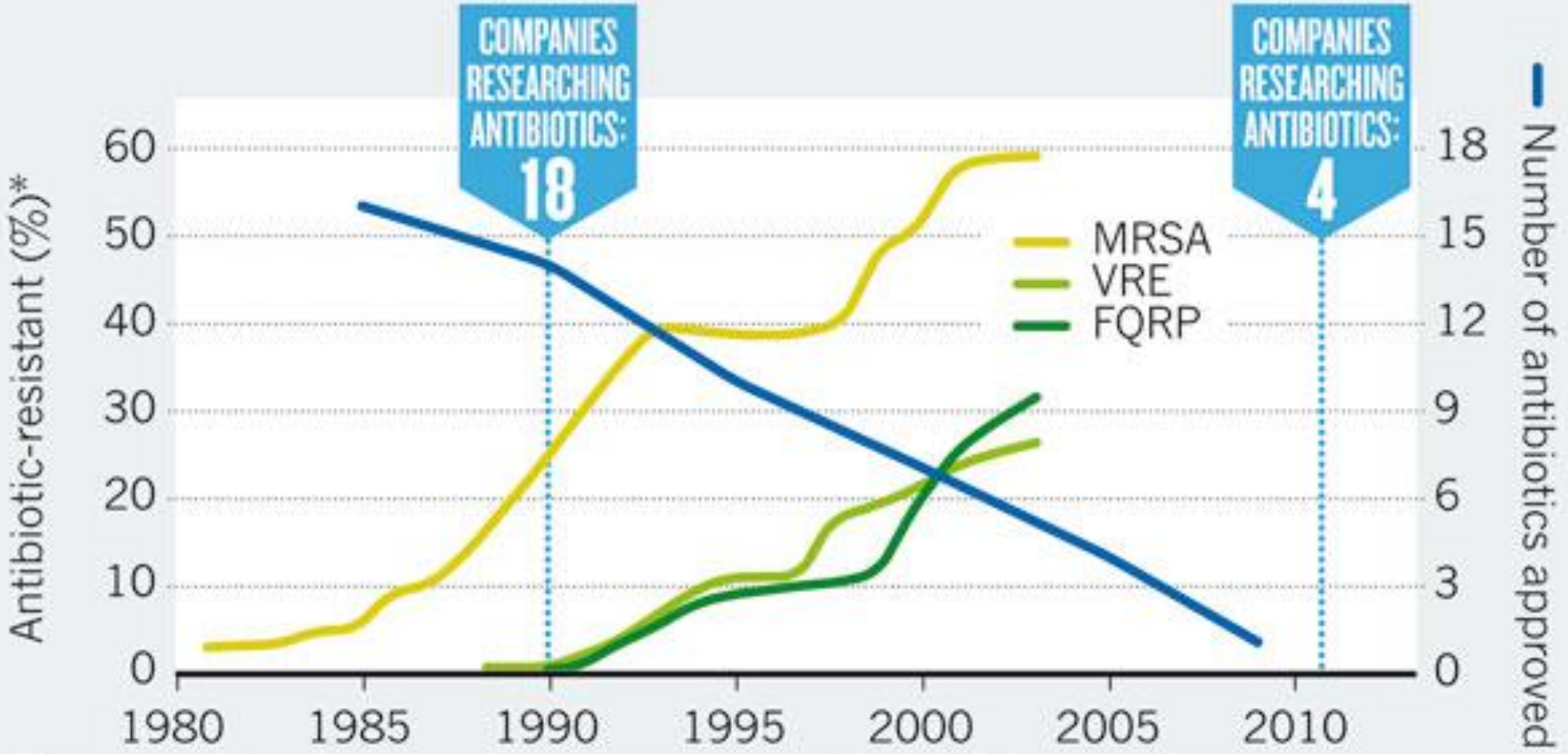
Antibiotics

Do we really know why they are made in Nature?

A PERFECT STORM

As bacterial infections grow more resistant to antibiotics, companies are pulling out of antibiotics research and fewer new antibiotics are being approved.



*Proportion of clinical isolates that are resistant to antibiotic. MRSA, methicillin-resistant *Staphylococcus aureus*. VRE, vancomycin-resistant *Enterococcus*. FQRP, fluoroquinolone-resistant *Pseudomonas aeruginosa*.

Silly use of antibiotics drives evolution of multidrug-resistant nosocomial pathogens

Forsberg *et al.* **The Shared Antibiotic Resistome of Soil Bacteria and Human Pathogens**
Science 31 August 2012: Vol. 337, pp. 1107-1111, DOI: 10.1126/science.1220761

Soil microbiota represent one of the ancient evolutionary origins of antibiotic resistance and have been proposed as a reservoir of resistance genes available for exchange with clinical pathogens. Using a high-throughput functional metagenomic approach in conjunction with a pipeline for the de novo assembly of short-read sequence data from functional selections (termed PARFuMS), we provide evidence for recent exchange of antibiotic resistance genes between environmental bacteria and clinical pathogens**. We describe multidrug-resistant soil bacteria containing resistance cassettes against five classes of antibiotics (β-lactams, aminoglycosides, amphenicols, sulfonamides, and tetracyclines) that have perfect nucleotide identity to genes from diverse human pathogens.** This identity encompasses noncoding regions as well as multiple mobilization sequences, offering not only evidence of lateral exchange but also a mechanism by which antibiotic resistance disseminates.

The Shared Antibiotic Resistome of Soil Bacteria and Human Pathogens

Forsberg *et al.* Science 31 August 2012: Vol. 337, pp. 1107-1111,
DOI: 10.1126/science.1220761

Table 1. Nonredundant antibiotic resistance genes with 100% identity to known human pathogens.

Gene name	GenBank ID	Number of selections*	Antibiotic class	Annotation [mechanism]	Pathogens hit (GI number)
AB95_PI_68.1	JX009363	4	β-lactam	blaP1 [enzymatic degradation]	*A. baumannii* (94960156), *K. pneumoniae* (114147191), *P. aeruginosa* (117321883), *S. typhimurium* (12719011), *P. mirabilis* (157674381)†
AB95_CH_13.1	JX009364	1	Amphenicol	Chloramphenicol efflux [efflux]	*A. baumannii* (169147133), *P. aeruginosa* (260677483)
AB95_TE_2.2	JX009366	3	Tetracycline	tetA(G) [efflux]	*A. baumannii* (169147133), *S. typhimurium* (12719011)
AB95_TE_1.1	JX009365	3	Tetracycline	tetA [efflux]	A. baumannii (169147133), *E. coli* (312949035), *K. pneumoniae* (290792160), *S. typhimurium* (37962716)†
AB95_GE_3.3	JX009367 JX009373	2	Aminoglycoside	aadB [covalent modification]	*E. cloacae* (71361871), *K. pneumoniae* (206731403), *P. aeruginosa* (37955767), *S. typhimurium* (17383994)†
AB95_GE_3.1	JX009368 JX009374	2	Sulfonamide	sul1 [target modification]	*C. diptheriae* (323714042) *E. cloacae* (71361871), *K. pneumoniae* (206731403), *P. aeruginosa* (37955767), *S. typhimurium* (17383994), *Yersinia pestis* (165913934)†
AB95_CH_21.1	JX009369	1	Aminoglycoside	aacA4 [covalent modification]	*A. baumannii* (164449567), *K. pneumoniae* (238865601), *P. aeruginosa* (219872982), *S. typhi* (34014739)†

*Number of selections in which the entirety of a given gene was captured. †More pathogens exist for which 100% nucleotide identity was observed than listed

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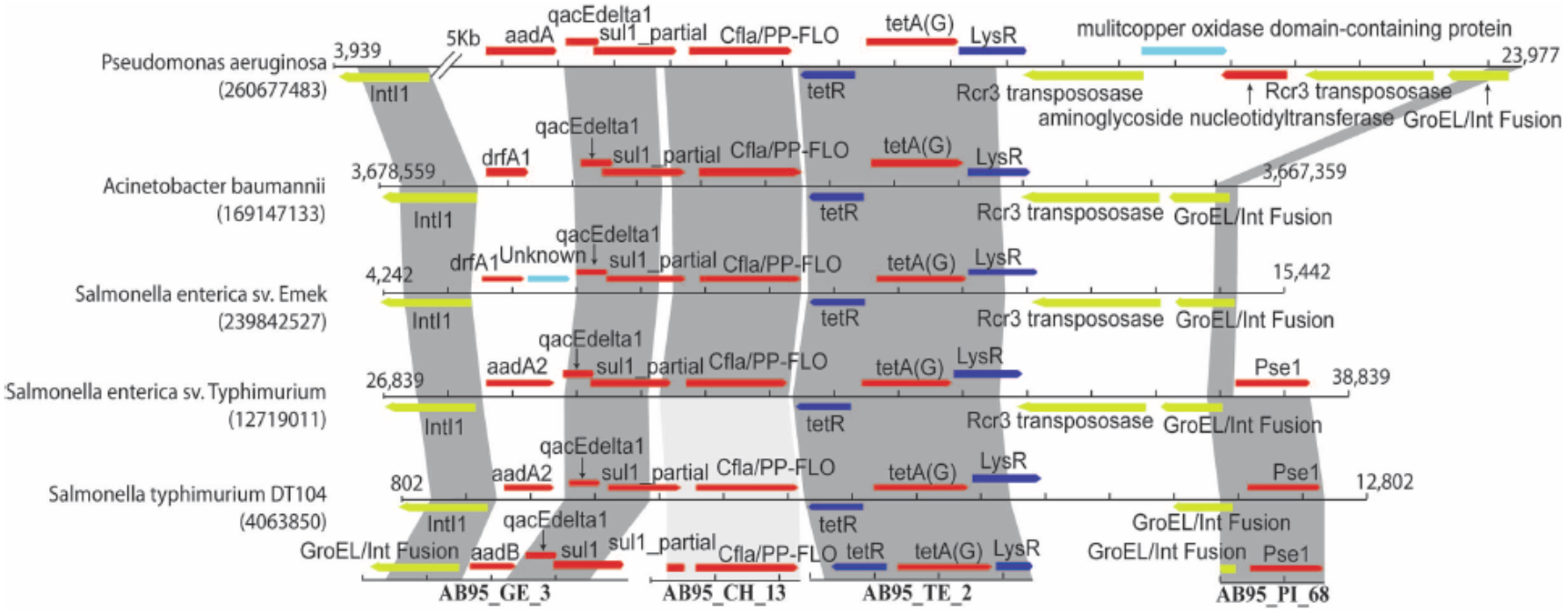
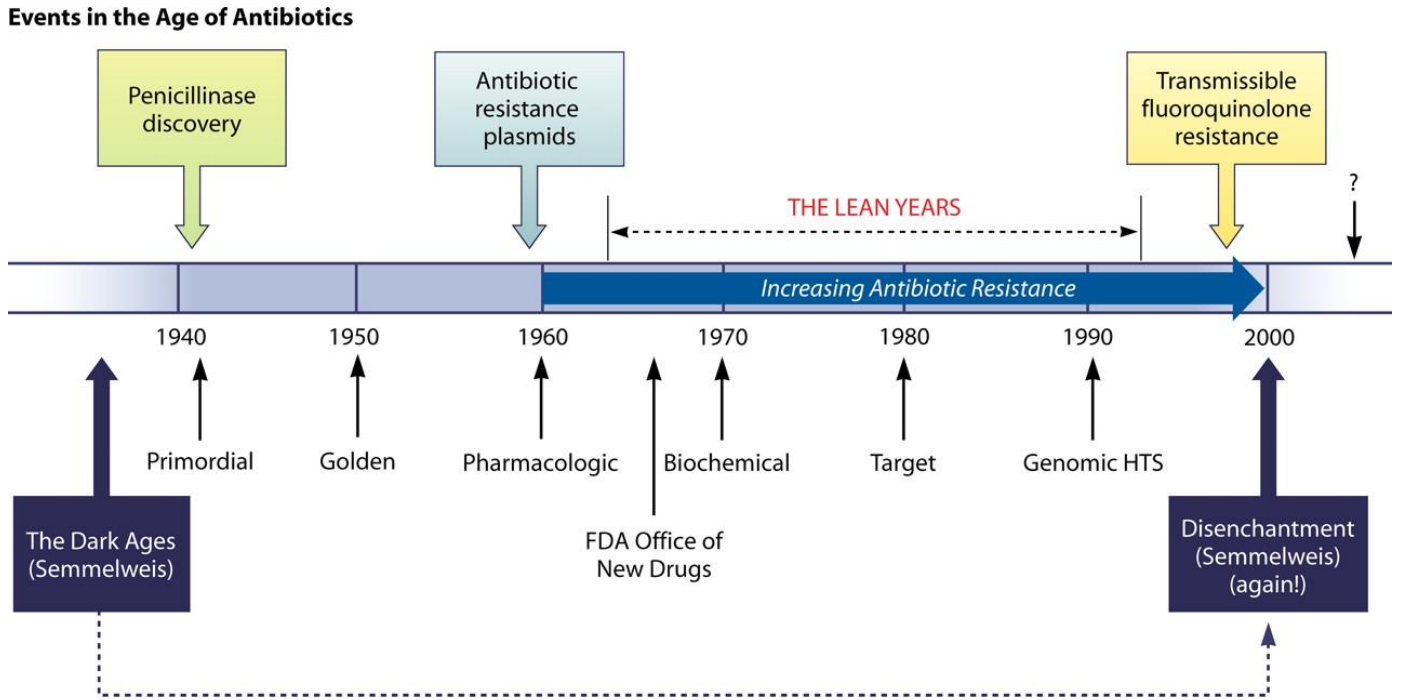


Fig. 3. Comparison of four AB95-derived resistance fragments to five human pathogenic isolates. The four fragments are depicted along the bottom, and shading indicates high nucleotide identity between the fragments and pathogens (NCBI GenInfo numbers identify each pathogenic isolate). Dark gray shading indicates >99% identity; light gray shading indicates ~88% identity. Base-pair coordinates flank pathogenic sequences, and the distance between each tick mark is 800 bp. Red ORFs represent resistance genes, yellow represents mobility elements, dark blue represents resistance-associated regulatory elements, and light blue represents other functions.

History of antibiotic discovery and concomitant development of antibiotic resistance



The dark ages, the preantibiotic era; primordial, the advent of chemotherapy, via the sulfonamides; golden, the halcyon years when most of the antibiotics used today were discovered; the lean years, the low point of new antibiotic discovery and development; pharmacologic, attempts were made to understand and improve the use of antibiotics by dosing, administration, etc.; biochemical, knowledge of the biochemical actions of antibiotics and resistance mechanisms led to chemical modification studies to avoid resistance; target, mode-of-action and genetic studies led to efforts to design new compounds; genomic/HTS, genome sequencing methodology was used to predict essential targets for incorporation into high-throughput screening assays; disenchantment, with the failure of the enormous investment in genome-based methods, many companies discontinued their discovery programs. Other milestones in this history include the creation of the FDA Office of New Drugs after the thalidomide disaster led to stricter requirements for drug safety, including the use of antibiotics. This slowed the registration of novel compounds. Before antibiotics were discovered, Semmelweis advocated hand washing as a way of avoiding infection; this practice is now strongly recommended as a method to prevent transmission.

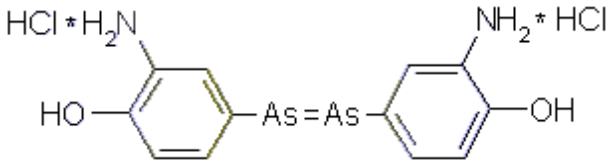
Davies, J. et al. 2010. Microbiol. Mol. Biol. Rev. 74(3):417-433

Did you know?

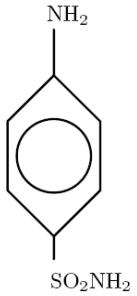
- Studies on transmission of resistance to antibiotics lead to discovery of bacterial plasmids….
- Characterization of plasmids allowed the birth of genetic engineering… S.N. Cohen wanted to understand how the genes of plasmids could make bacteria resistant to antibiotics. In 1972, Cohen's investigations, combined with those of Paul Berg and Herbert Boyer, led to the development of methods to combine and transplant genes…
- In 1975 they got the Nobel Prize….

What are antibiotics?

Salvarsan (antisyphilitic, 1910, Paul Ehrlich) > sulfonamides (war injuries, 1935) > penicillin (1928, A. Fleming, 1940s usage) > current antibiotics (70% produced by *Streptomyces spp.)*



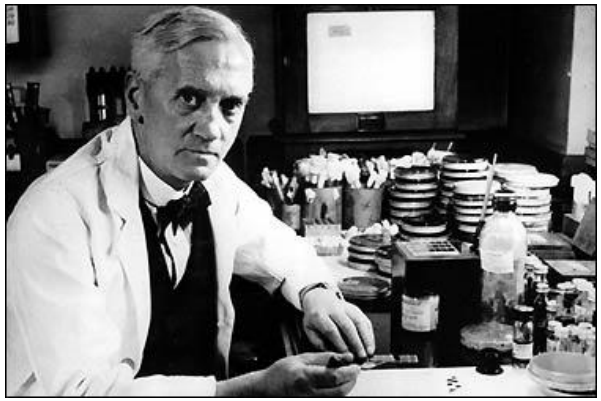
salvarsan: 3-diamino-4-dihydroxyl-l-arseno benzene hydrochlorid



sulfanilamid

- Antibiotics are chemicals that kill bacteria (bactericidal), or stop their growth (bacteriostatic)
- Have been used by fungi to kill bacteria for many millions of years?
  - They are secondary metabolites and it is not all that clear how they serve the producer
- Their introduction was arguably the biggest medical breakthrough since sanitation
- First discovered in 1928 by Sir A. Fleming, penicillin was brought into widespread use in the 1940s

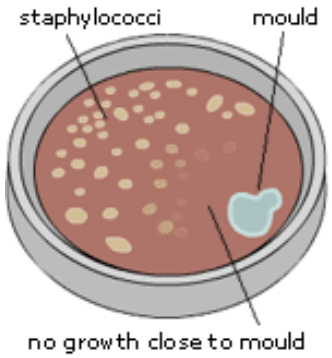
Penicillin: A discovery by accident?

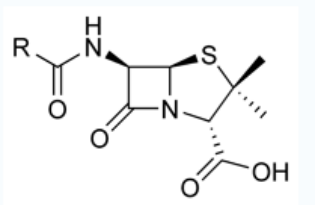


Serendipity plays a crucial role in science!

ser·en·dip·i·ty (srn-dp-t):

1. The faculty of making fortunate discoveries by accident.
2. The fact or occurrence of such discoveries.
3. An instance of making such a discovery.

