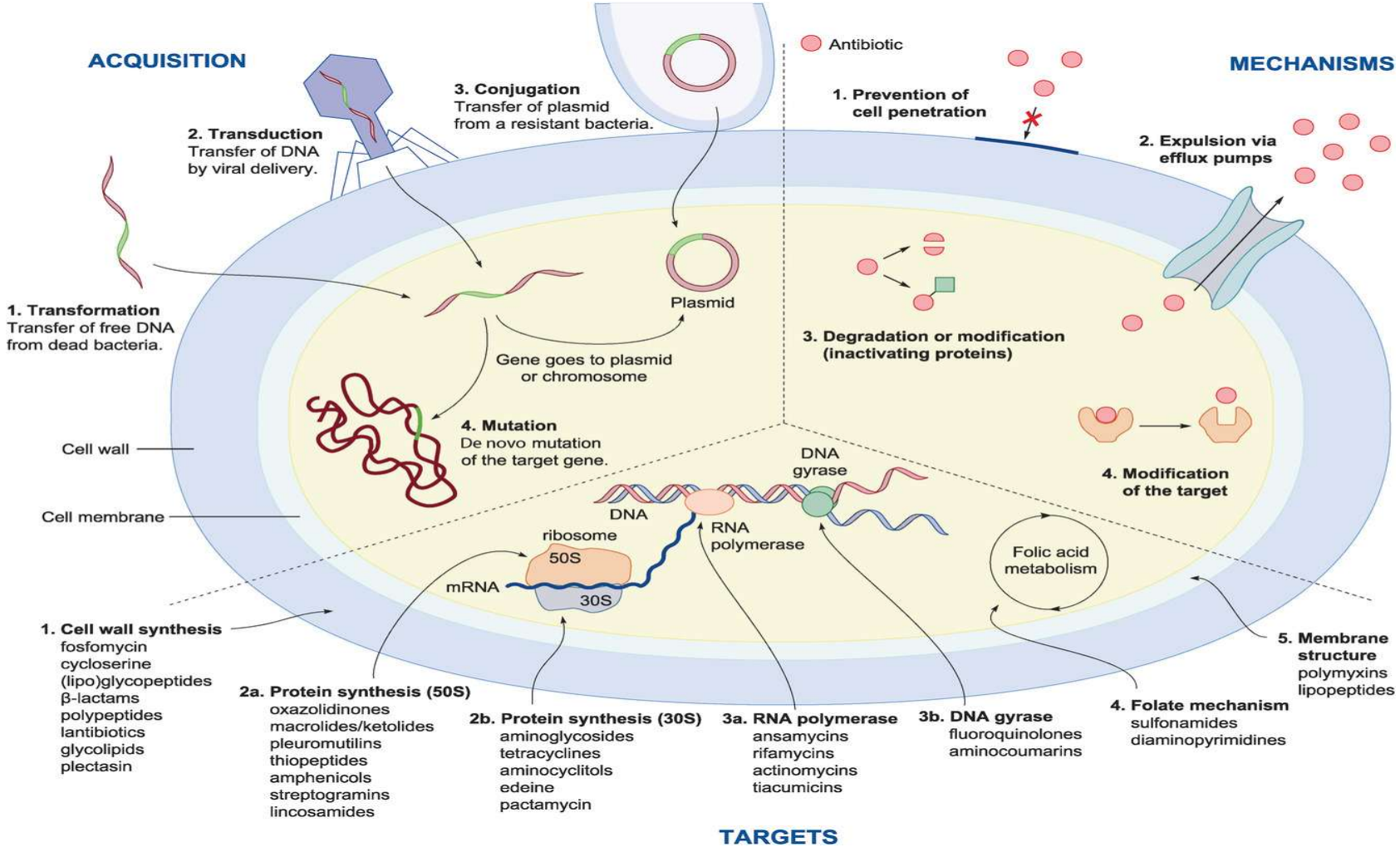
REVISION OF ANTIMICROBIALS
AWaRE CLASSIFICATION

Diagram of Antibiotic Target and Resistance Mechanisms



Ref: Angew Chem Int Ed, Volume: 55, Issue: 23, Pages: 6600-6626, First published: 22 March 2016, DOI: (10.1002/anie.201506818)

Mechanisms of Antibiotic Resistance in Bacteria

Mechanisms of ATB Resistance

NATURAL/INTRINSIC

- Intrinsic resistance is **when a bacterial species is naturally resistant to a certain antibiotic or family of antibiotics, without the need for mutation or gain of further genes**. This means that these antibiotics can never be used to treat infections caused by that species of bacteria. Intrinsic resistance usually **mediated by the bacterial outer membrane** but also by antibiotic efflux.

MAIN ACQUIRED RESISTANCE MECHANISMS

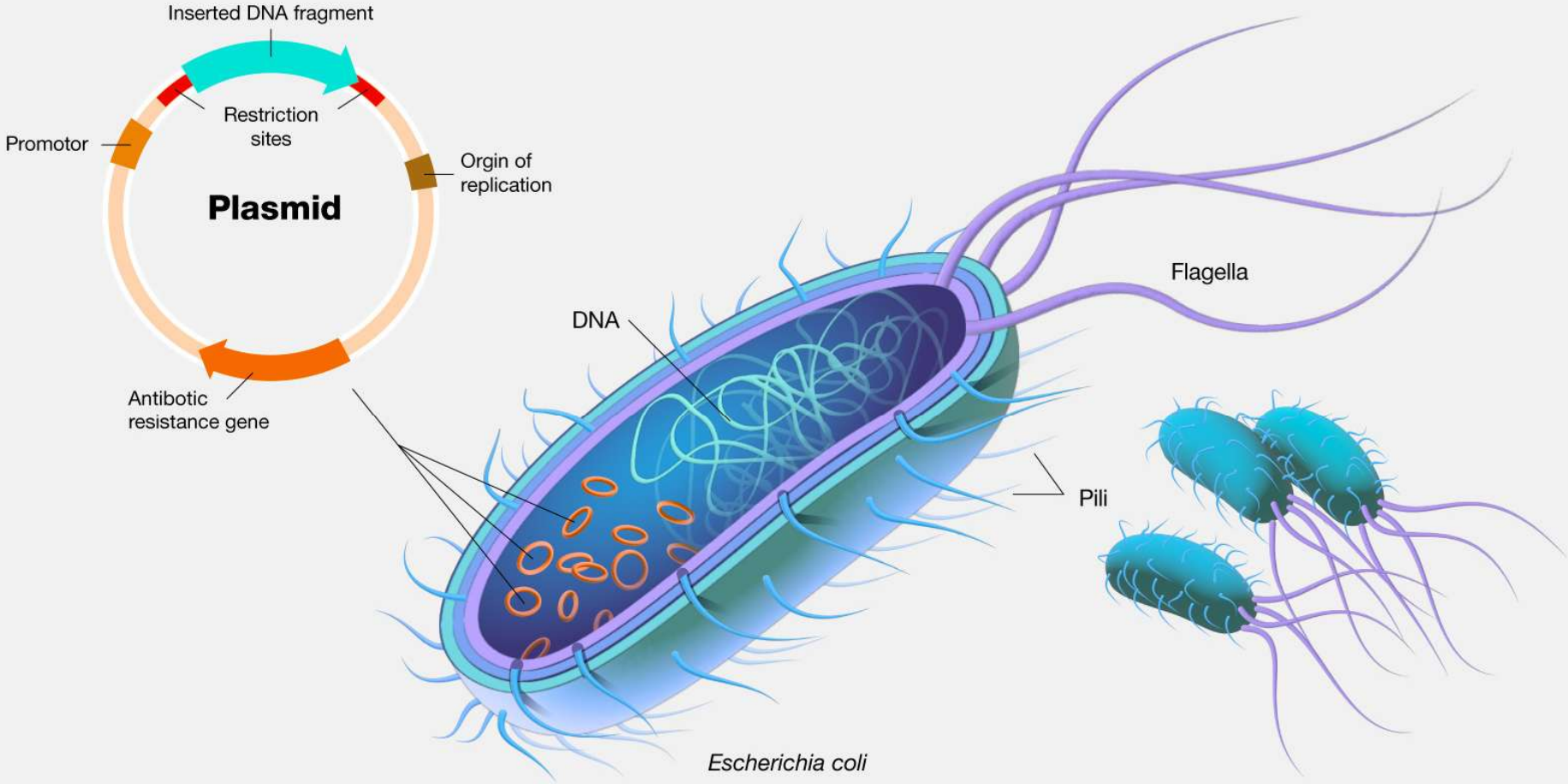
- 1. ENZYMATIC INACTIVATION OF ANTIBIOTICS
- 2. ANTIBIOTIC MODIFICATION
- 3. ALTERED TARGET SITE
- 4. MECHANISMS OF ANTIBIOTIC EFFLUX
- 5. DECREASED PERMEABILTY OF BACTERIAL MEMBRANES

