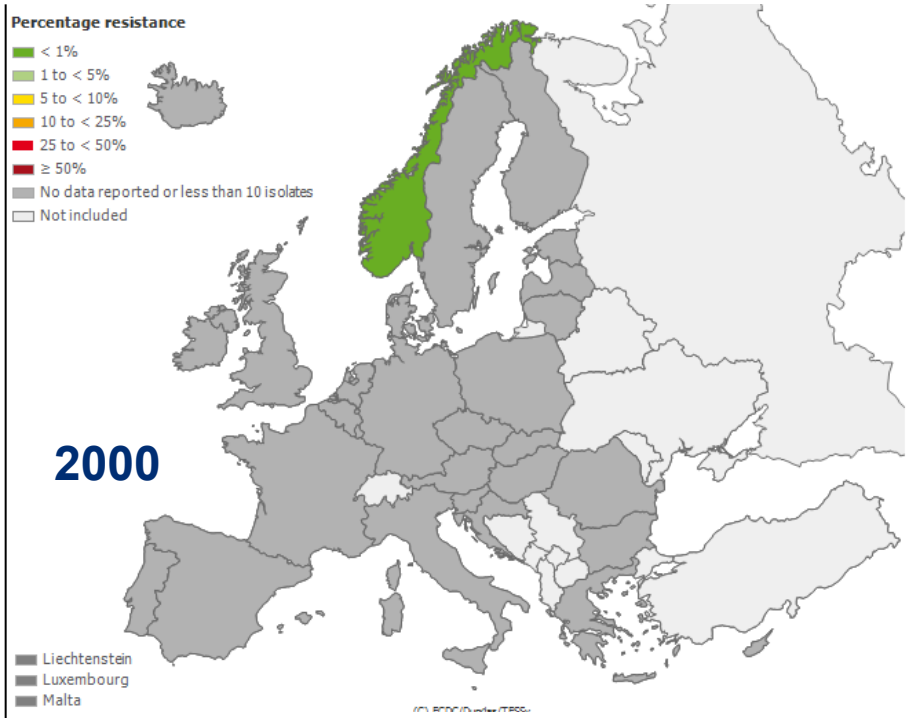


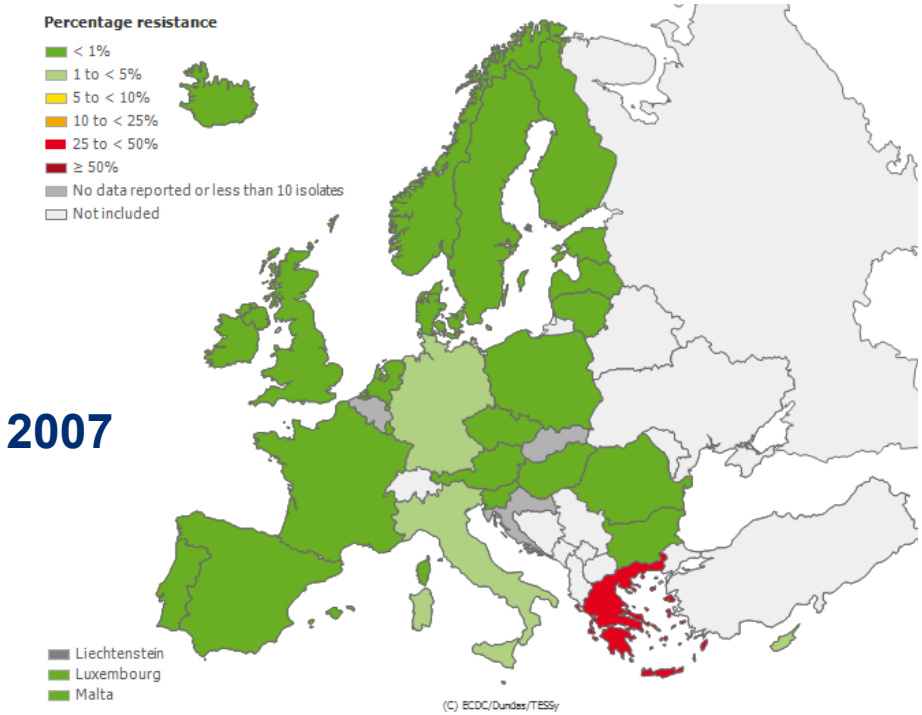


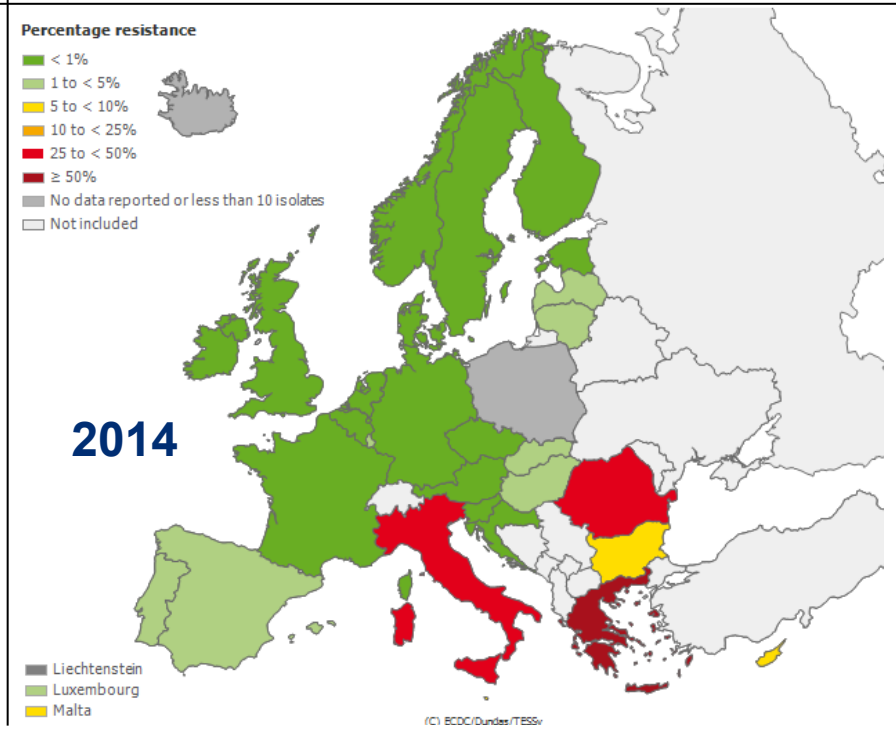


Klebsiella pneumoniae
KPC

Invasive infection







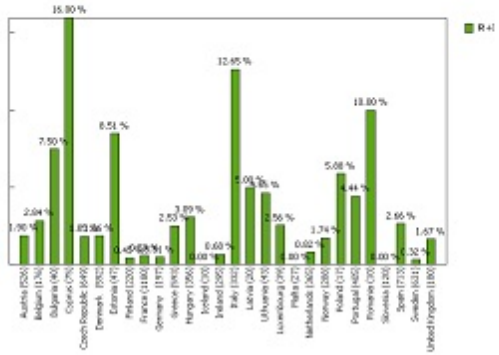
Antimicrobial resistance
Antimicrobial resistance interactive database: EARS-Net
Maps
Graphs
Tables
Antimicrobial consumption interactive database: ESAC-Net

Antimicrobial resistance interactive database (EARS-Net)

The results of the EARS-Net are available from the interactive database that provides information on the occurrence and spread of antimicrobial resistance in Europe.

ACCESS THE DATABASE

The EARS-Net interactive database allows user-friendly display of selected results in various downloadable formats, such as tables, figures, and maps.



ABOUT THE DATABASE

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How representative are the data?

The data have been collected at the national level under the responsibility of each participating country. The laboratories in the countries serve a variety of health-care institutions (e.g. university or specialised hospitals; general and district hospitals;

http://ecdc.europa.eu/en/healthtopics/antimicrobial_resistance/database/Pages/