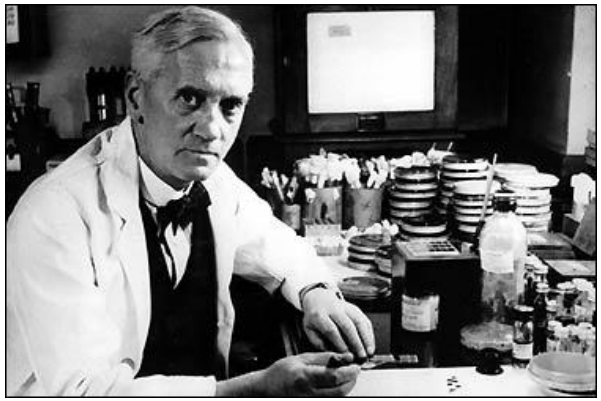




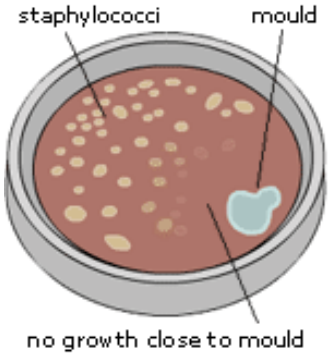
penicillin (β-lactam)

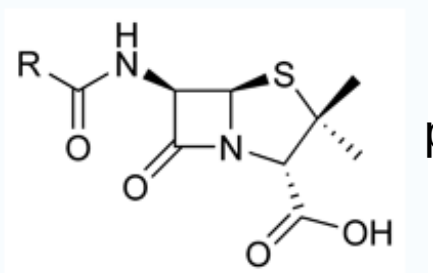
A discovery by accident?

(Fleming was working for 10 years before on anti-bacterial components of body fluids etc… **serendipity** serves a prepared mind…)



- A fungal spore that the wind might have blown into the plate with bacteria
- A. Fleming named the substance Penicillin, after the mould *Penicillium notatum* – but was unable to isolate the substance
- In the late 1930s and early 1940s, E. B. Chain & H. Florey managed to produce larger amounts of penicillin
- Nobel prize in 1945 (A. Fleming, E. B. Chain, H. Florey) *"for the discovery of penicillin and its curative effect in various infectious diseases"*.
- *http://nobelprize.org/nobel_prizes/medicine/laureates/1945/#*





penicillin (β-lactam)

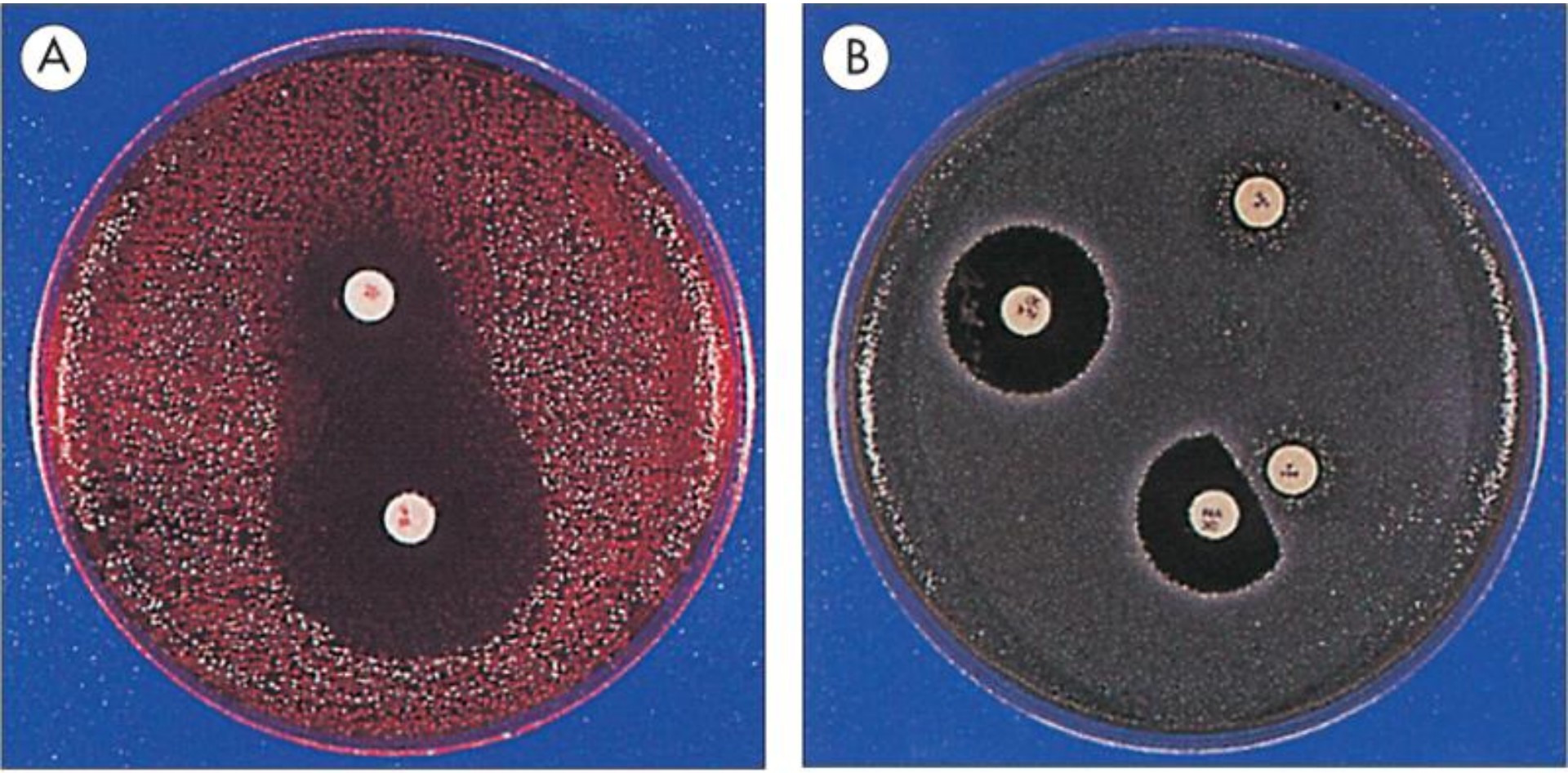
Czechoslovakia belonged to the first countries pioneering industrial penicillin production

Professor Ivan Málek, was the founder of this Institute of Microbiology of the Czechoslovak Aacademy of Sciences
As early as 1942, he was named a consultant to the chemical and pharmaceutical factory B. Frágner, in Dolní Měcholupy (later Zentiva), where he and a team of researchers succeeded in manufacturing a small quantity of penicillin. The penicillin manufactured at B. Frágner was successfully tested in 1943–1944 on civilian patients suffering from neisserial meningitis, staphylococcal osteomyelitis,
and pneumococcal pneumonia.

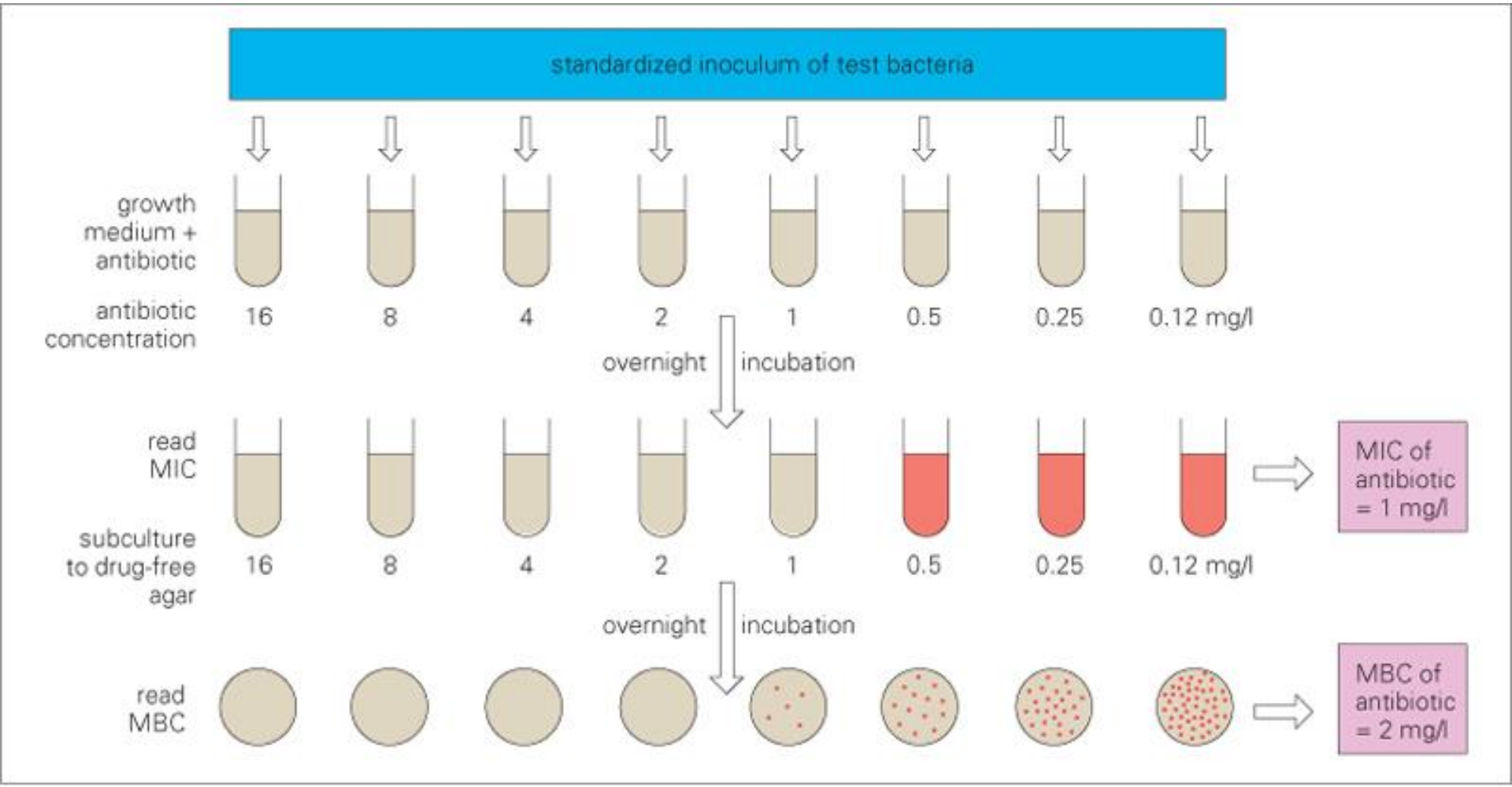
In 1947–1948, Czechoslovakia received equipment for industrial production of penicillin, courtesy of the United Nations Relief and Rehabilitation Administration (UNRRA).

Málek founded Czechoslovakia's first penicillin manufacturing plant in Roztoky near Prague, in October 1949.

Inhibitory zone of antibiotic action
Resistance testing



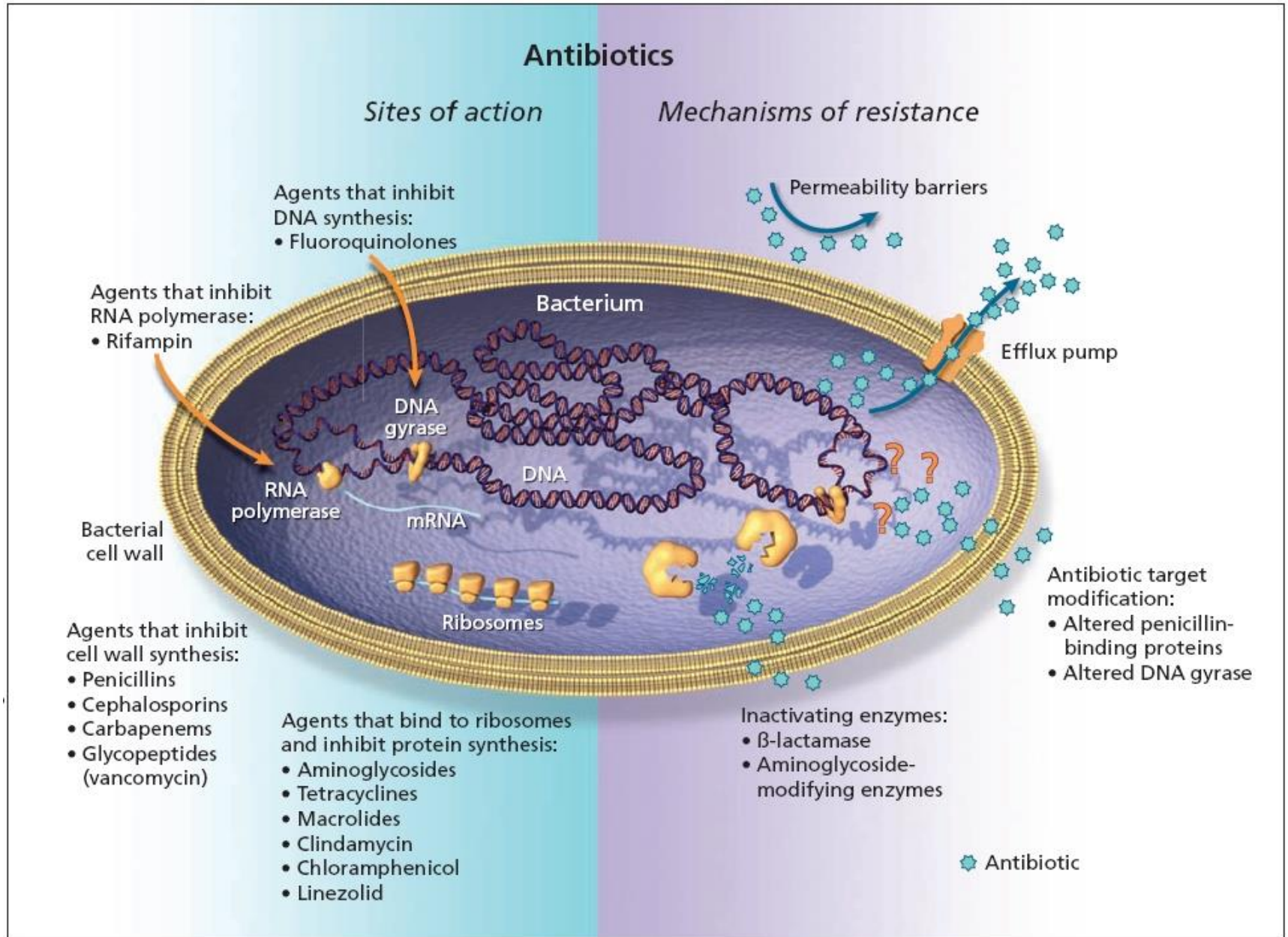
Determination of minimal inhibitory concentration



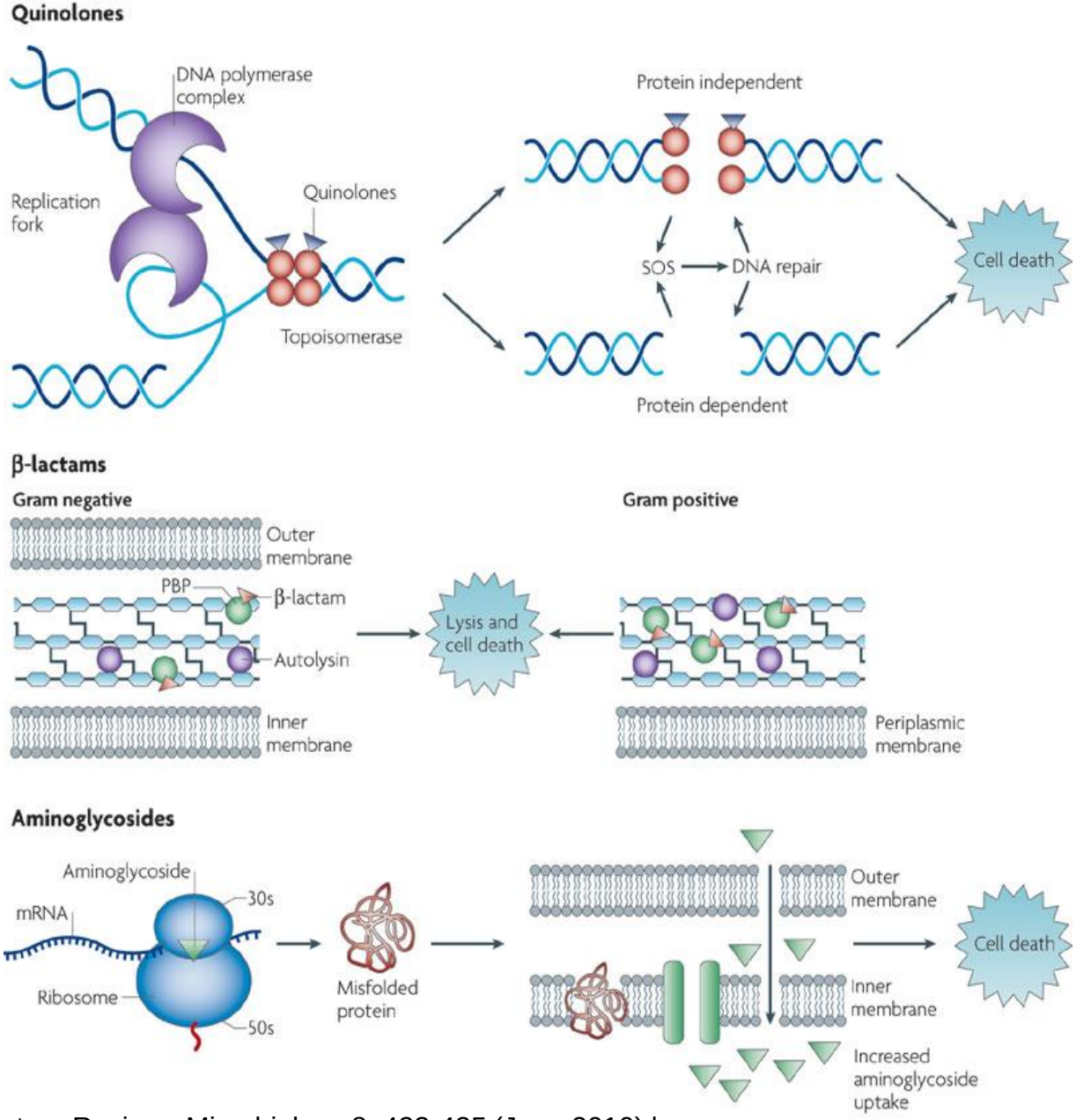
Requirements for antibiotics

- **Spectrum of efficiency**
  - broad-spectrum antibiotics - life-saving
  - other antibiotics – mild to physiological microflora
- **Selectivity of antibiotics** - specific interaction with microbial compounds not with host
- **Pharmacological a pharmacodynamic properties**