ACQUIRED MECHANISMS OF RESISTANCE

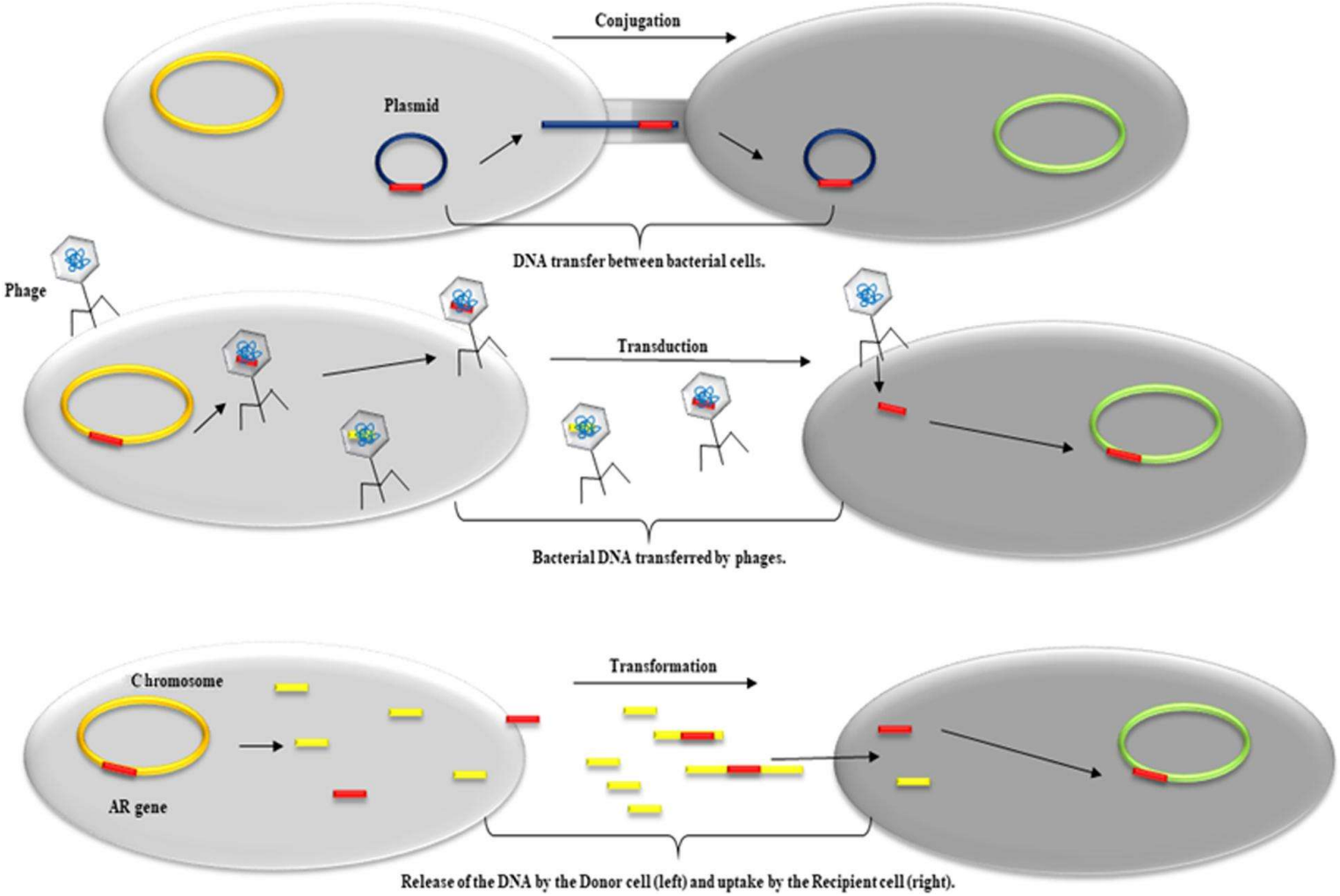
- Microbial genetic variability through variety of mechanisms (**point mutations**, **rearrangement of large DNA segments** – **inversions, duplications, insertions, deletion or transpositions** ususally generated by integrons, transposons, insertion sequences, acquisitions of foreign DNA carried by plasmids, bacteriophages, naked DNA sequences, transposable genetic elements) is **essential for microbial evolution to occur**
- **Antimicrobials (ATB) exert strong selective pressures on microbial populations**
- **ATB resistence genes** were **present in the era before ATB** therapy was available – probably **originated from antibiotic-producing bacteria**
- **These resistant bacterial populations spread** ATB **resistance vertically** to subsequent generations and horizontally **to susceptible strains of related bacteria**, even to different species or genera

Plasmids

- **Extrachromosomal elements** – agents of genetic exchange and resistance-gene dissemination
- **Autonomously replicating – double-stranded DNA circular,** covalently closed **(10-400 kbp)**
- Extremely **common in bacteria, multiple copies** of specific plasmid **or multiple different plasmid** – in a bacterial cell
- ***tra* genes needed for transfer** make conjugative plasmids larger
- **small plasmids** using conjugation **apparatus from coresident conjugative plasmids or conjugative transposons**


Inserted DNA fragment
Restriction sites
Promotor
Orgin of replication
Plasmid
Antibotic resistance gene
DNA
Flagella
Pili
Escherichia coli

Plasmids



Ref: https://www.frontiersin.org/articles/10.3389/fmicb.2020.00761/full

Transposable genetic elements (transposons - Tn, isertion sequences – IS)

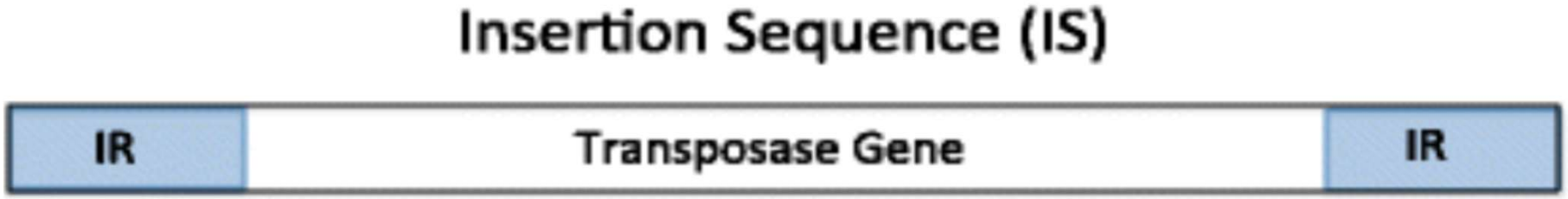
- Transposons translocates a unit **from one area of the bacterial chromosome to another** or **between the chromosome and plasmid or bacteriophage** DNA
- **Transposable genetic elements** posses **specialized system of recombination**

(recA independent recombination system) **transposase – occurs between nonhomologous sequences of DNA, results in wholesale modifications of large sequences of DNA**

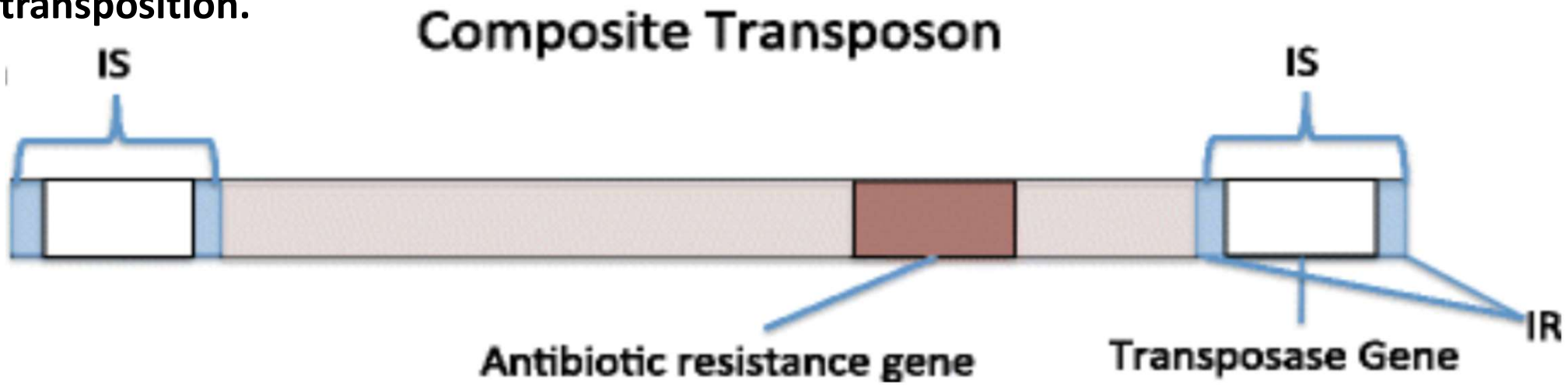
- **Tn, IS** (except conjugative transposons) **– incapable of autonomous self-replication and must exist on a replicon** (chromosome, bacteriophage, plasmid)

- **Transposition is a continuous, ongoing proces** in bacterial population (e.g. spread of tetracyclin-resistance Tn among. *N. gonorrhoeae, Mycoplasma hominis* and *Ureoplasma urealyticum; vanA gene* mediated in enterococci by a composite transposon*)*
- **Transposons – essential** in the **evolution of resistance plasmids**

Structure of transposable genetic elements (transposons - Tn, insertion sequences – IS)



The insertion sequence (IS) is the smallest transposon present in bacterial chromosomes and plasmids. It is composed of two inverted repeats (IR) flanking genes necessary for transposition.

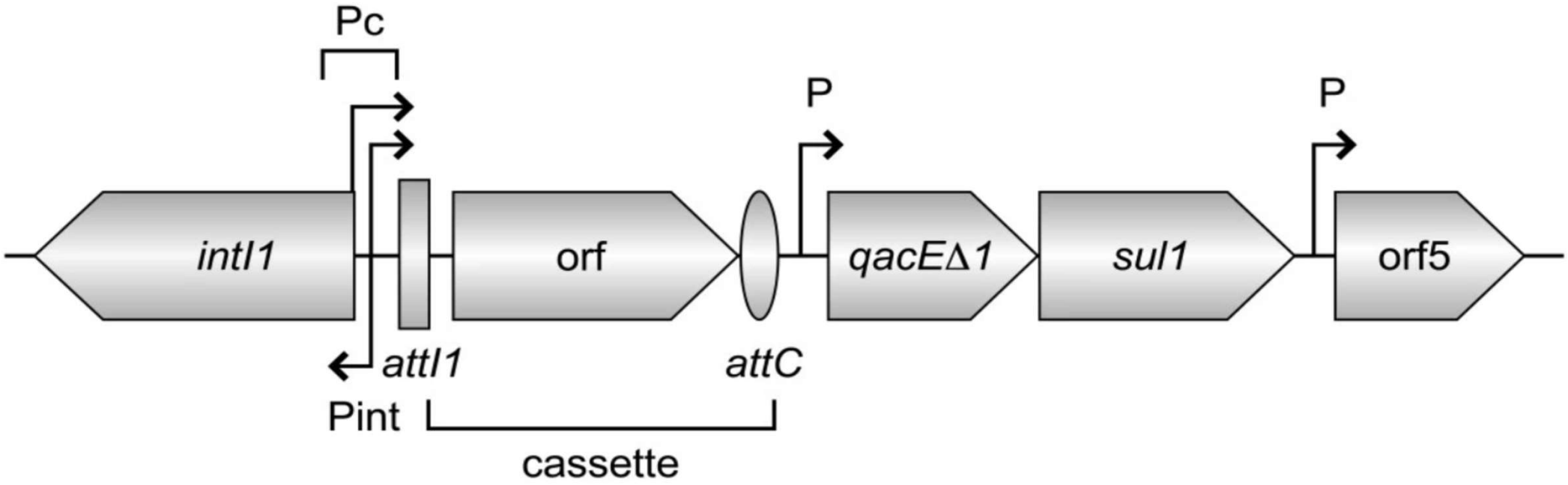


The composite transposon is composed of two IS elements flanking a central protein coding DNA region. This central region often contains genes for antibiotics resistance