Mechanisms of antibiotic action and resistance



How antiobitics kill bacteria



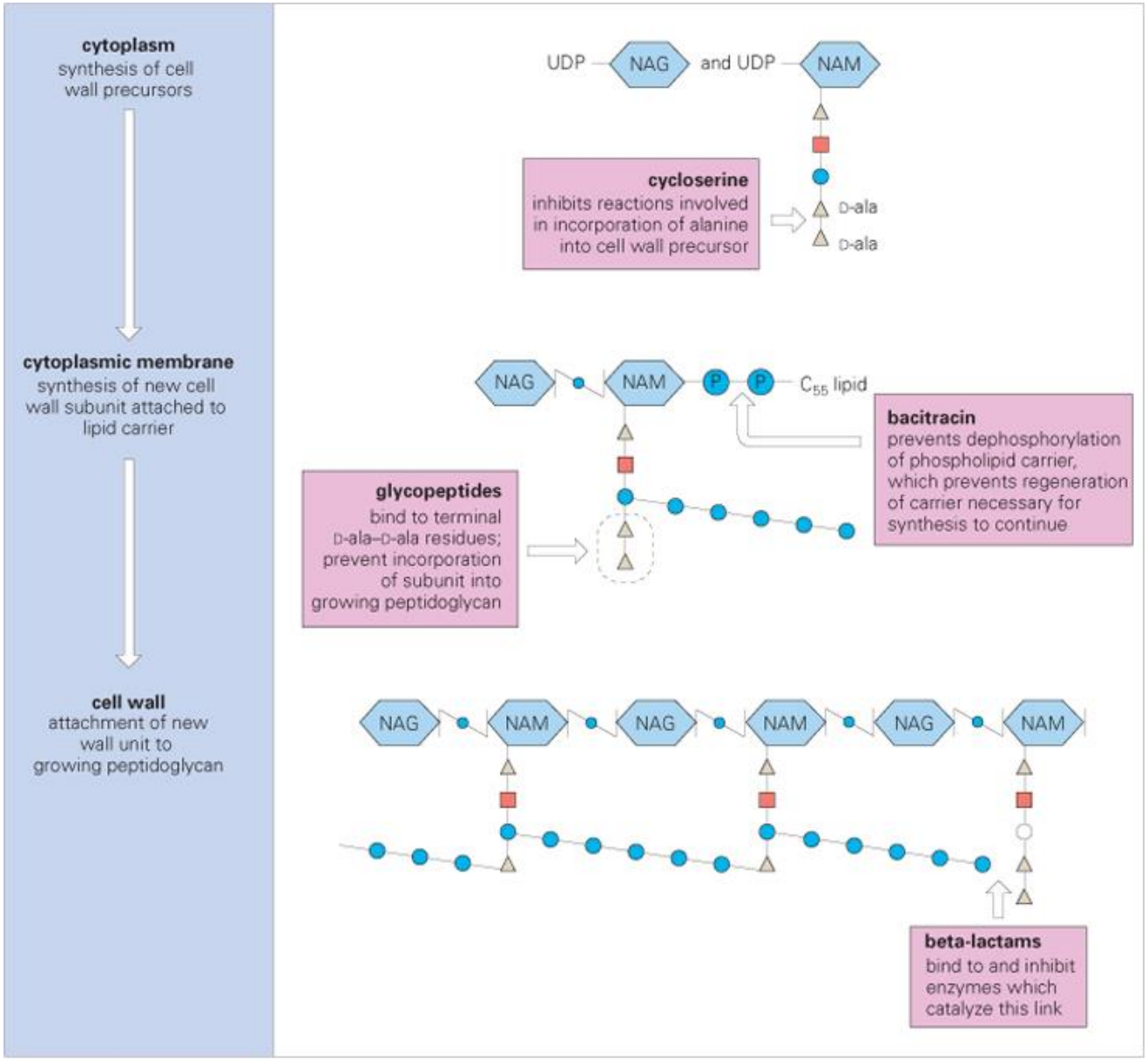
Quinolone antibiotics / DNA
interfere with changes in DNA supercoiling by binding to topoisomerase II or topoisomerase IV. This leads to the formation of double-stranded DNA breaks and cell death in either a protein synthesis-dependent or protein synthesis-independent manner.

β-lactams / cell wall
inhibit transpeptidation by binding to penicillin-binding proteins (PBPs) on maturing peptidoglycan strands. The decrease in peptidoglycan synthesis and increase in autolysins leads to lysis and cell death.

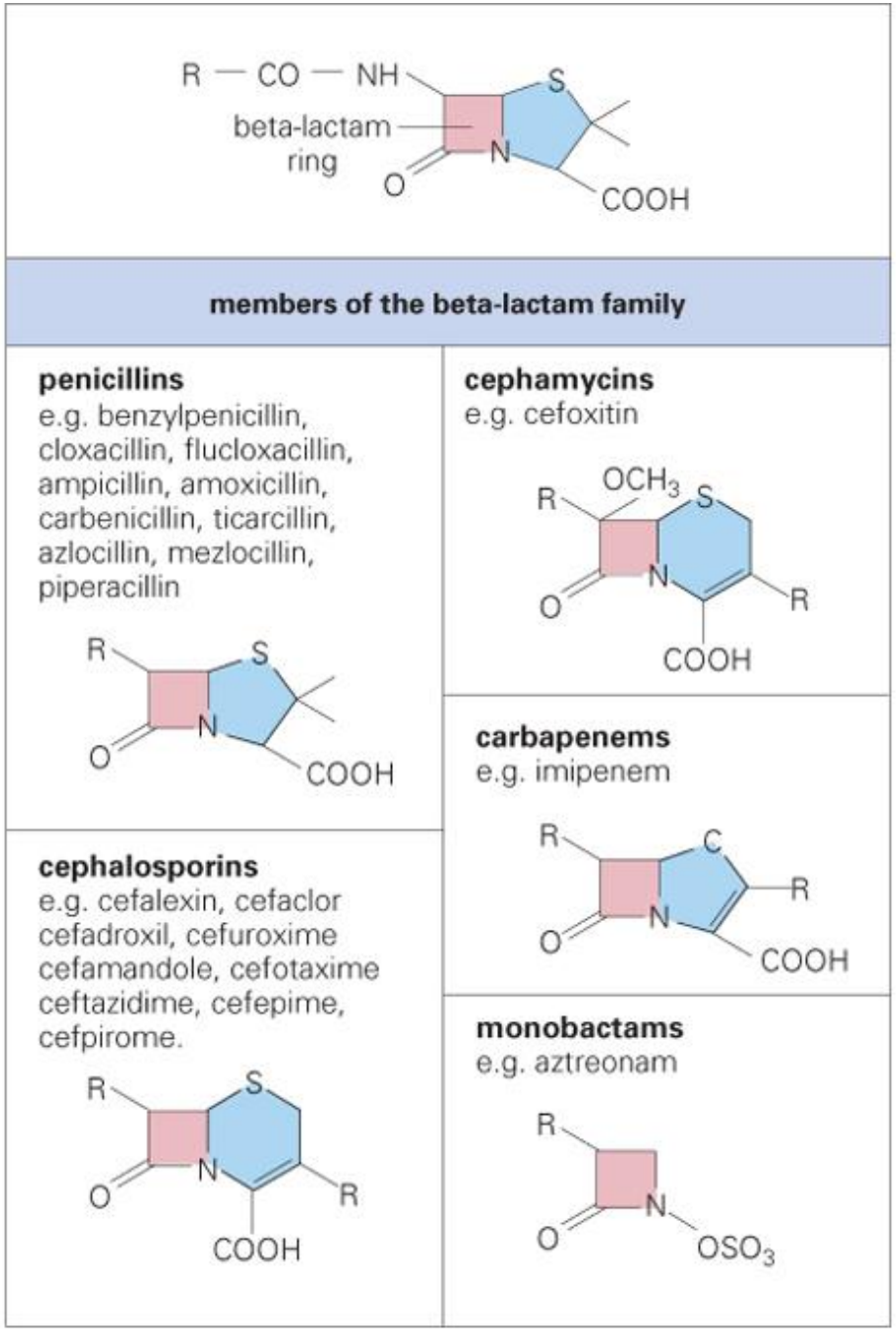
Aminoglycosides/ proteosynthesis
bind to the 30S subunit of the ribosome and cause misincorporation of amino acids into elongating peptides. These mistranslated proteins can misfold, and incorporation of misfolded membrane proteins into the cell envelope leads to increased drug uptake. This, together with an increase in ribosome binding, has been associated with cell death.

Nature Reviews Microbiology 8, 423-435 (June 2010) | doi:10.1038/nrmicro2333

Inhibitors of cell wall synthesis



β-lactam antibiotics



β-lactams

- Function

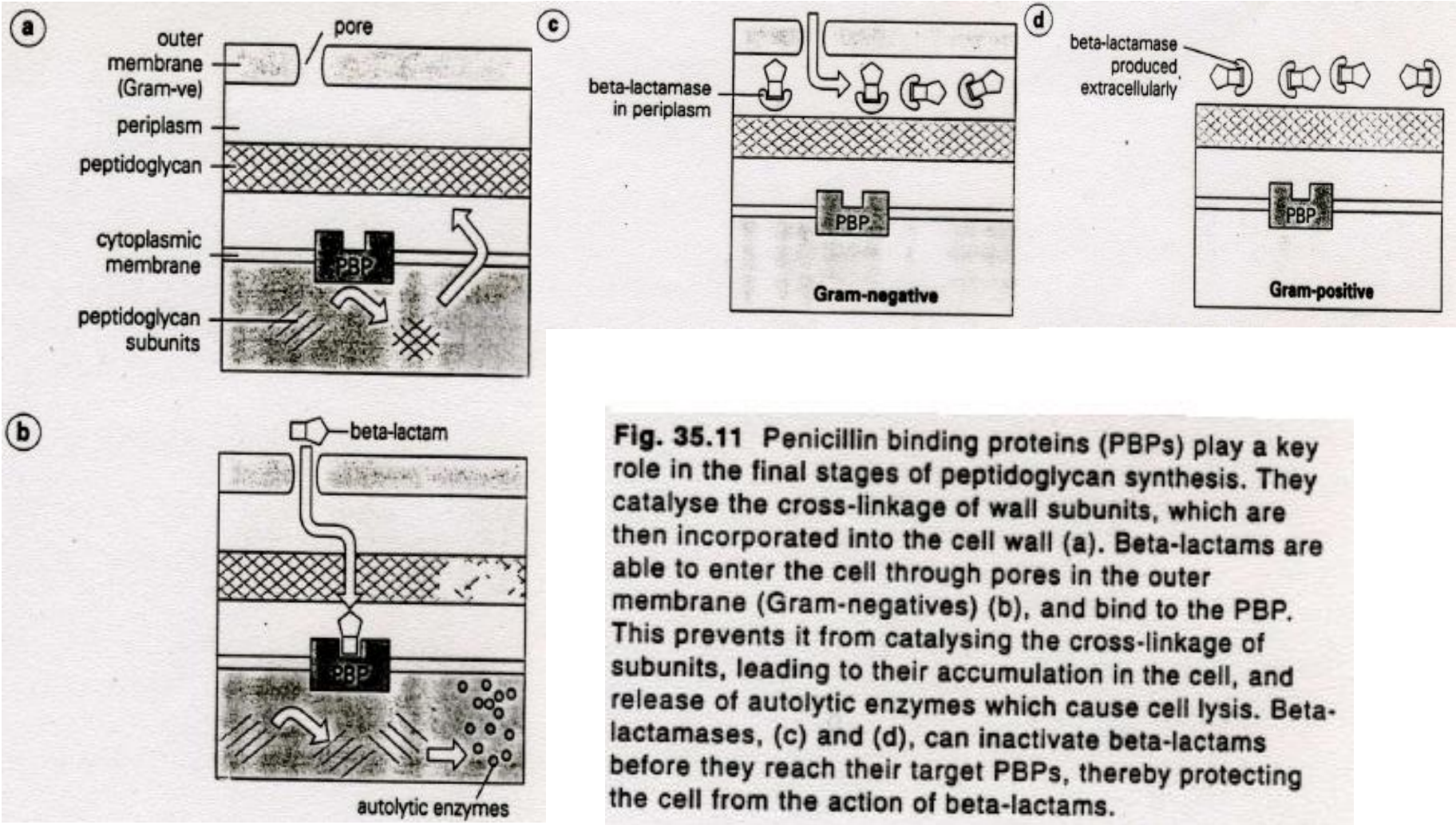
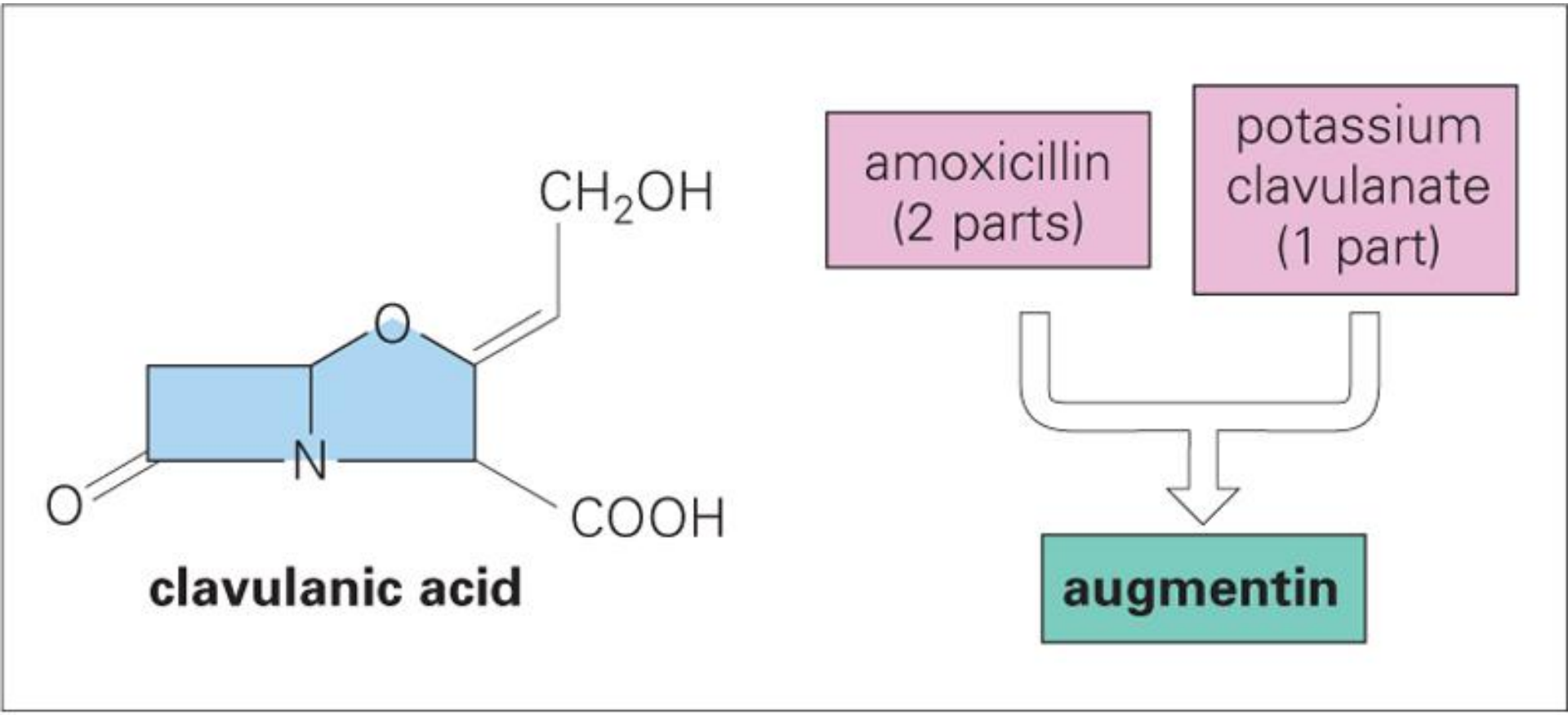


Fig. 35.11 Penicillin binding proteins (PBPs) play a key role in the final stages of peptidoglycan synthesis. They catalyse the cross-linkage of wall subunits, which are then incorporated into the cell wall (a). Beta-lactams are able to enter the cell through pores in the outer membrane (Gram-negatives) (b), and bind to the PBP. This prevents it from catalysing the cross-linkage of subunits, leading to their accumulation in the cell, and release of autolytic enzymes which cause cell lysis. Beta-lactamases, (c) and (d), can inactivate beta-lactams before they reach their target PBPs, thereby protecting the cell from the action of beta-lactams.

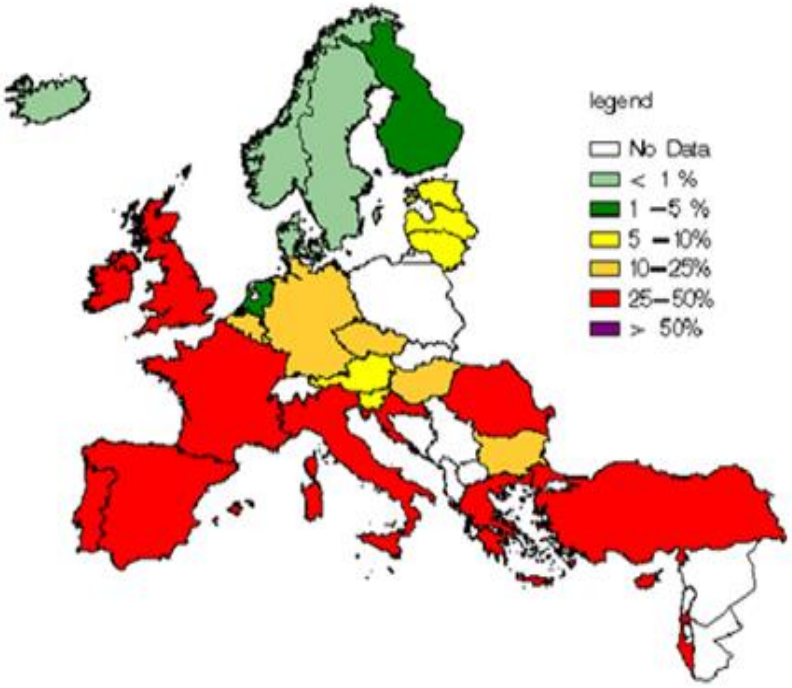
β-lactamase inhibitors



MRSA-methicillin resistant *Staphylococcus aureus* the "superbug"

Resistance is conferred by the *mecA* gene, which codes for an altered penicillin-binding protein (PBP2a or PBP2') that has a lower affinity for binding β-lactams.
This allows for resistance to all β-lactam antibiotics and obviates their clinical use during MRSA infections. As such, the glycopeptide vancomycin is often deployed against MRSA.