DNA Integration Elements

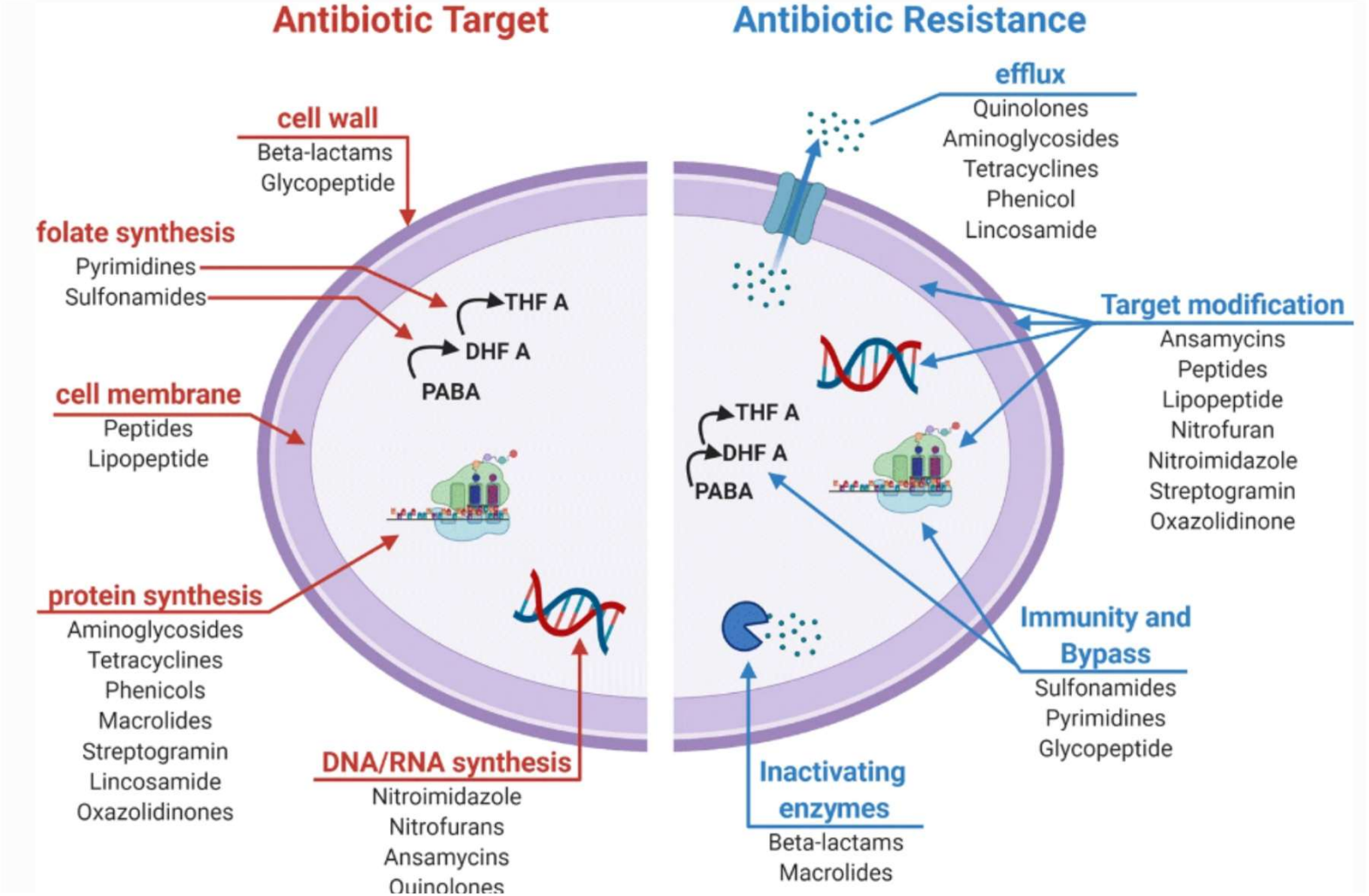
- **Integrons -** ATB resistance genes are often closely linked, may exist in tandem along bacterial chromosome or plasmid
- **Principal role** – provide a convenient **insertion site for ATB resistence genes from foreign DNA sources**
- **Integrons -** often exist **near promoter site**
- **recombinational „hot spots“ for site-specific recombination events between large nonhomologous sequences**
- Own **integrase function (integrated specialized attachment and integration site** – from 57 – 141 bp**)** – mediated ATB resistance genes from **mobile gene cassettes**
- **Frequency of transcription of integrated cassetes of ATB resistance genes depends on proximity to the promoter at the 5´** upstream end of the region

General structure of class 1 integrons



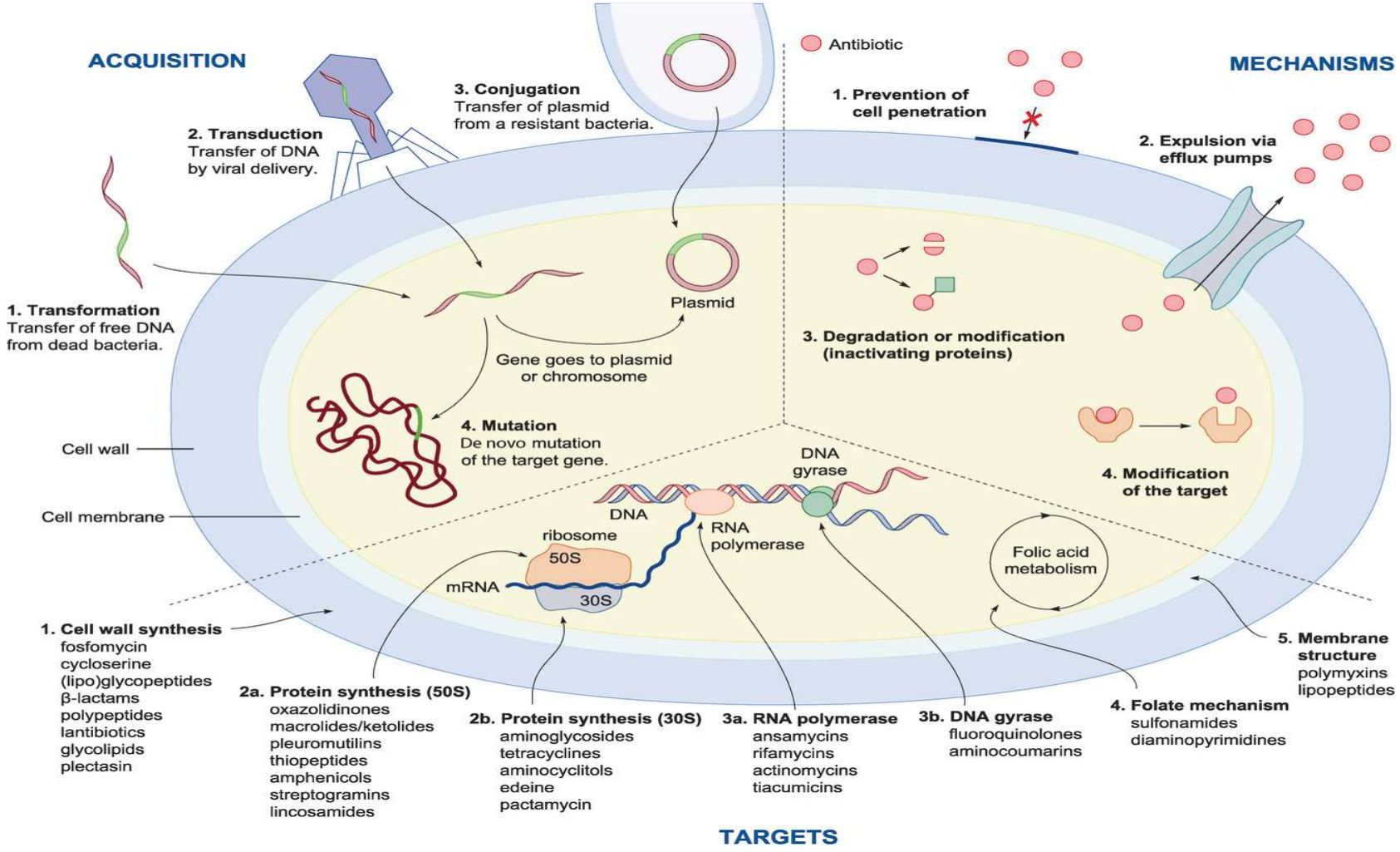
General structure of class 1 integrons. Cassettes are inserted in the variable region of integrons by a site-specific recombination mechanism. The *attI1* and *attC* sites are shown by a vertical rectangle and oval, respectively, and promoters are denoted by Pint, Pc and P. Integrated cassettes are composed of a gene and an *attC* recombination site. Genes are as follows: *intI1*, integrase gene; *qacEΔ1*, antiseptic resistance gene; *sul1*, sulphonamide resistance gene; orf5, gene of unknown function.

Diagram of Antibiotic Target and Resistance Mechanisms



Ref: Cardoso P. Molecular engineering of antimicrobial peptides: microbial targets, peptide motifs and translation opportunities, 2021

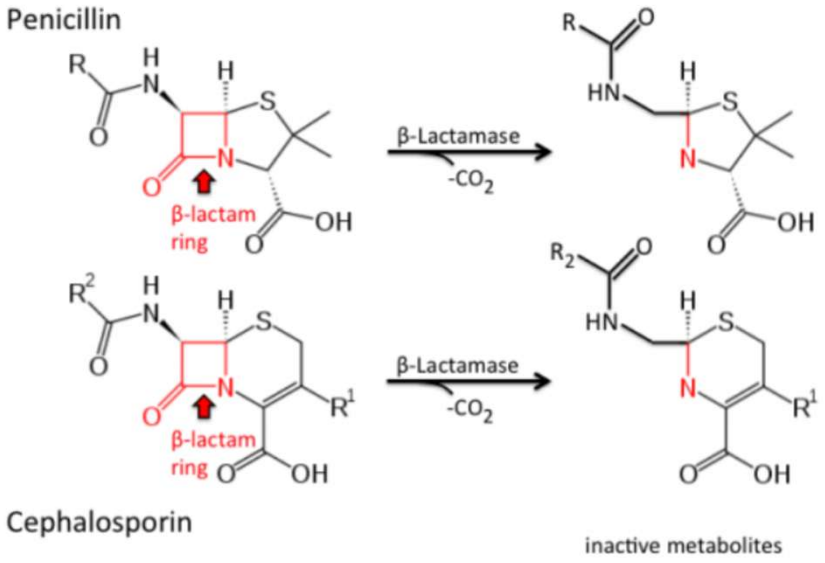
Diagram of Antibiotic Target and Resistance Mechanisms



Ref: Angew Chem Int Ed, Volume: 55, Issue: 23, Pages: 6600-6626, First published: 22 March 2016, DOI: (10.1002/anie.201506818)

1. ENZYMATIC INACTIVATION OF ANTIBIOTICS

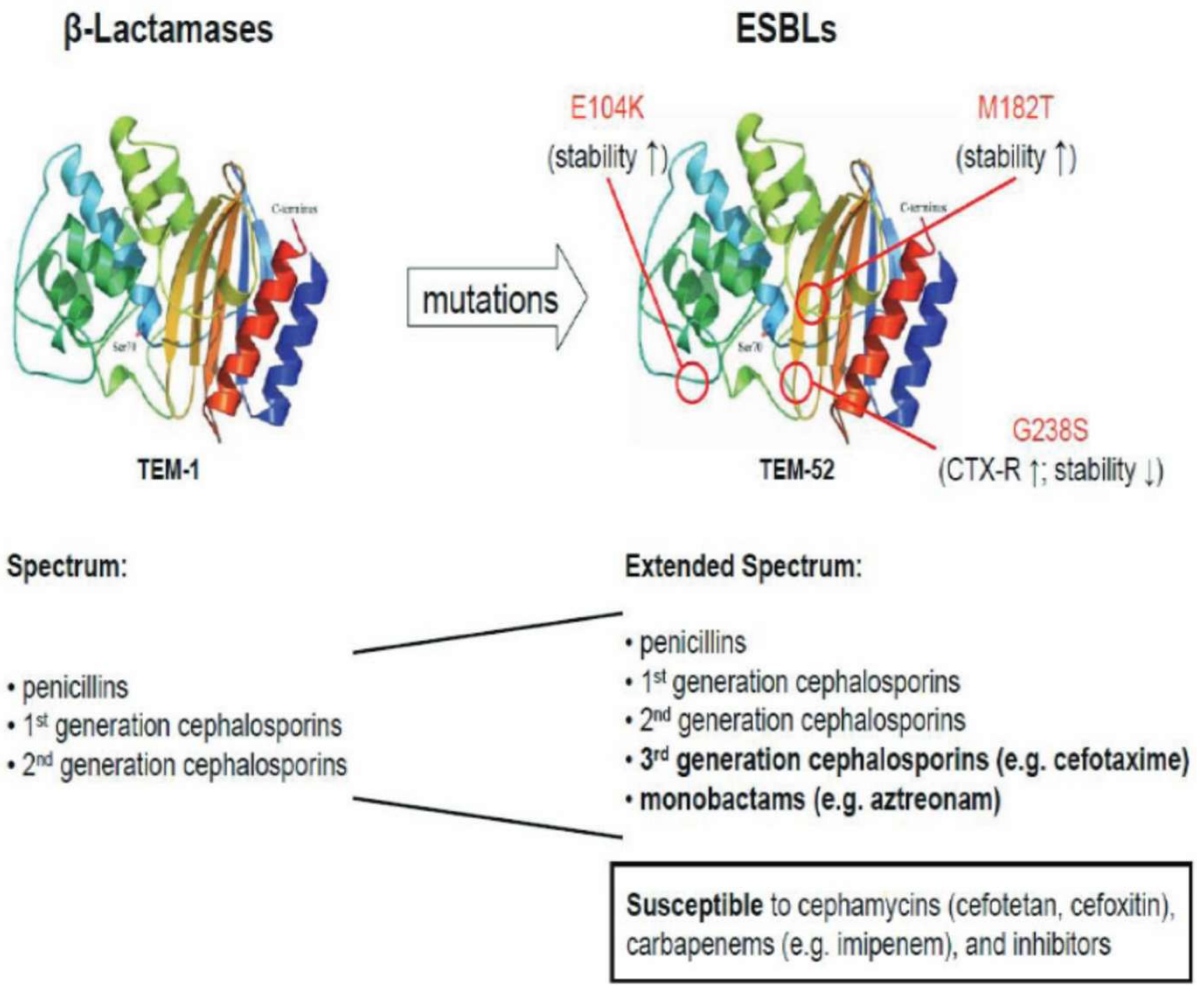
- **Betalactamases**
- a) **resistance to betalactams primarily occurs through betalactamases** – splitting the amide bond of the betalacm ring
- b) Extended-Spectrum Betalactamases
- c) Carbapenemases