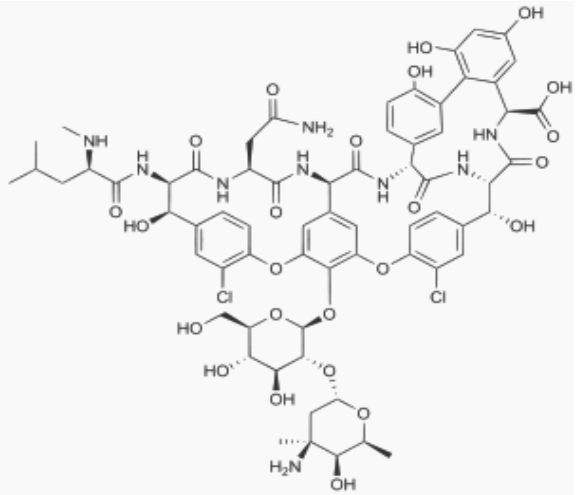
- Usually resistant to several antibiotics, shows a particular ability to spread in hospitals
- MRSA frequently causes nosocomial infections
- An increase in the trend of death due to MRSA infection (severe infections including septicemia, endocarditis and meningitis)
- Infections caused by MRSA can be expensive in terms of antibiotic therapy, isolation facilities, materials and length of hospital stay (Kumary, N.: J*NMA* 1998)



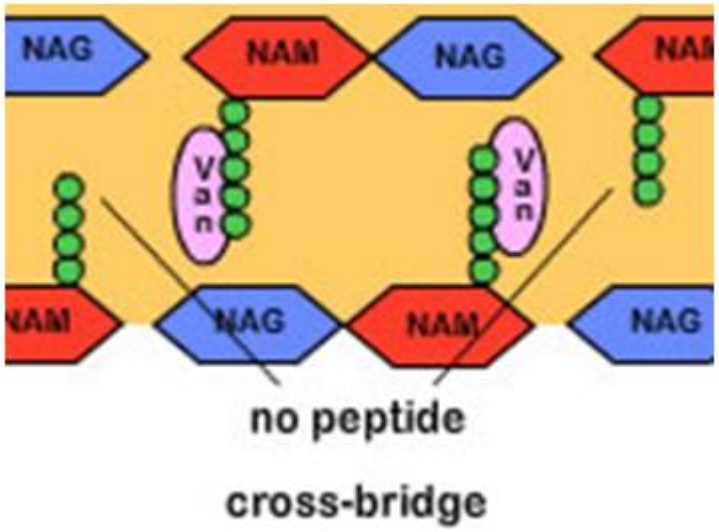
Epidemiology of MRSA in Europe 2008
http://www.uniklinik-freiburg.de/onlinemagazin/live/aktuelles/antibiotika/antibiotika1.jpg

Glycopeptides

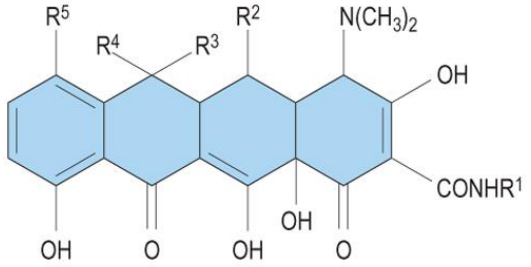
- Structure
  - teichoplanin, vancomycin-treatment of serious, life-threatening infections by Gram-positive bacteria that are unresponsive to other less-toxic antibiotics



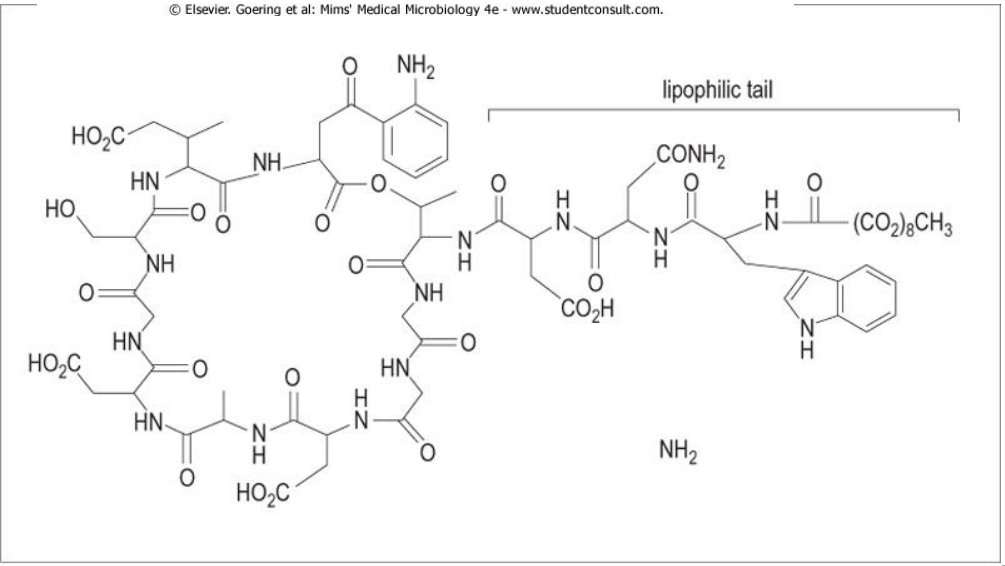
- Function
  - bind to D-Ala-D-Ala moiety of precursor subunit blocking transpeptidation

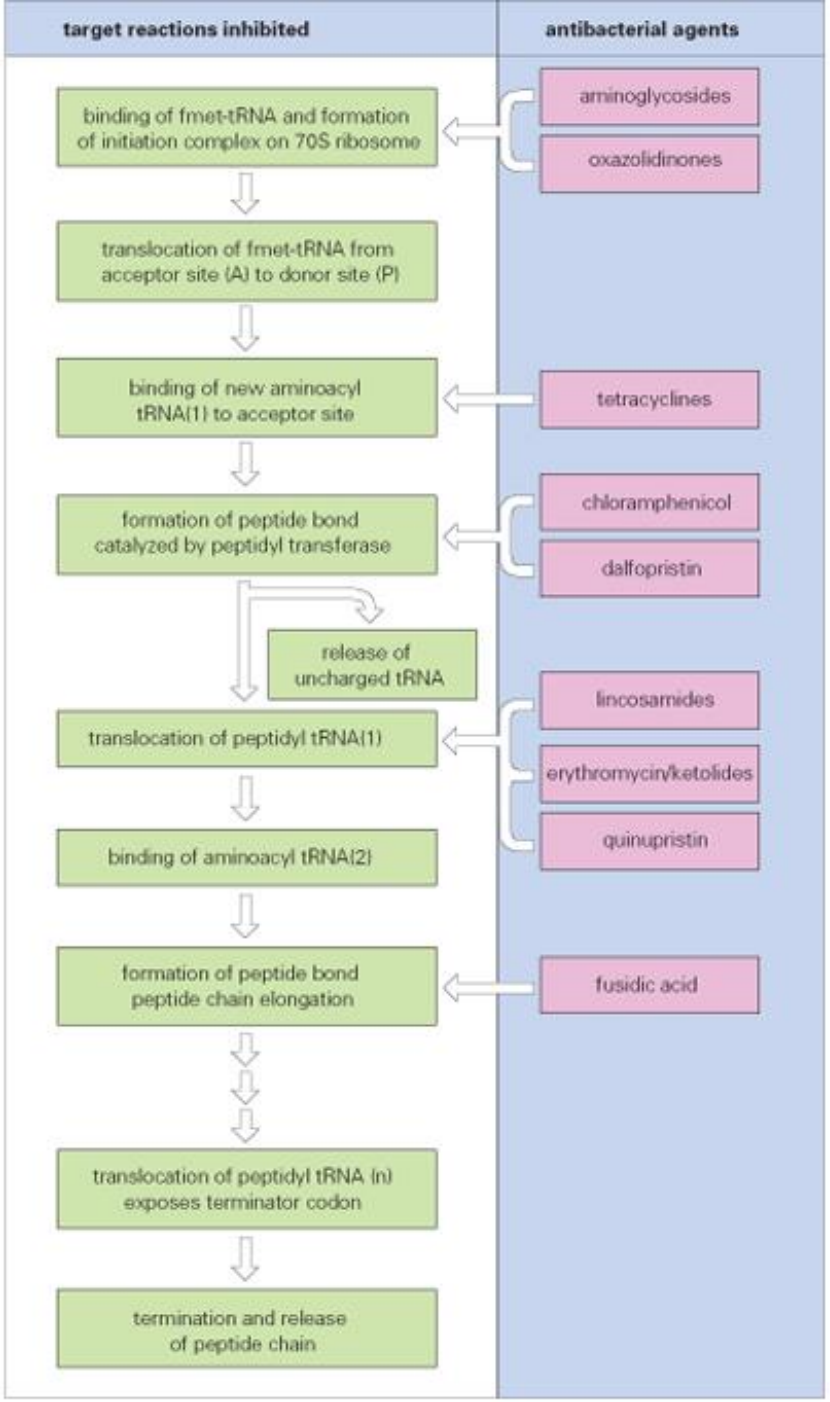


Inhibitors of proteosynthesis



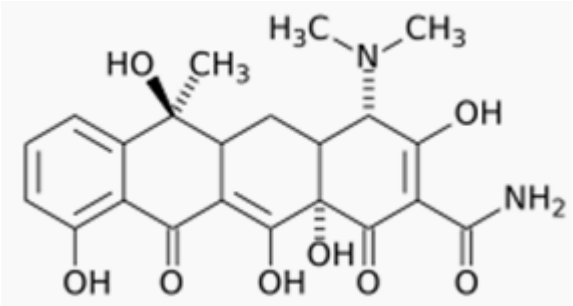
	R1	R2	R3	R4	R5	R6
tetracycline	H	H	CH_3	OH	H	H
chlortetracycline	H	H	CH_3	OH	Cl	H
oxytetracycline	H	OH	CH_3	OH	H	H
doxycycline	H	OH	CH_3	H	H	H
minocycline	H	H	H	H	$N(CH_3)_2$	H
tigecycline	H	H	H	H	$N(CH_3)_2$	NH-O-$NH(CH_3)_3$





Tetracyclins

- Structure



- Function
  - reversible inhibition of protein synthesis (binding to 30S ribosomal subunit)
- Bacterial tetracycline resistence
  - EF-G-like protein confer ribosome protection
  - Oxidative destruction of tetracycline
  - Tetracycline antiporter system

Mechanism of tetracycline resistance

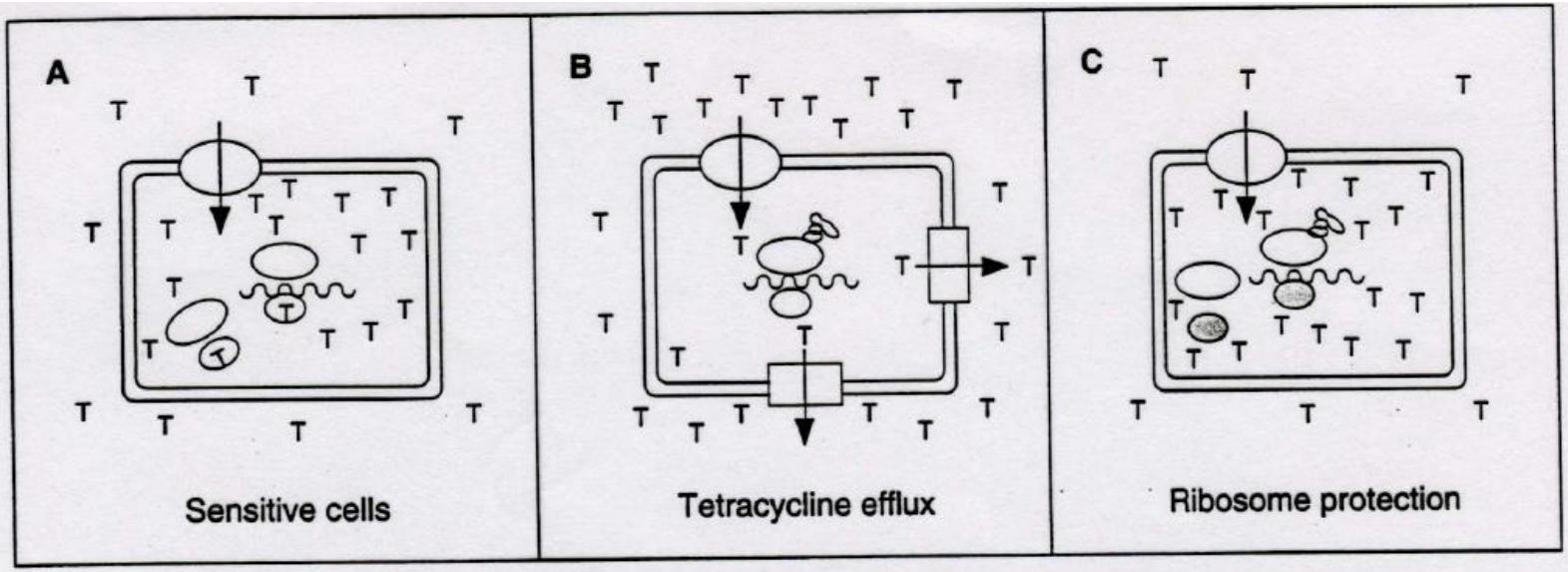
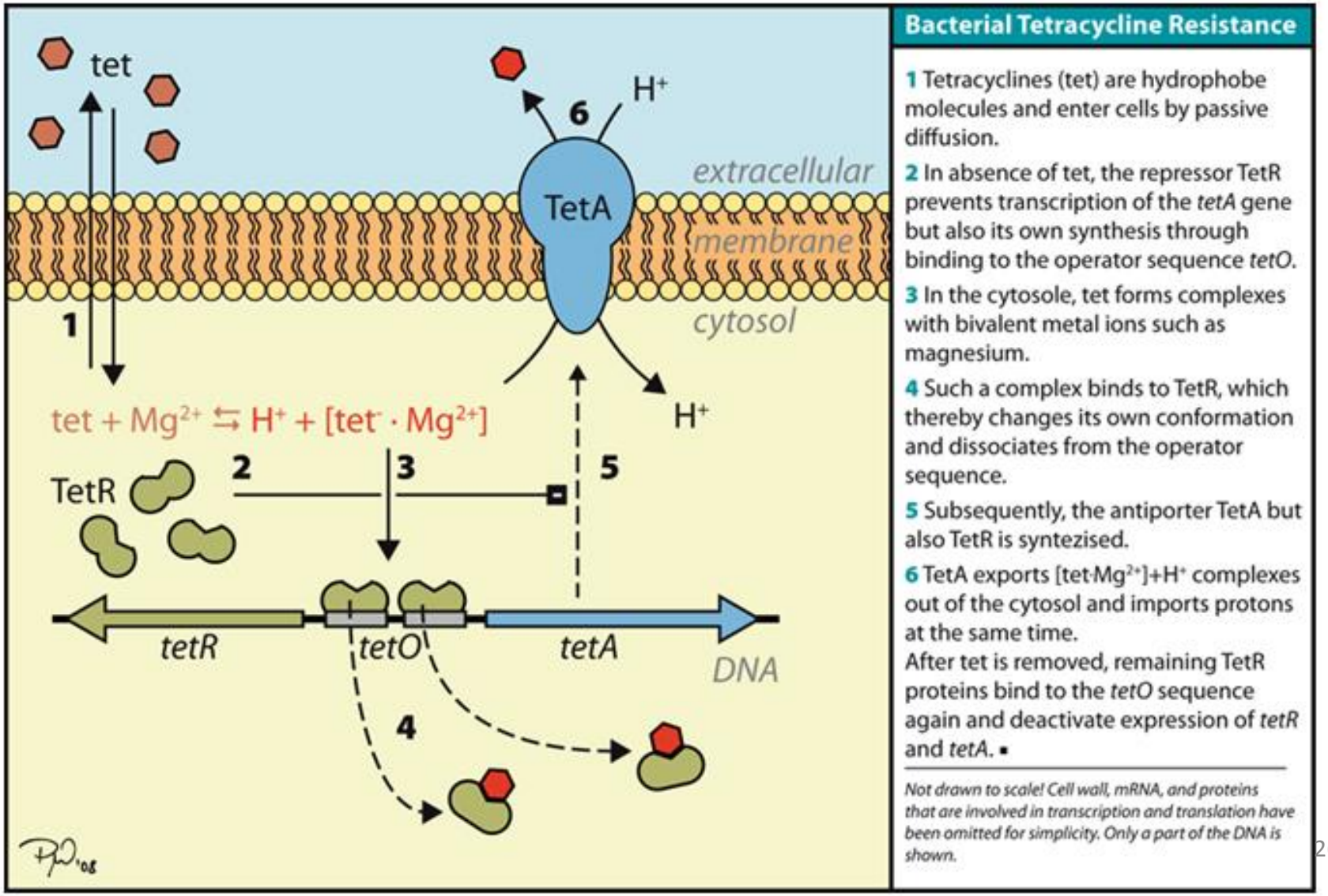


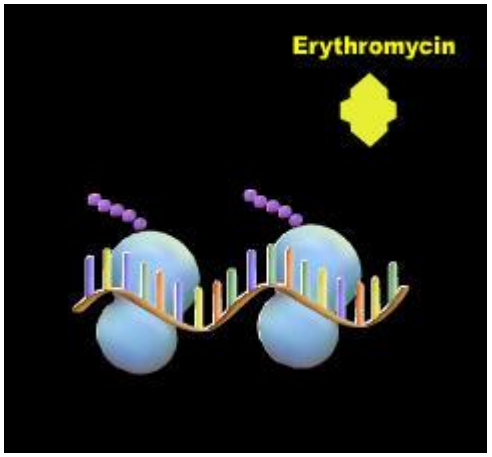
Figure 8-13 Mechanisms of tetracycline resistance. **A**, Tetracycline (T) is taken up by a transporter (open ellipse); intracellular concentration becomes higher than extracellular concentration; tetracycline binds to ribosomes and stops protein synthesis. **B**, Cytoplasmic membrane protein (open square) pumps tetracycline out of the cell as fast as the transporter takes it up; intracellular concentration remains too low for effective binding to ribosomes. **C**, Tetracycline accumulation within cell is similar to that in sensitive cell, but ribosome is protected (shading), so tetracycline no longer binds to it. B. Speer N. Shoemaker, and A. Salyers. 1992. Bacterial resistance to tetracycline: mechanisms, transfer, and clinical significance. Clin. Microbiol. Rev. 5:387–399.

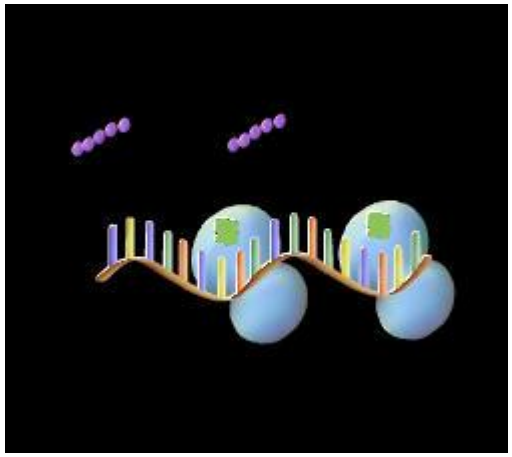
Bacterial tetracycline resistence- inducible tetracycline antiporter system

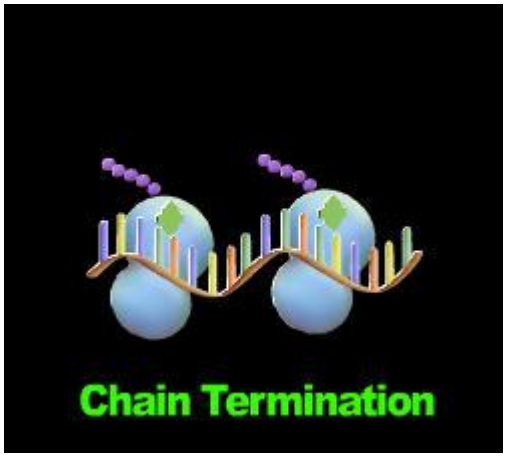


Macrolides a lincosamides

- **Macrolides** - erythromycin, spiramycin, roxitromycin, josamycin, azitromycin, claritromycin, diritromycin
- Function
  - bind to 50S ribosomy and cause termination of polypeptide strain → proteosynthesis inhibition

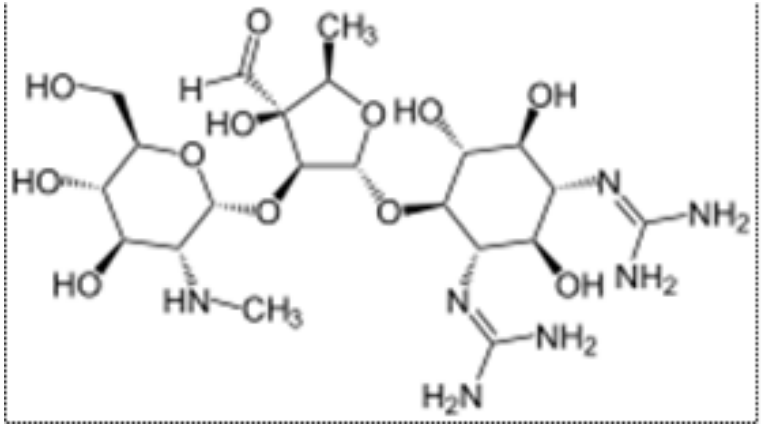






Aminoglycosides

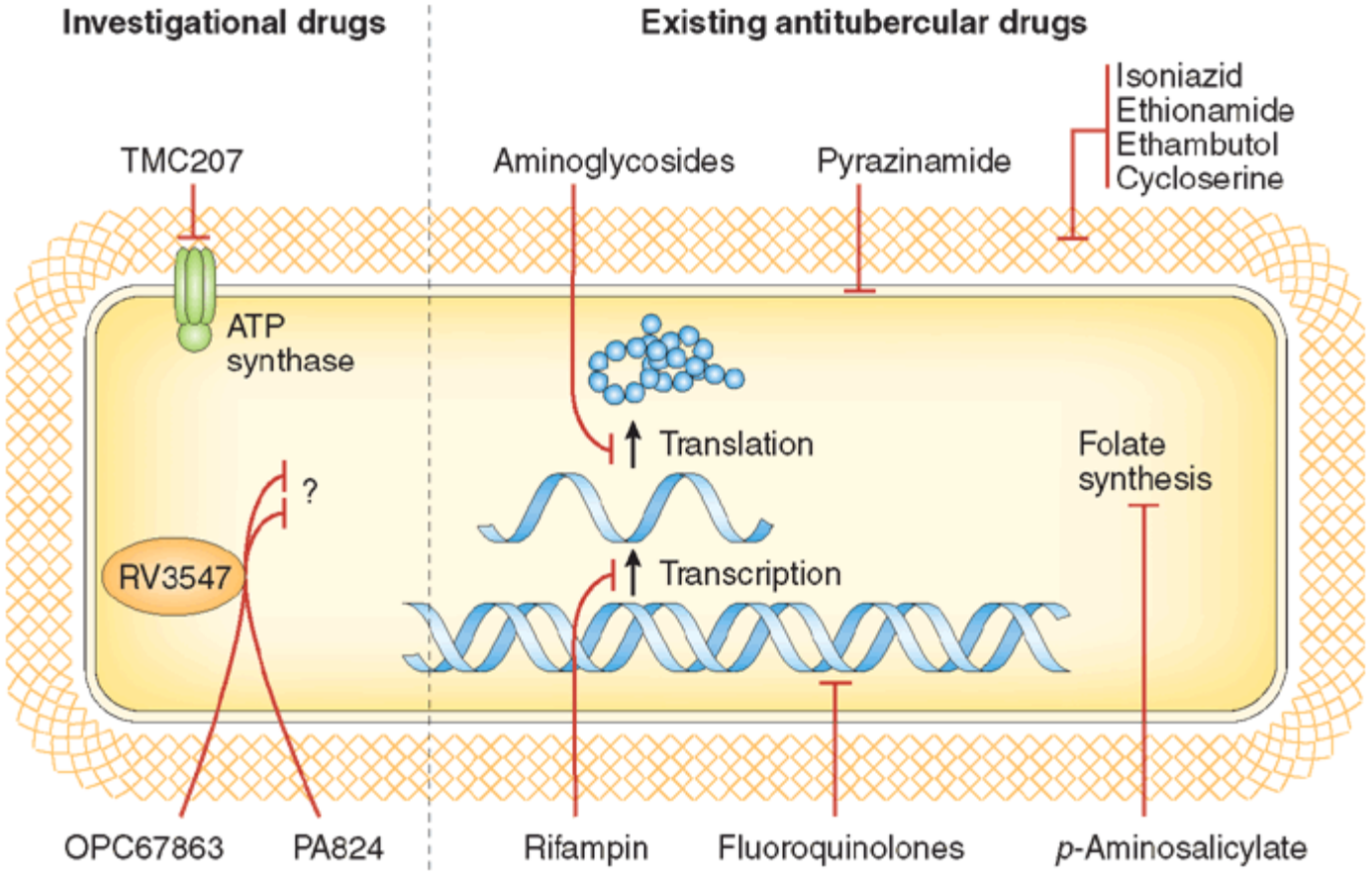
- Structure
  - f.e.Streptomycin (*Mycobacterium tuberculosis*, *M. bovis* and G-negative bacteria), kanamycin, neomycin, tobramycin, amikacin, gentamicin, netilmicin



Aminoglycosides

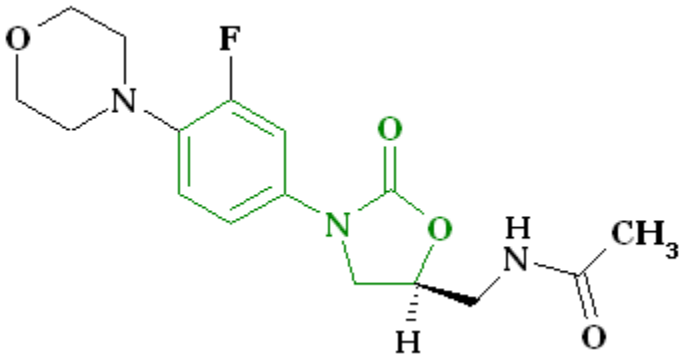
- Function
  - bind to the bacterial 30S ribosomal
  - interfere with the proofreading process, causing increased rate of error in synthesis with premature termination
  - inhibition of ribosomal translocation where the peptidyl-tRNA moves from the A-site to the P-site
  - disruption the integrity of bacterial cell membrane

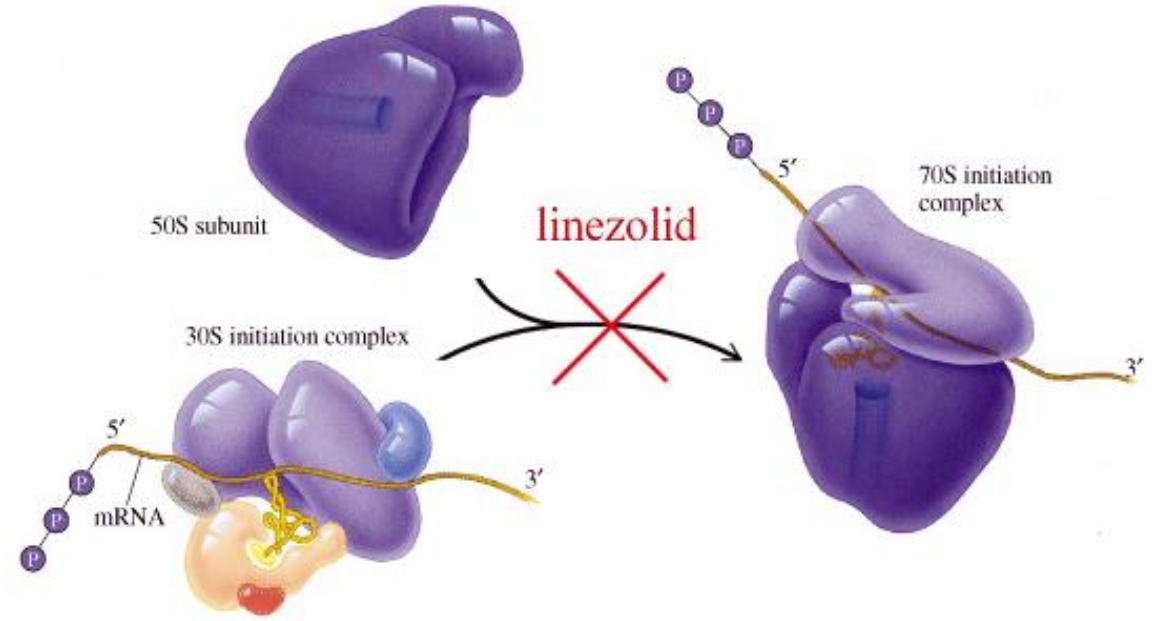
Drugs againts tuberculosis



http://www.nature.com/nm/journal/v13/n3/images/nm0307-279-F1.gif

New hope for Multiresistant tuberculosis treatment





Clifton E. Barry III, Ph.D.
Chief, Tuberculosis
Research Section, NIH

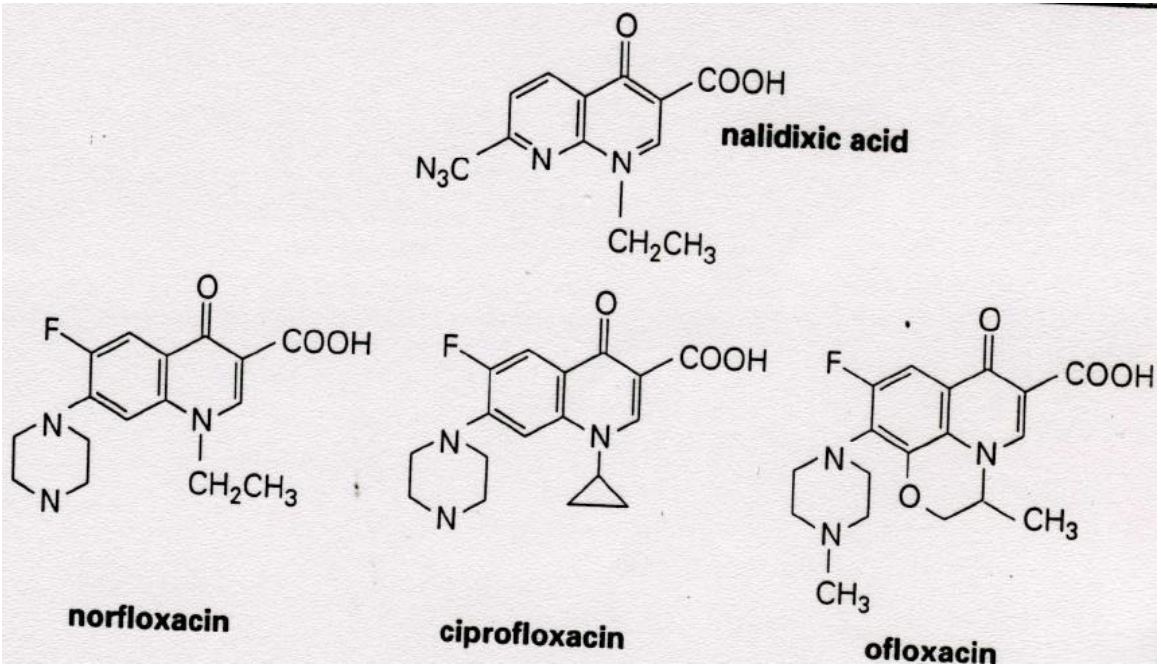
N Engl J Med. 2012 Oct 18;367(16):1508-18. doi: 10.1056/NEJMoa1201964.

Linezolid for treatment of chronic extensively drug-resistant tuberculosis.

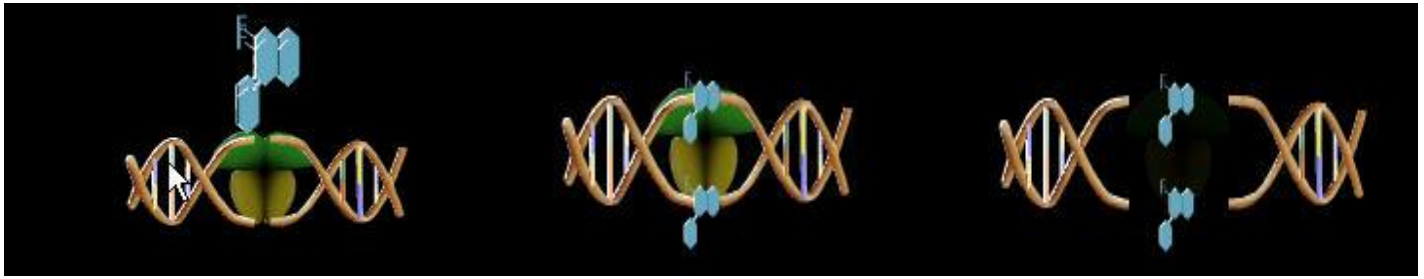
Lee M,…. Barry CE 3rd. NIH and International Tuberculosis Research Center, Changwon, South Korea.

Antimicrobial chemoterapeutics

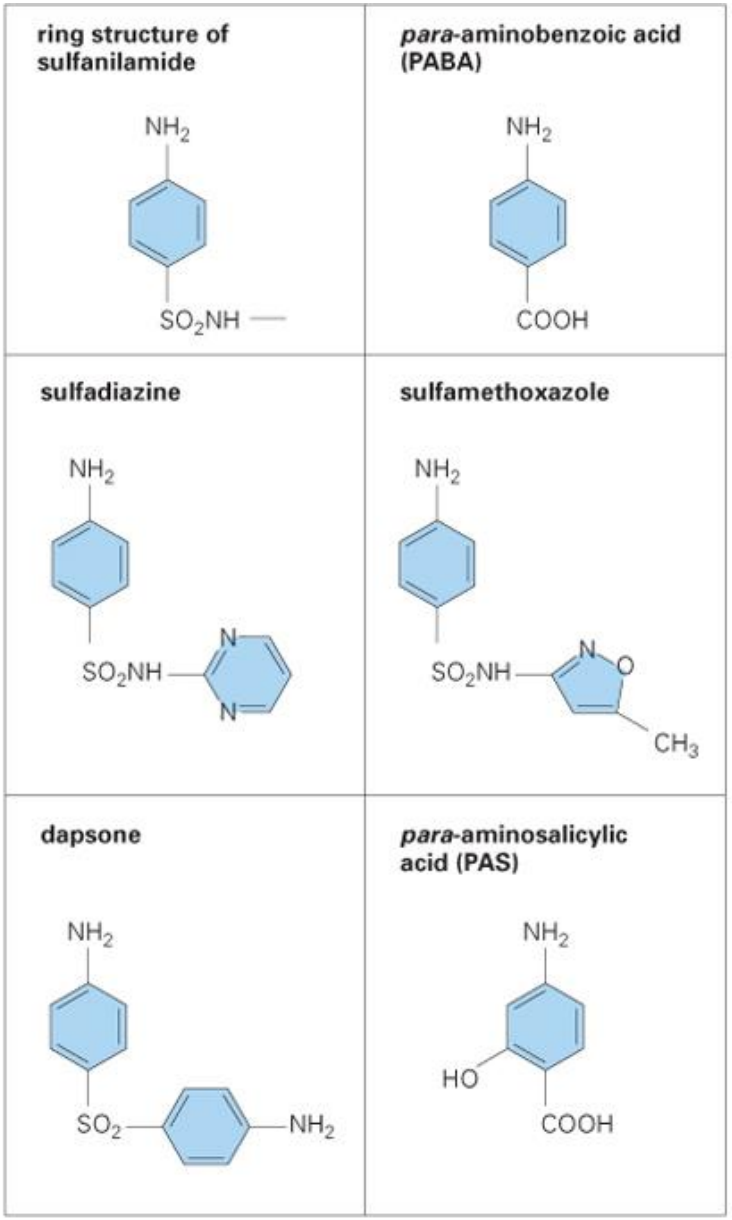
- Quinolones

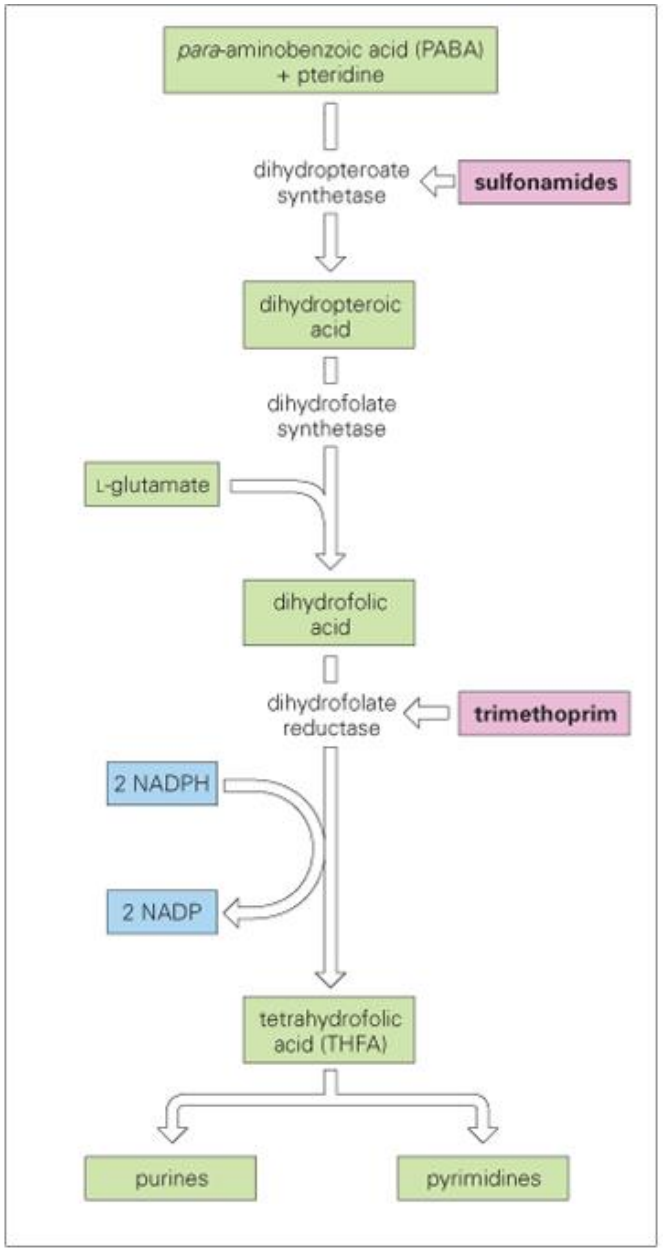


- Quinolones inhibit DNA synthesis – fluoroquinolons bind to complex gyrase/DNA and DNA is broken