Ref: https://tmedweb.tulane.edu/pharmwiki/doku.php/betalactam_pharm

- Most likely **co-evolved wit bacteria as mechanisms against natural antibiotics**
- Selective presure exerted by **widespread use of ATB** have **acclerated** their **development** and **spread**
- Can be **located** either on **chromosomes** or transferable genes locate on **plasmids** or **transposons, integrons** (can facilitate MDR resistance).
- **Classification** (Ambler – according to their **amino acid structure** A-D or Bush-Jacoby-Medeiros according to **functional substrate profile and susceptibility to inhibitors**)

Betalactamases structure



Ref: Ghafourian S., Extended Spectrum Beta-lactamases, Curr. Issues Mol. Biol. (2015) 17: 11-22.

Ambler classification of betalactamases (classes A – D)

	Active site	Enzyme Type	Substrates	Examples
A	Serine	**Penicilinases** Broad-spectrum	benzylpenicillin,aminopenicillinis,carboxypenicillins,ureidopenicillins,narow-spectrum cephalosporins	PC1 in S. aureus,TEM-1,SHV-1 in *E.coli,K.pneumonia* and other Gramneg.bacteria
		Extended-spectrum (ESBL)	Substrates of broad-spectrum plus oxyimino-betalactams (cefotaxime,ceftazidime,ceftriaxone), aztreonam	e.g. *E.coli* (derived from TEM,SHV,CTX-M), *P. aeruginosa* IBC-2
		Carbapenemases	Substrates of ESBL plus cephamycins (e.g. cefuroxime) and carbapenems	e.g. *K. pneumonaie* KPC-1, 2, 3
B	Metallo-ß-lactamases (Zn^{2+})	**Carbapenemases**	Substrates of ESBL plus cephamycins (e.g. cefuroxime) and carbapenems	e.g. VIM, IMP, SIM lineages in *P. aeruginosa*
C	Serine	**Cephalosporinases**	Substrates of ESBL plus cephamycins (e.g. cefuroxime)	e.g. AmpC-type enzymes in Enterobacteriaceae, *Acinetobacter*
D	Serine	**Oxacillinases**		
		Broad-spectrum	aminopenicillins, ureidopenicillins, oxacillin, some narow-spectrum cephalosporins	e.g. OXA family in *P.aeruginosa*
		Extended-spectrum	Spectrum of broad-spectrum plus oxyiminobetalactams (cefotaxime,ceftazidime) and monobactam (aztreonam)	e.g. OXA-derived in *P.aeruginosa*
				e.g. OXA-derived in *Acinetobacter*

Note: Classification A – C is most relevant for medical students to know

Betalactamases

- One of the first betalactamase described was **penicillinase in *S. aureus*** (could be used and inhibitor b-lactamase–b-lactamase inhibitor complex binding the enzyme). **High levels of resistance to penicillin (80-95%)** are standard **for community strains** in almost all countries now.
- **In Gramnegative bacteria** – rise in **ampicilin** in 1960s emergence of TEM-1 (Greek patient Temoneira), plasmid encoded, was later disseminated as **family TEM betalactamases in *P. aeruginosa*, Enterobacteriaceae, *H. influenzae*, *N. gonorrhoeae*.**
- **Similarly chromosomaly- and plasmid-mediated SHV-type betalactamases** (molecular structure similar to TEM) became **widely prevalent among *E. coli* and *K. pneumoniae*.**
- **Third-generation cephalosporin were stable to them but ESBL are capable of hydrolyzing broad-spectrum cephalosporins and monobactam (aztreonam).**
- In addition, **increasing reports of carbapenemases** have arisen **concern** about currently **limited number of antimicrobial arsenal against infection caused by MDR Gramnegative bacteria.**

ESBL

- **TEM-derived: the most common in Gramneg. bacteria**, **hydrolyze penicillin and narow-spectrum cephalosporins** in Enterobactariaceae, *N. gonorrhoeae*, *H. influenzae*. **ESBL** is obtained **through changes** in a **single or few amino acids** that **alter configuration of the enzyme active site** more **accesible to** oxyimino-side chain of **3rd cephalosporines** (more than 160 enzymes, primarily in *E. coli*, *K. pneumoniae*, majority TEM-derived ESBL remain susceptible to clavulanic acid)
- **SHV-derived:** SHV-1 similar to that of TEM-1, primarily in *K. pneumoniae*
- **CTX-M-derived:** probably acquired by plasmid from the chromosomal AmpC enyzymes of low pathogenic Granegative rod *Kluyvera*, hydrolyze cefotaxime, ceftriaxone, ceftazidime, most prevalent in Europe and South America
- **OXA-derived ESBL:** hydrolyze oxacillin and its derivate, described mainly in *P. aeruginosa*
- **AmpC enzymes: primarily chromosomal enzymes that confer resistence to penicillins, narow-spectrum cephalosporins, oxyimino-betalactams, cephamycins (e.g. cefoxitin), not susceptible to inhibitor of betalactamases** (detected in some clinical strains of e.g. *Enterobacter, Citrobacter, Serratia*)

SIGNIFICANT NOTE*: if we do not know what type of broad-spectrum beta-lactamase the bacterium produces, we cannot use beta-lactam with a beta-lactamase inhibitor in treatment !!!*

Carbapenemases

- **confer resistance the largest ATB spectrum**
- **KPC the most important carbapenemases** (initially reported *K. pneumoniae*)
- **Resistant to inhibitors** - clavulanic acid, tazobactam, sulbactam
- Confer **resistance to all betalactams and monobactam**
- **chromosomaly encoded metallo-betalactamases (e.g. VIM, IMP…) primarily found in environmental isolates of *Aeromonas, Chryseobacterium and Stenotrophomonas***
- **typically transmitted by mobile genetic elements (MGE)** inserted into **integrons – have** spread through *P. aeruginosa, Acinetobacter*, other Nonfermenters and enteric bacterial pathogens
- class D carbapenemases (OXA – 23,24,40,58) primarily found in Acinetobacter