Inhbitors of nucleic acid synthesis and replication





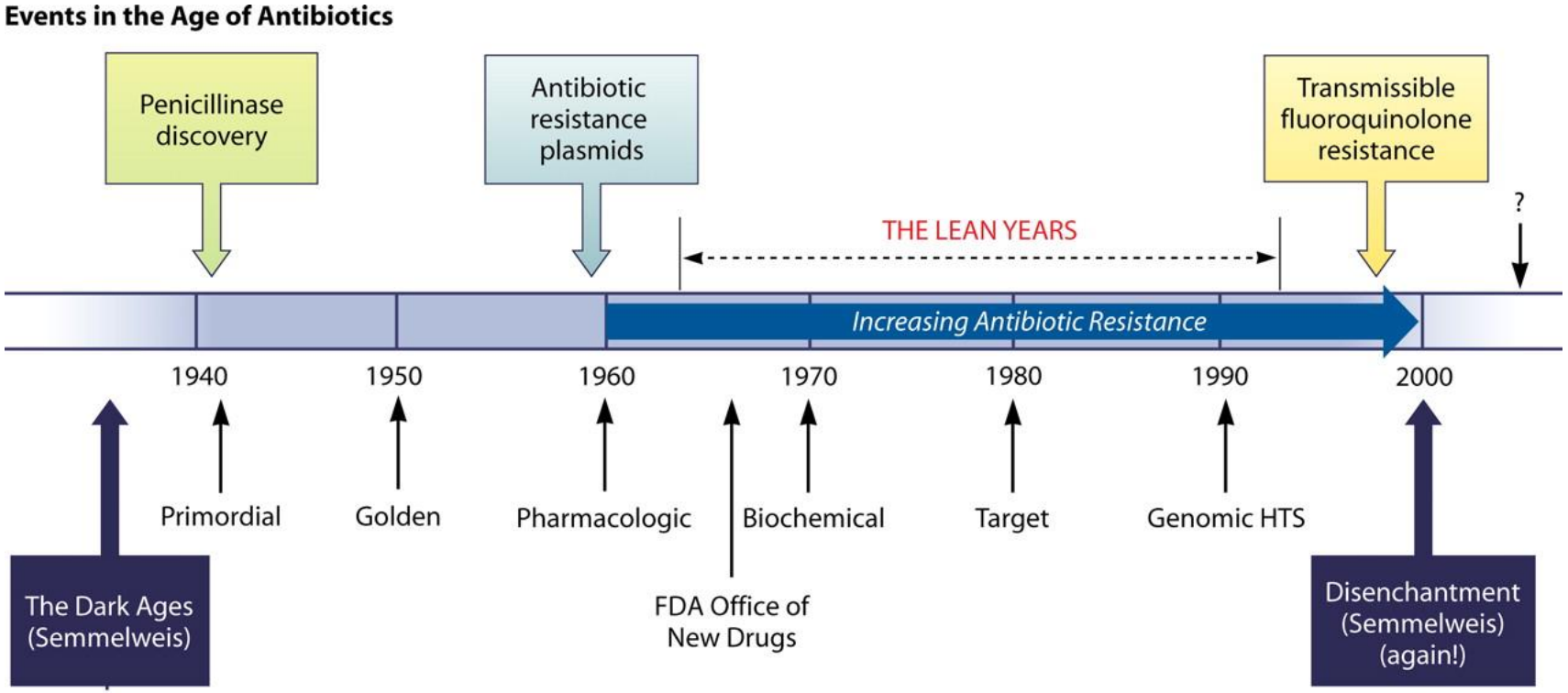
Virulence inhibitors:

A promissing trend: Limited pressure for developing resistance
NEW drugs for septisemic ddisease in the pipeline

DO NOT perturb development of commensal bacteria

- comparative genomics, Tn mutagenesis
- Identification of virulence factors – validation of targets
- structure solving
- computer assisted rational drug design
- chemical synthesis
- preclinical development and toxicology
- clinical testing

History of antibiotic discovery and concomitant Development of antibiotic resistance

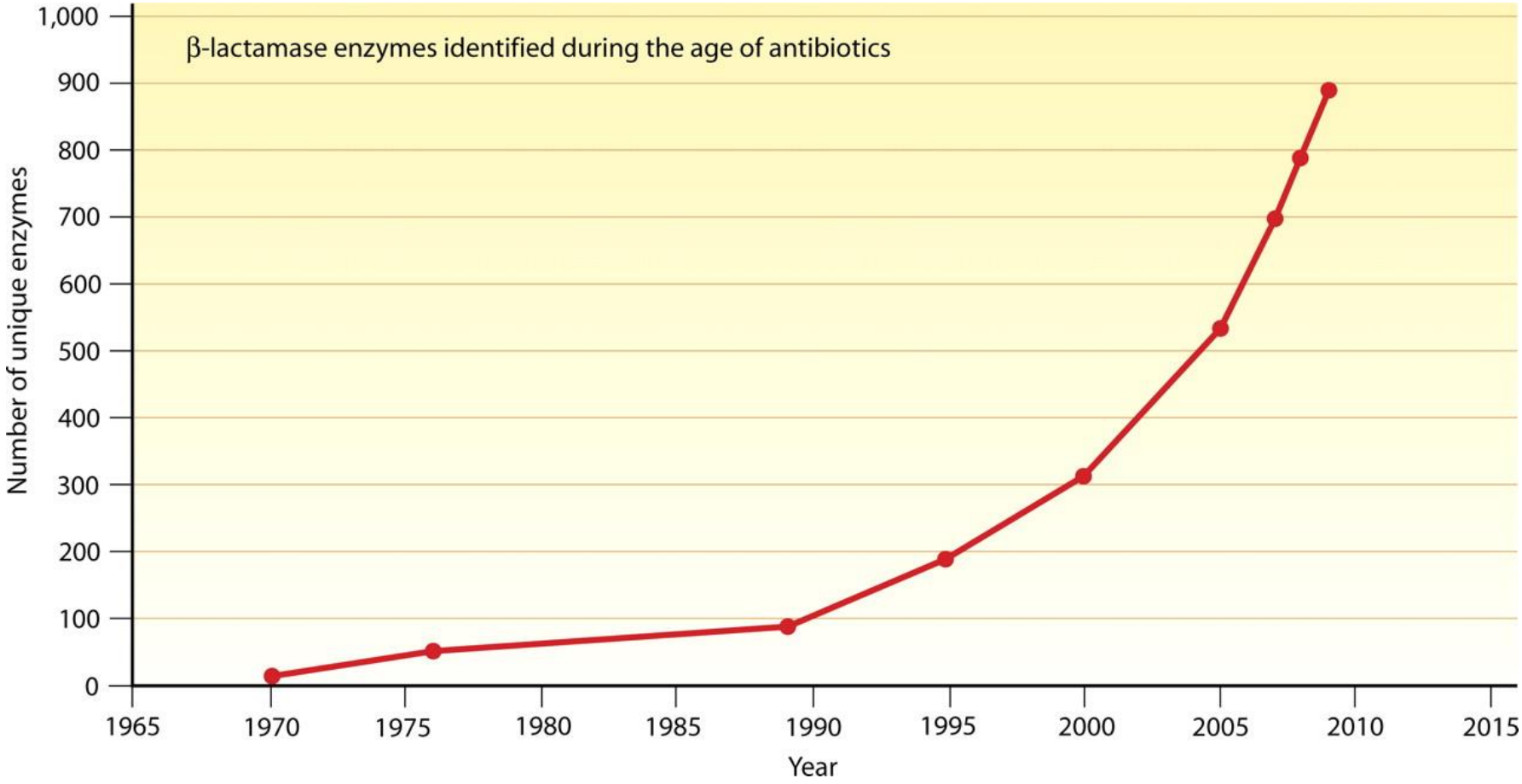


The dark ages, the preantibiotic era; primordial, the advent of chemotherapy, via the sulfonamides; golden, the halcyon years when most of the antibiotics used today were discovered; the lean years, the low point of new antibiotic discovery and development;, genome sequencing methodology was used to predict essential targets for incorporation into high-throughput screening assays; disenchantment, with the failure of the enormous investment in genome-based methods, many companies discontinued their discovery programs. Creation of the FDA Office of New Drugs after the thalidomide disaster led to stricter requirements for drug safety. This slowed the registration of novel compounds. **Before antibiotics were discovered, Semmelweis advocated hand washing as a way of avoiding infection; this practice is now strongly recommended as a method to prevent transmission.**

Davies, J. et al. 2010. Microbiol. Mol. Biol. Rev. 74(3):417-433

Microbiology and Molecular Biology Reviews

Numbers of unique {beta}-lactamase enzymes identified since the introduction of the first β-lactam antibiotics



Davies, J. et al. 2010. Microbiol. Mol. Biol. Rev. 74(3):417-433

Antibiotic use and misuse

- During the 1940s and 1950s antibiotics were extremely effective
- They were (and still are) widely prescribed, often for medical conditions that did not require them
- Antibiotics started to be used in agriculture: dosing cattle with antibiotics increases yield, and battery farming relies on antibiotics to control infection
- By the 1970s the World was awash with antibiotics
- Millions of metric tons of antibiotic produced and released into environment…
- No new principally new antibiotic introduced in the past 30 years
- multidrug-resistent superbugs, vancomysin resisten streptococci and enterococci etc…
- Heading towards the postantibiotic era…?

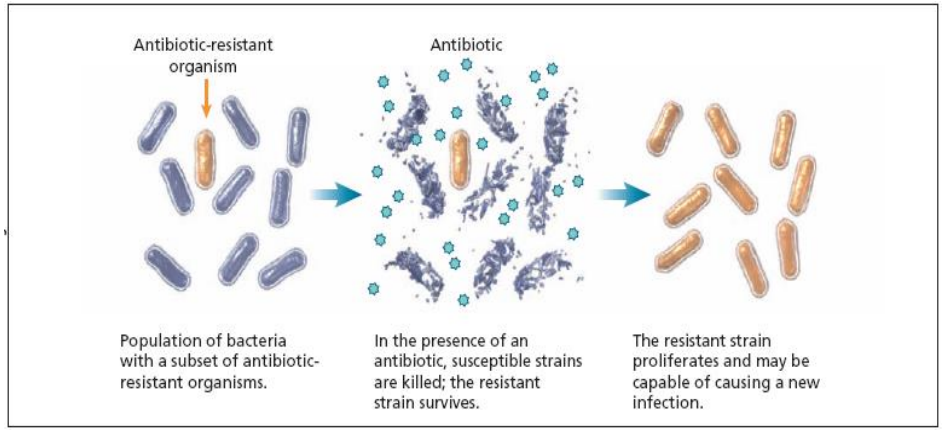
Mechanisms of resistance

- Intrinsic (or inherent) resistance

  Resistance to an agent is normal for a genus, species or bacterial group (lack the target, or drug can't get to target)
  - Glycopeptide resistance in Gram-negatives
  - Aztreonam resistance in Gram-positives

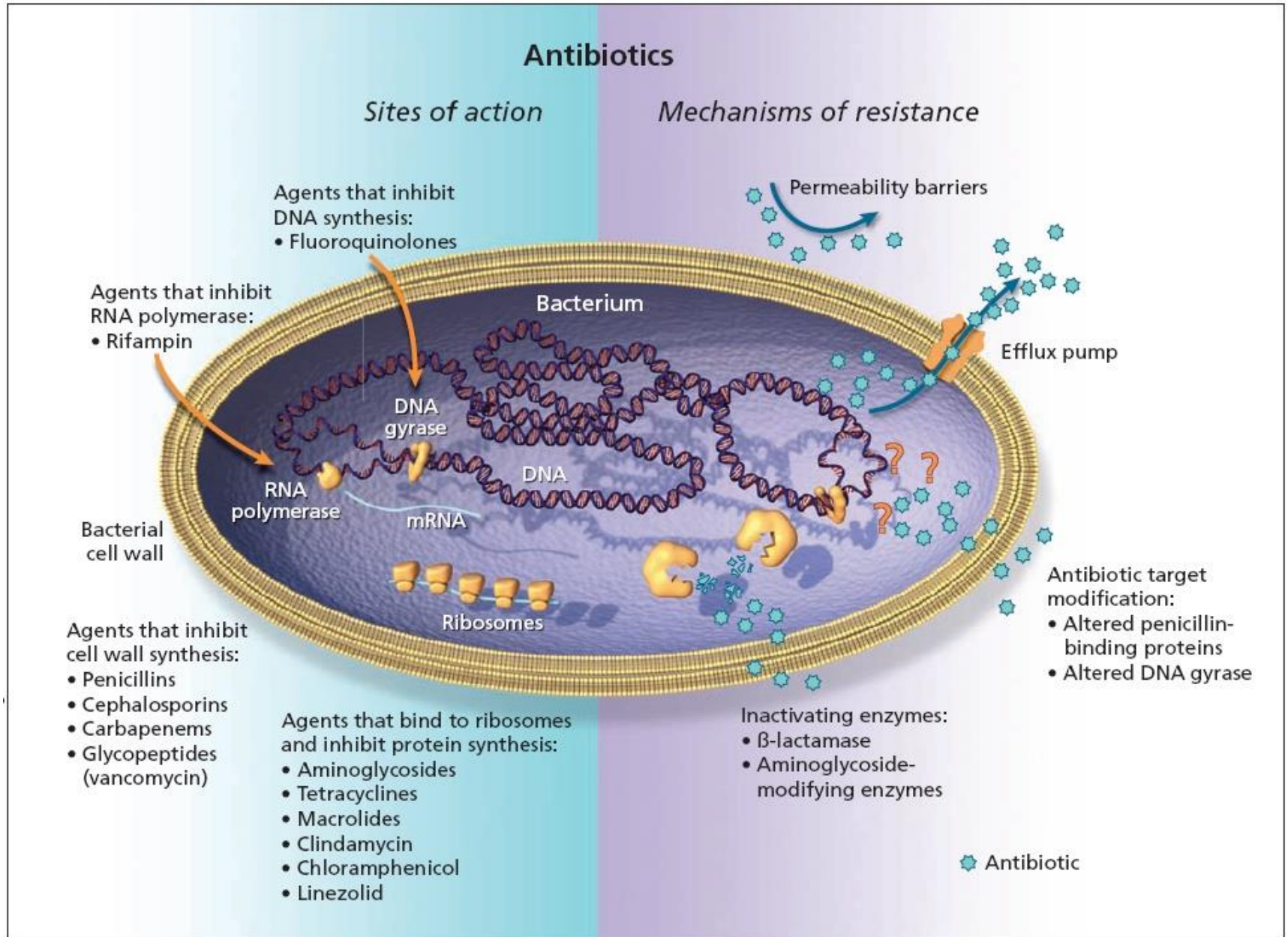
- Acquired resistance

  Most isolates of a genus, species or bacterial group are susceptible, but resistance may arise *via*:
  - Mutation (usually of a chromosomal gene) *e.g.,* Rif R; FQ R
  - Acquisition of new DNA conferring resistance (horizontal spread)

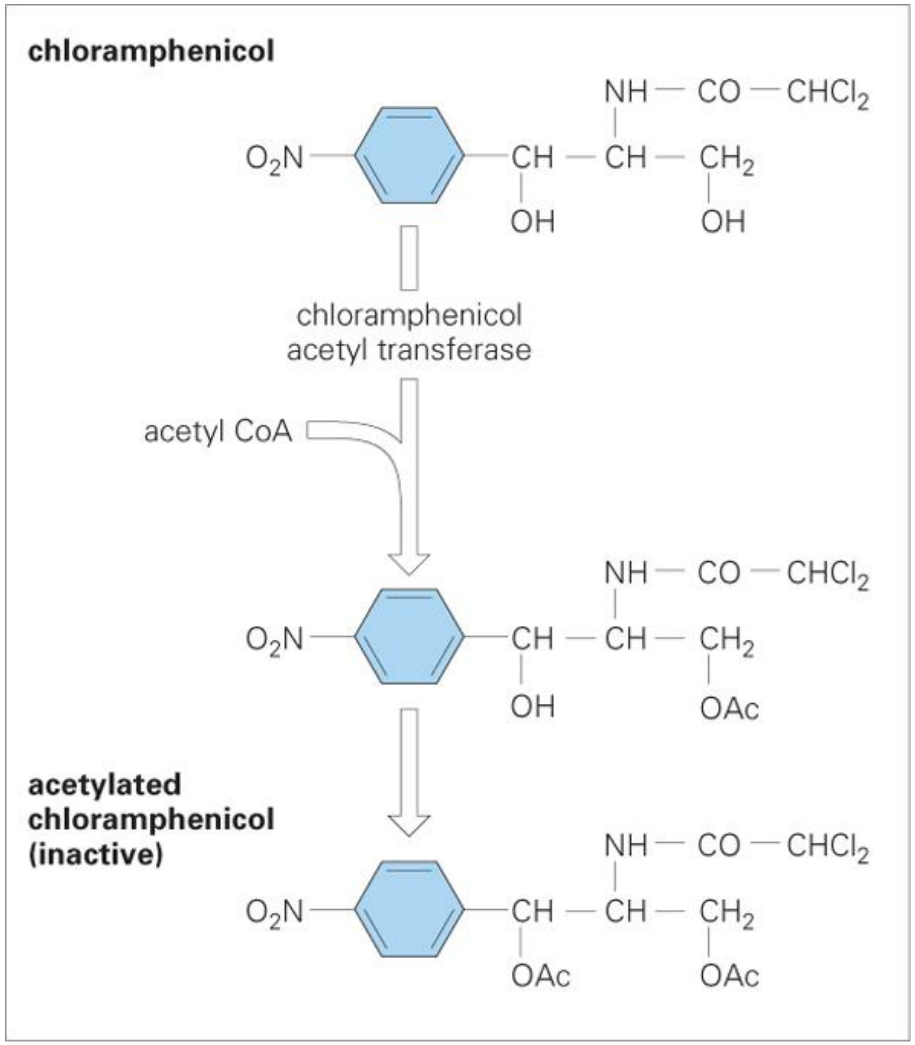


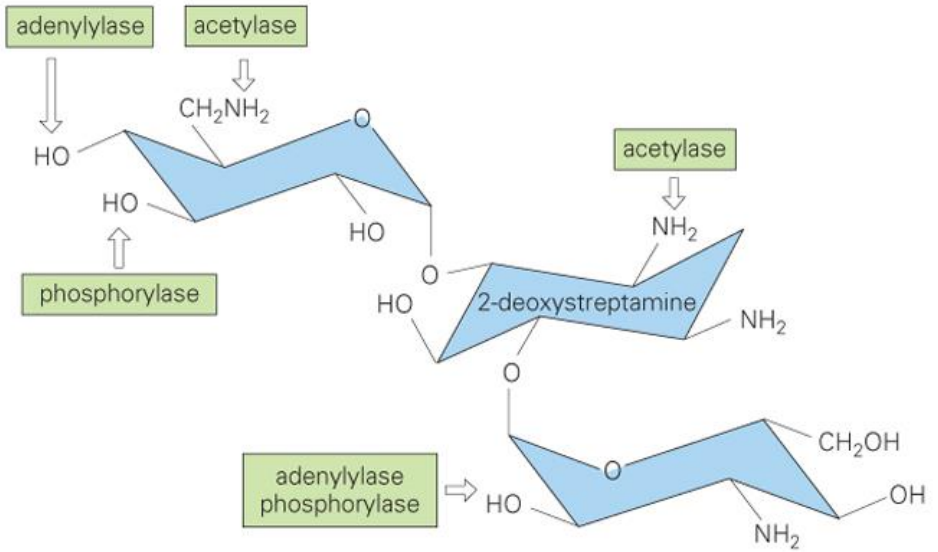
Mulvey, M: *CMAJ* 2009

Mechanisms of antibiotic action and resistance



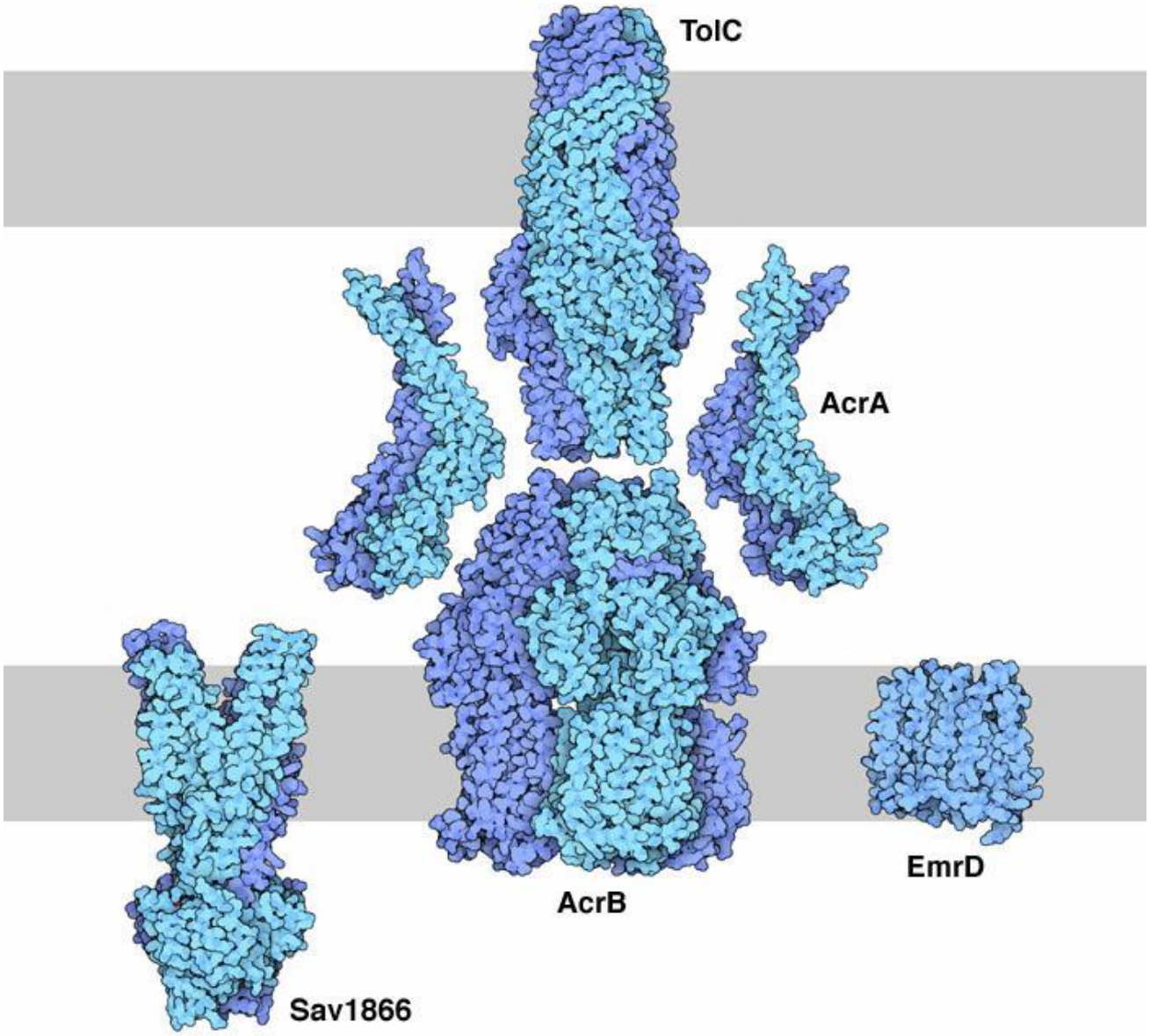
Resistance to chloramphenicol and aminoglycosides resistance due to enzymatic modification



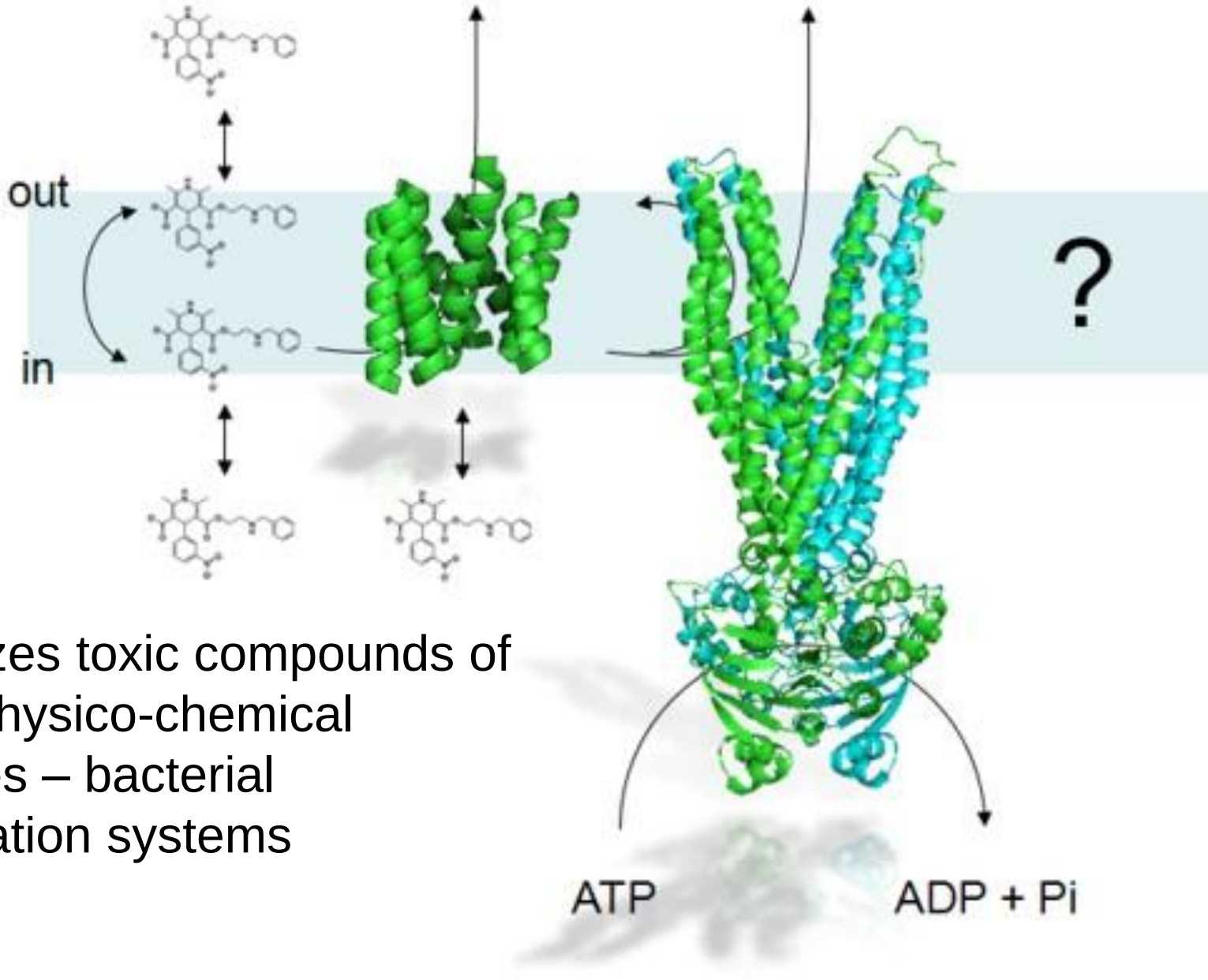


aminoglycoside modifying enzyme	reactive group on aminoglycoside	co-factor	modified aminoglycoside product
acetylase	$-NH_2$	acetyl CoA	–NHAc
adenylylase (nucleotidyl transferase)	–OH	ATP	–O–AMP
phosphorylase	–OH	ATP	$-O-PO_2-OH$

Multidrug resistance in Gram-negative



Multidrug resistance in general - the vacuum cleaner



Recognizes toxic compounds of Similar physico-chemical Properties – bacterial detoxification systems

Acquiring resistance

- **Horizontal transfer of genes on:**
  - **Plasmids**
  - **Transposon -** “jumping genes “
  - **integrons**

- **Induction of latent gene expression** inducible β-lactamases

- **Transformation by DNA from lyzed bacteria and recombination etc..**

The Shared Antibiotic Resistome of Soil Bacteria and Human Pathogens

Forsberg *et al.* Science 31 August 2012: Vol. 337, pp. 1107-1111,
DOI: 10.1126/science.1220761

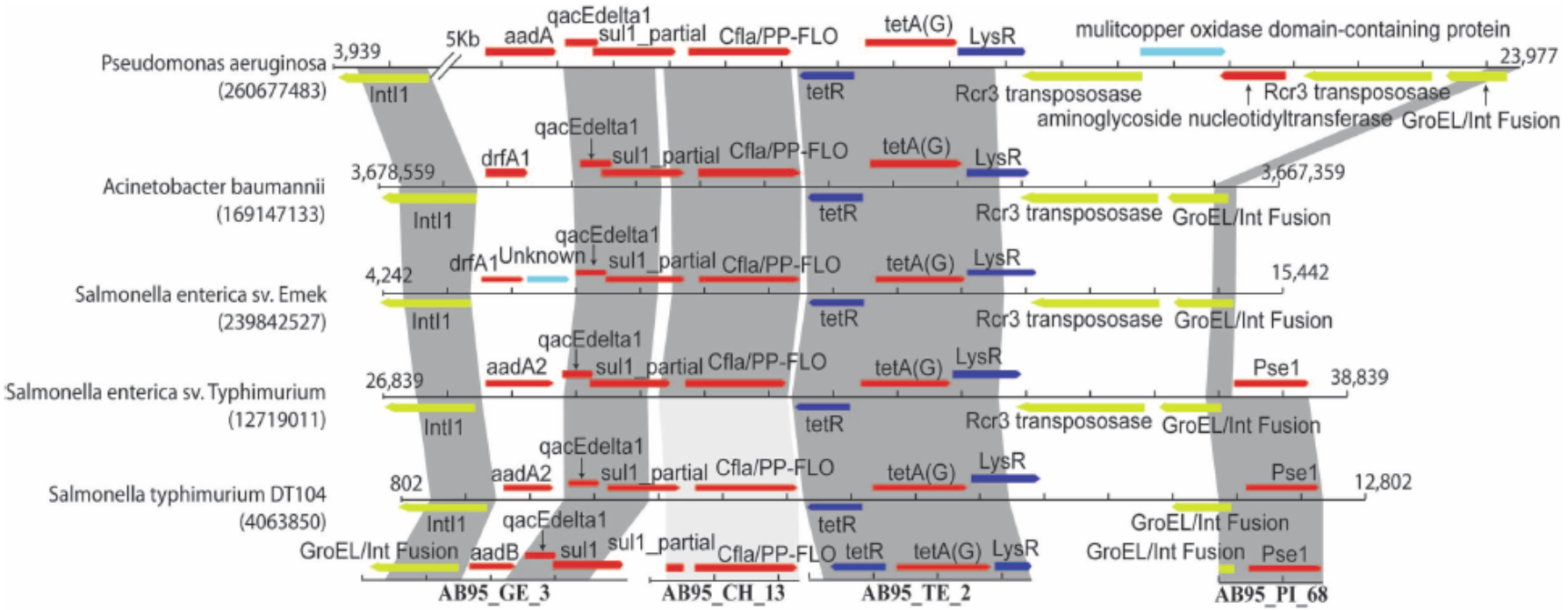
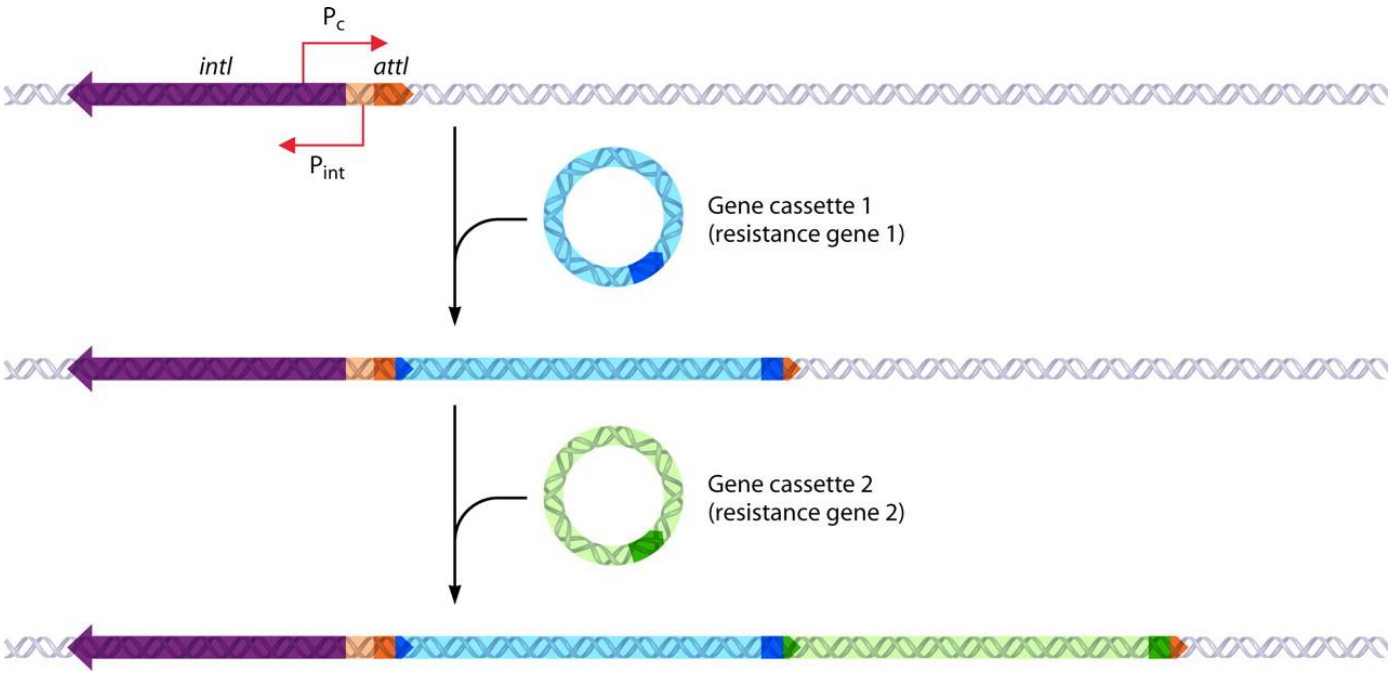


Fig. 3. Comparison of four AB95-derived resistance fragments to five human pathogenic isolates. The four fragments are depicted along the bottom, and shading indicates high nucleotide identity between the fragments and pathogens (NCBI GenInfo numbers identify each pathogenic isolate). Dark gray shading indicates >99% identity; light gray shading indicates ~88% identity. Base-pair coordinates flank pathogenic sequences, and the distance between each tick mark is 800 bp. Red ORFs represent resistance genes, yellow represents mobility elements, dark blue represents resistance-associated regulatory elements, and light blue represents other functions.

Integron structure and gene capture mechanism



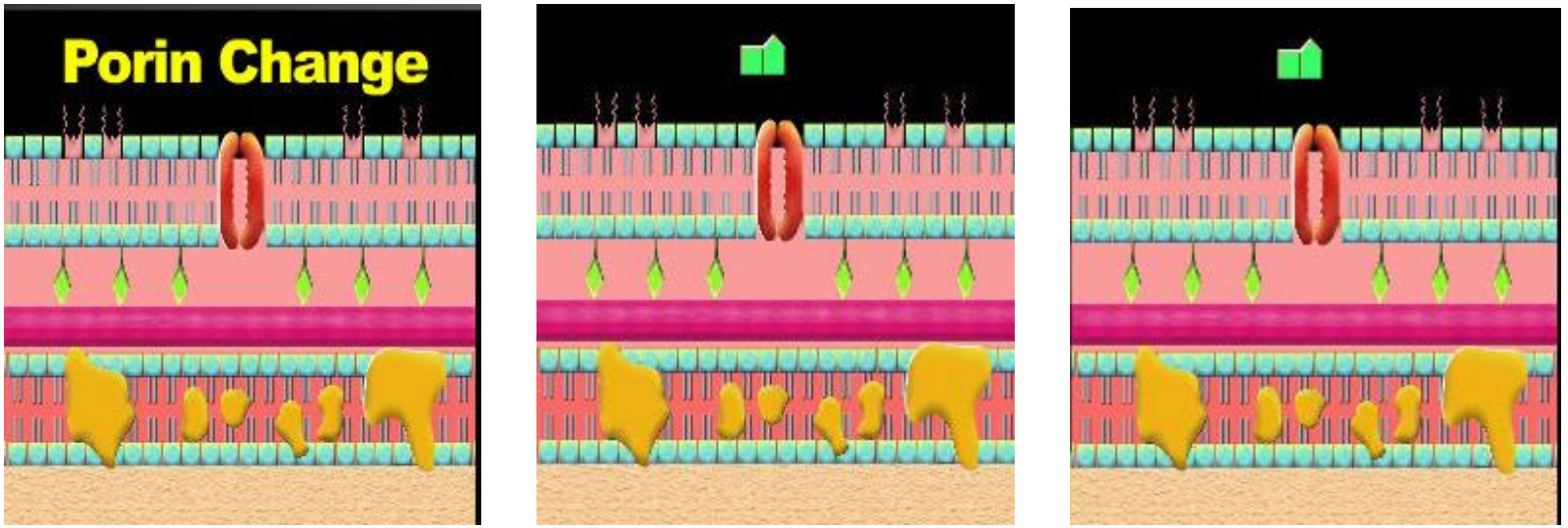
Integrons are not themselves mobile genetic elements but can become so in association with a variety of transfer and insertion functions. They are critical intermediates in the pickup and expression of resistance genes

Integron structure and gene capture mechanism. This figure indicates the basic elements of integrons, as found in bacterial genomes. The structure consists of an integrase (Int) with the P_{int} and P_C promoters in the 3' end of the gene, with its associated cassette attachment or insertion site (attI). The integrase catalyzes the sequential recombination of circularized gene cassettes into the distal attachment site to create an operon-like arrangement (ant1^r, ant2^r, and so on) of r genes transcribed from the strong P_C promoter (132). Three classes of integrons have been identified that differ in their integrase genes.