2. ANTIBIOTIC MODIFICATION

- **Aminoglycoside (AMG) Resistance-Modifying Enzymes** (more than 30 enzymes)
- AMG resistance is **the most commonly caused by modifying enzymes**
- encoded **on plasmid** or **chromosome**
- **3 general reactions: N-acetylation, O-nucleotidylation, O-phosphorylation** (attack specific amino or hydroxyl group)
- **Nomenclature: where the modification occurs**
- Modification of ATB during transport across the cytoplasmic membrane
- **APH (3´) and APH (3´´)** distributed widely among **Grampositive** and **Gramnegative** bacteria
- **AAC(6´)APH(2´)** is a **bifuntional enzyme (acetylation/phosporylation)** widespread in **staphylococci** and **enterococci**), residing in a common transpozon Tn4001

Representative aminoglycosides and modification sites by AAC, ANT, and APH enzymes

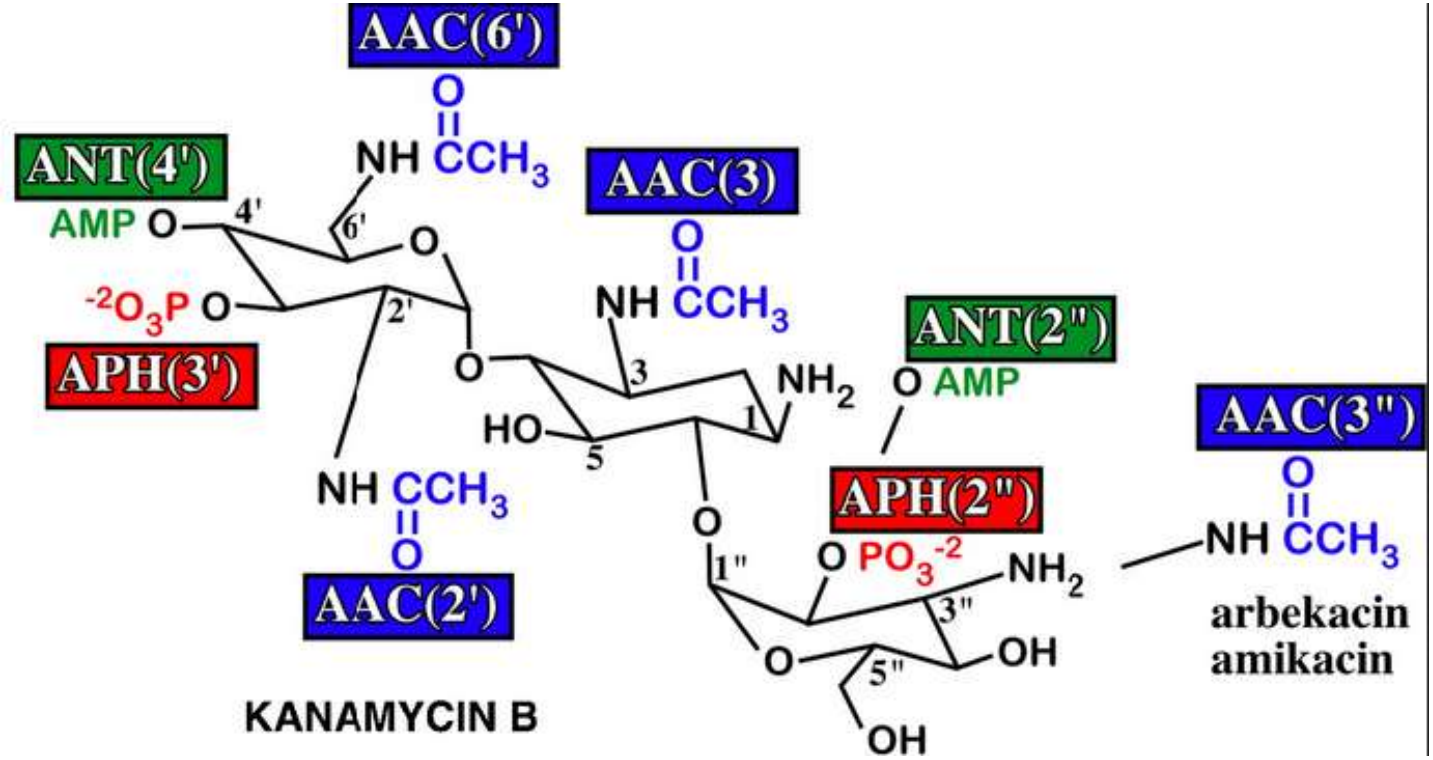


Fig. An example of each kind of modification is shown on one of the substrates. The square and oval on positions 2′ and 6″ in paromomycin I indicate that although this molecule is preferentially acetylated at the position 1, 1,2′-di-N-acetylparomomycin and 1,6″-di-N-acetylparomomycin are also found as products of the enzymatic reaction (Sunada et al., 1999). AAC(3)-X can catalyze acetylation at the 3″-amino group in arbekacin and amikacin (Hotta et al., 1998). (Ref: https://www.sciencedirect.com/science/article/pii/S1368764610000385#fig0005)

Mechanisms of Chloramphenicol Resistance

- **Chloramphenicol acetyltransferase (plasmid- or chromosome-borne) and acetylation** is primary mechanism of the resistance in **Grampositive** and **Gramnegative bacteria**

Macrolide-, Linkosamide-, Streptogramin- Inactivating Enzymes

- **Erythromycin esterases – hydrolyse the lactone ring** and limit **erythromycin and other macrolides** use to treat **Gramnegative** bacterial pathogens