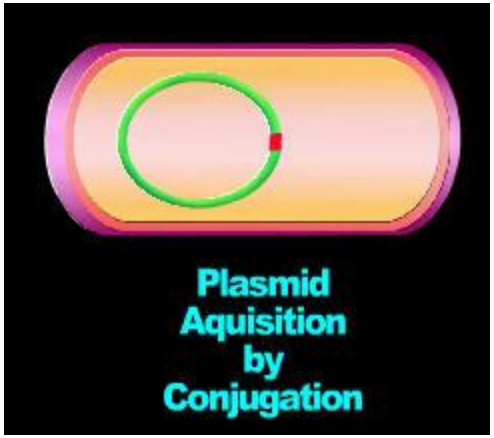
Davies, J. et al. 2010. Microbiol. Mol. Biol. Rev. 74(3):417-433

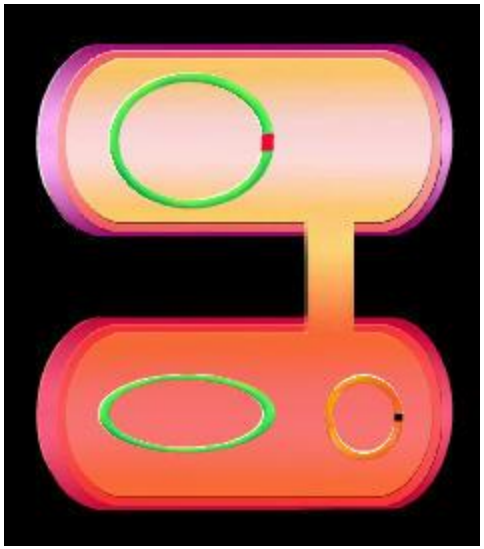
Permeability barrier

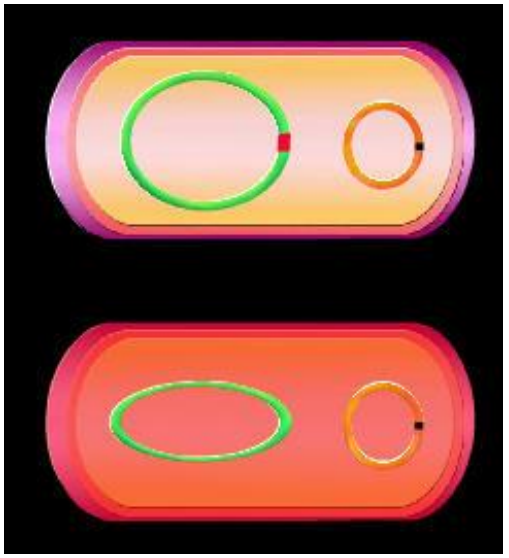
- Gram-negative bacteria may acquire resistence due to porin permability change



Acquired resistamce due to conjugative plasmids

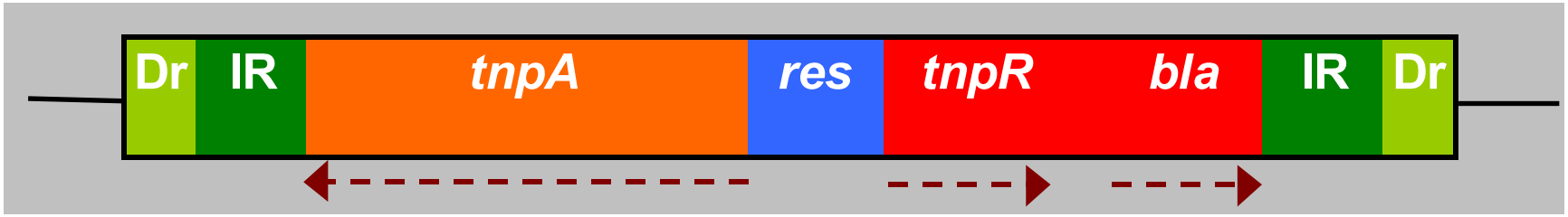






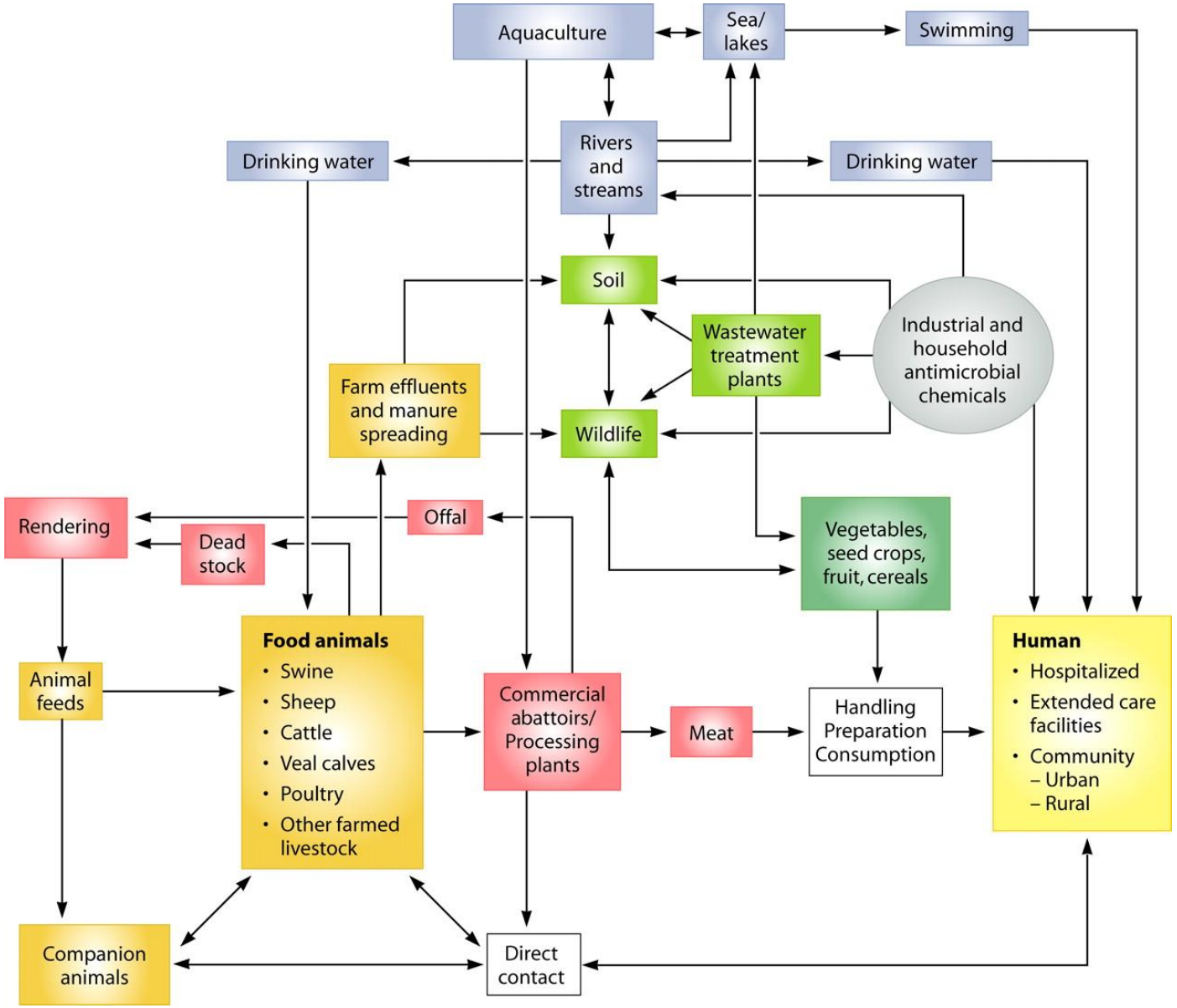
Transposons

Transposon T3



Dr	5	*direct repeat*	
IR	38	*inverted repeats*	
			res resolution site
			tnpA transposase
			tnpR resolvase
			bla β-laktamase

Dissemination of antibiotics and antibiotic resistance within agriculture, community, hospital, wastewater treatment, and associated environments



Davies, J. et al. 2010. Microbiol. Mol. Biol. Rev. 74(3):417-433

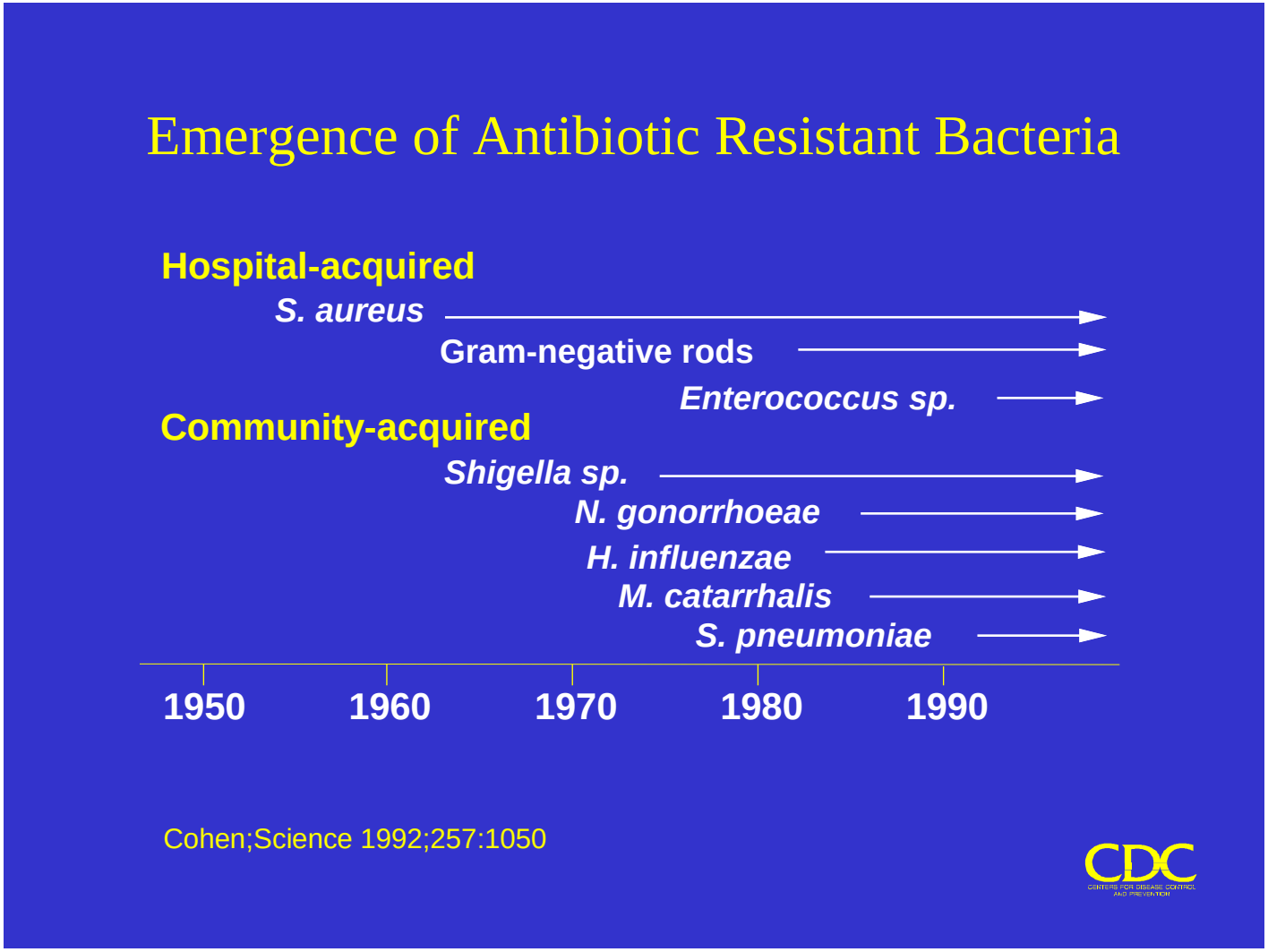
Antibiotic resistance spread in the food chain

Lactococci function as starter cultures for lactic fermentation in cheese … **streptomycin-, tetracycline- and chloramphenicol-resistant *Lactococcus lactis*** *lactis* strain K214 was isolated in 1993 from a raw milk soft cheese ($2x10^8$ c.f.u./g)

….analysed in 1991 and 1995, this cheese brand had also contained different enterococci resistant to tetracycline, chloramphenicol, gentamycin, penicillin, erythromycin, lincomycin and vancomycin (mechanism unknown but neither vanA nor vanB) at 10^6-10^7 c.f.u. g^{-1}

Nature **389**, 801-802 (23 October 1997) | doi:10.1038/39767

Development of antibiotic resistance

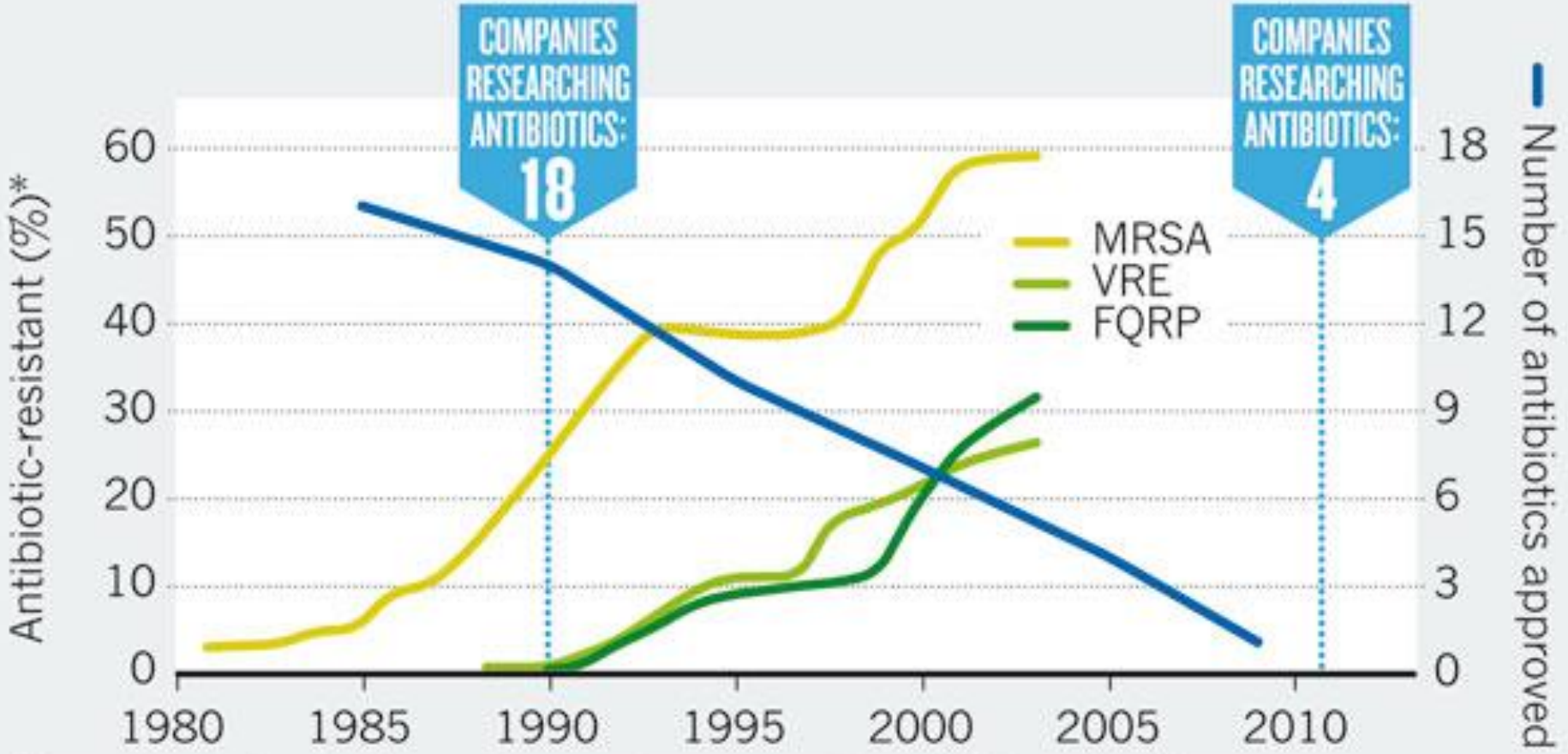


Modes of action and resistance mechanisms of commonly used antibiotics

Antibiotic class	Example(s)	Target	Mode(s) of resistance
β-Lactams	Penicillins (ampicillin), cephalosporins (cephamycin), penems (meropenem), monobactams (aztreonam)	Peptidoglycan biosynthesis	Hydrolysis, efflux, altered target
Aminoglycosides	Gentamicin, streptomycin, spectinomycin	Translation	Phosphorylation, acetylation, nucleotidylation, efflux, altered target
Glycopeptides	Vancomycin, teicoplanin	Peptidoglycan biosynthesis	Reprogramming peptidoglycan biosynthesis
Tetracyclines	Minocycline, tigecycline	Translation	Monooxygenation, efflux, altered target
Macrolides	Erythromycin, azithromicin	Translation	Hydrolysis, glycosylation, phosphorylation, efflux, altered target
Lincosamides	Clindamycin	Translation	Nucleotidylation, efflux, altered target
Streptogramins	Synercid	Translation	C-O lyase (type B streptogramins), acetylation (type A streptogramins), efflux, altered target
Oxazolidinones	Linezolid	Translation	Efflux, altered target
Phenicols	Chloramphenicol	Translation	Acetylation, efflux, altered target
Quinolones	Ciprofloxacin	DNA replication	Acetylation, efflux, altered target
Pyrimidines	Trimethoprim	C_1 metabolism	Efflux, altered target
Sulfonamides	Sulfamethoxazole	C_1 metabolism	Efflux, altered target
Rifamycins	Rifampin	Transcription	ADP-ribosylation, efflux, altered target
Lipopeptides	Daptomycin	Cell membrane	Altered target
Cationic peptides	Colistin	Cell membrane	Altered target, efflux

A PERFECT STORM

As bacterial infections grow more resistant to antibiotics, companies are pulling out of antibiotics research and fewer new antibiotics are being approved.



*Proportion of clinical isolates that are resistant to antibiotic. MRSA, methicillin-resistant *Staphylococcus aureus*. VRE, vancomycin-resistant *Enterococcus*. FQRP, fluoroquinolone-resistant *Pseudomonas aeruginosa*.

Antibiotics types

- **β-lactames : penicillins, cephalosporins, carbapenems, monobactams** reaktivní, tvoří konjugáty se sérovými proteiny, alergie, až smrtelné inhibice transpeptidace peptidoglykanu (PBP`s). turgor >>>eploze buňky funguje pouze na ROSTOUCÍ buňky, >>> použití pro selekci auxotrofů , základ bakt. genetiky, stovky semisyntetických derivátů
- **tetracyclines** - vazba na 30S podjednotku ribosomu, inhibice proteosynthesy, několik mechanismů resistence, používáno jako přídavek do krmných směsí…..!, produced by bacteria of the genus *Streptomyces*
- **glycopeptides** - vazba na D-Ala-D-Ala UDP-muramyl pentapetidu, inhibice transglykosylace a transpeptidace při biosynthese peptidoglykanu
  - **vankomycin, teichoplanin, hlavně na G+ bakterie** (permeabilita OM), někdy poslední spása (multiresistentní *S. aureus)*
- **aminoglycosides -** kanamycin, gentamycin, **vazba na 30S podjednotku ribosomu** baktericidní, akumulace 30S podjednotky toxická**, při předávkování toxicita, poruchy sluchu a ledvin**
- **antimicrobial chemoterapeutics**
  - **chinolony - kyselina nalidixová**, **fluorochinolony** inhibují DNA gyrasu, baktericidní, **proniká také dovnitř makrofágů a PMN** >>> také na intracelulární bakterie!!!, nepůsobí na anaeroby a streptokoky, resistence bodovou mutací snadná
  - **pyrimidiny (trimetoprim) a sulfonamidy- inhibice metabolismu folátu** (savci jej neumí dělat)
- **ansamyciny** - rifampicin, rifabutin **-** inhibuje RNA polymerasu léčení TBC
- **macrolides a lincosamids -** vazba na 50S podjednotku ribosomu, inhibice elongace na peptidyltransferase