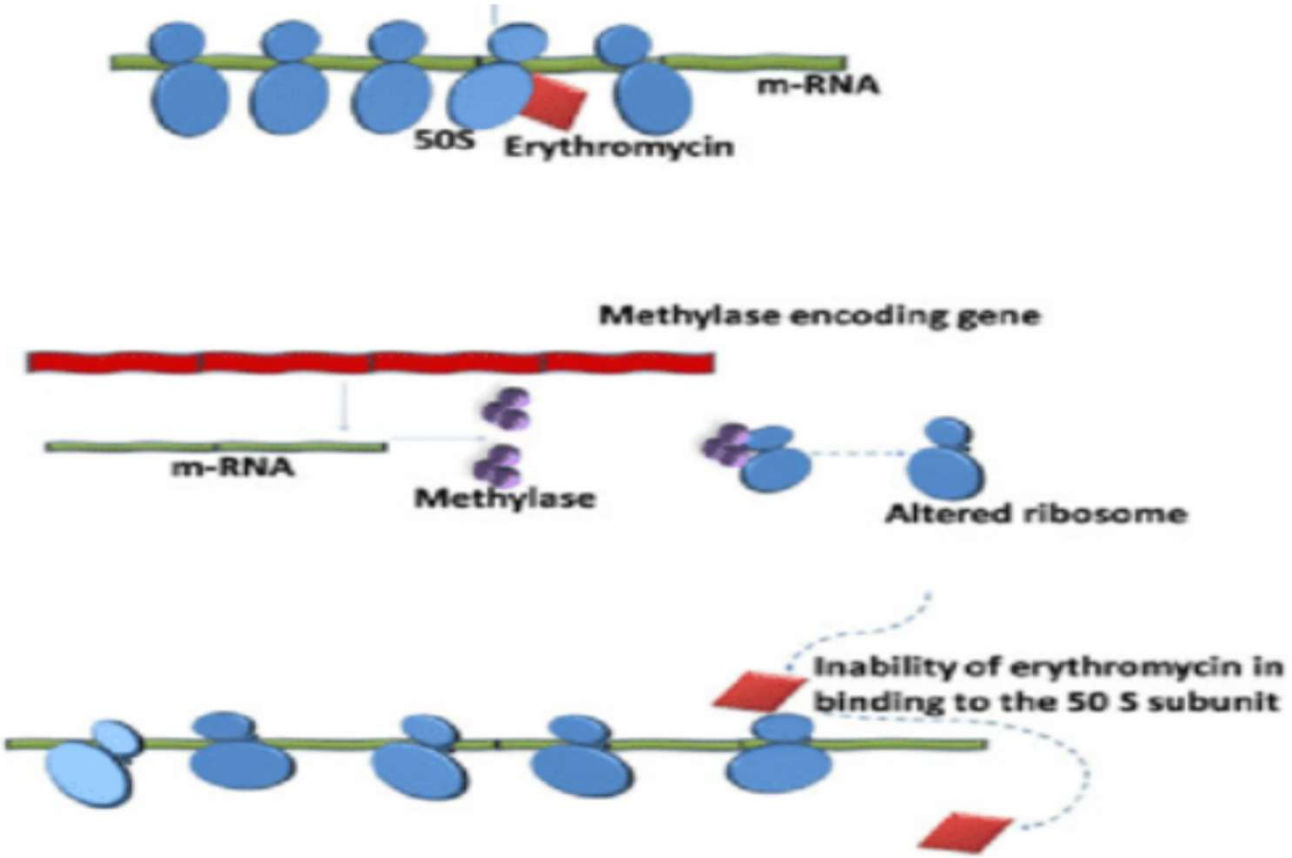
Mechanisms of Tetracycline Inactivation

- **TetX enzyme found in Bacteroides inactivating tetracycline** (it is unusual mechanisms)

3. ALTERED TARGET SITE

- **e.g. Macrolides, Lincosamides, Streptogramins** – disrupts its ability to inhibit protein synthesis and bacterial cell growth, principal mechanism of multiple-agent resistence to MLSb antibiotics among aerobic and anaerobic Grampositive bacteria (e.g. S. aureus, S. pneumoniae, C. perfringens…), may **be located on plasmids or chromosomes**
- ***erm*** (A, B, C) genes determined the **methylases that dimethylate adenine residues on the 23S ribosomal RNA** (50S subunit) **disrupting binding of MLS antibiotic to the ribosome**
- **Oxazolidones (linezolid):** determined by **point mutation within the gene encoding 23S rRNA** of the 50S ribosomal subunit (described in *S. aureus*, *S. epidermidis*, enterococci)
- **Vancomycin resistence: alteration of cell wall precursor in enterococci** determined by **vanA gene (rarely also in staphylococci as VRSA), thickened cell walls in VISA (vankomycin resistant *S. aureus*)**
- **Alteration of target enzymes: mecA** located on **staphylococcal cassete chromosome mec (SCCmec) (located chromosomally) determines alternative PBP2a**
- **PBPs changes also known in betalactams resistant *N. gonorrhoeae, N. meningitidis, S. pneumoniae***
- **Quinolones – mutations in gyrA and/or topoisomerase IV** lead to the resistance in Enterobacteriaceae or P. aeruginosa

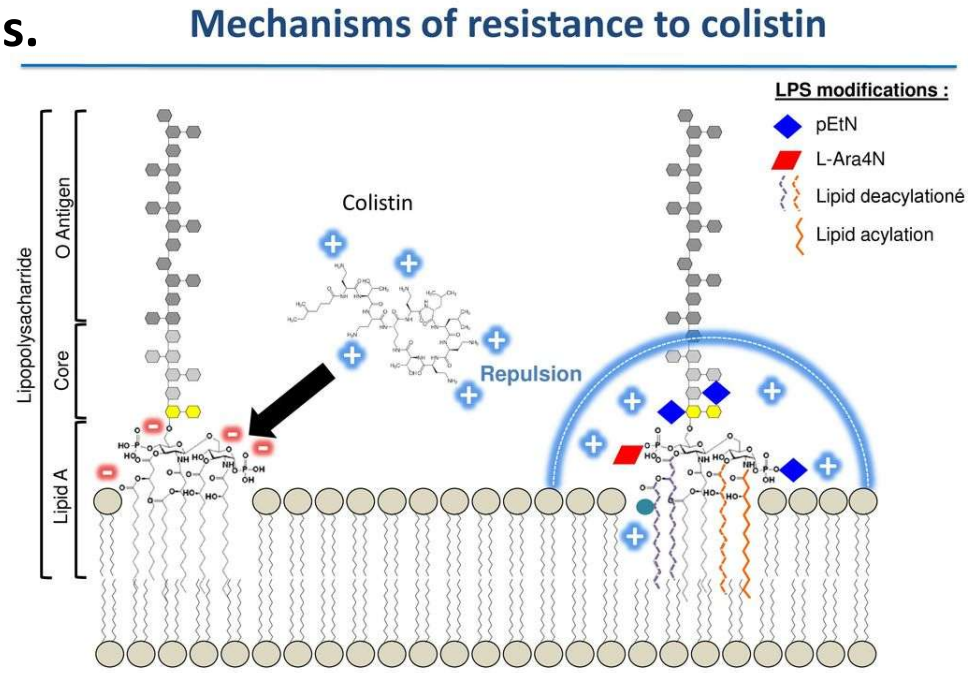
Mechanism of Macrolides, Lincosamides, Streptogramins Resistance



Ref: https://www.researchgate.net/figure/Mechanisms-of-bacterial-resistance-to-macrolide-lincosamide-streptogramin-antibiotics_fig1_257769651

Resitance to colistin in Gramnegative rods

The mechanism of resistance of the MCR gene is a **phosphatidylethanolamine transferase**. The enzyme **transfers** a **phosphoethanolamine** residue **to the lipid A** present **in the cell membrane of gram-negative bacteria**. The altered lipid A has much lower affinity for colistin and related polymyxins resulting in reduced activity of the antimicrobial. Although the same mechanism has been observed before with enzymes like eptA, mcr-1 is the first polymyxin resistance gene known to be capable of **horizontal transfer between different strains of a bacterial species.**

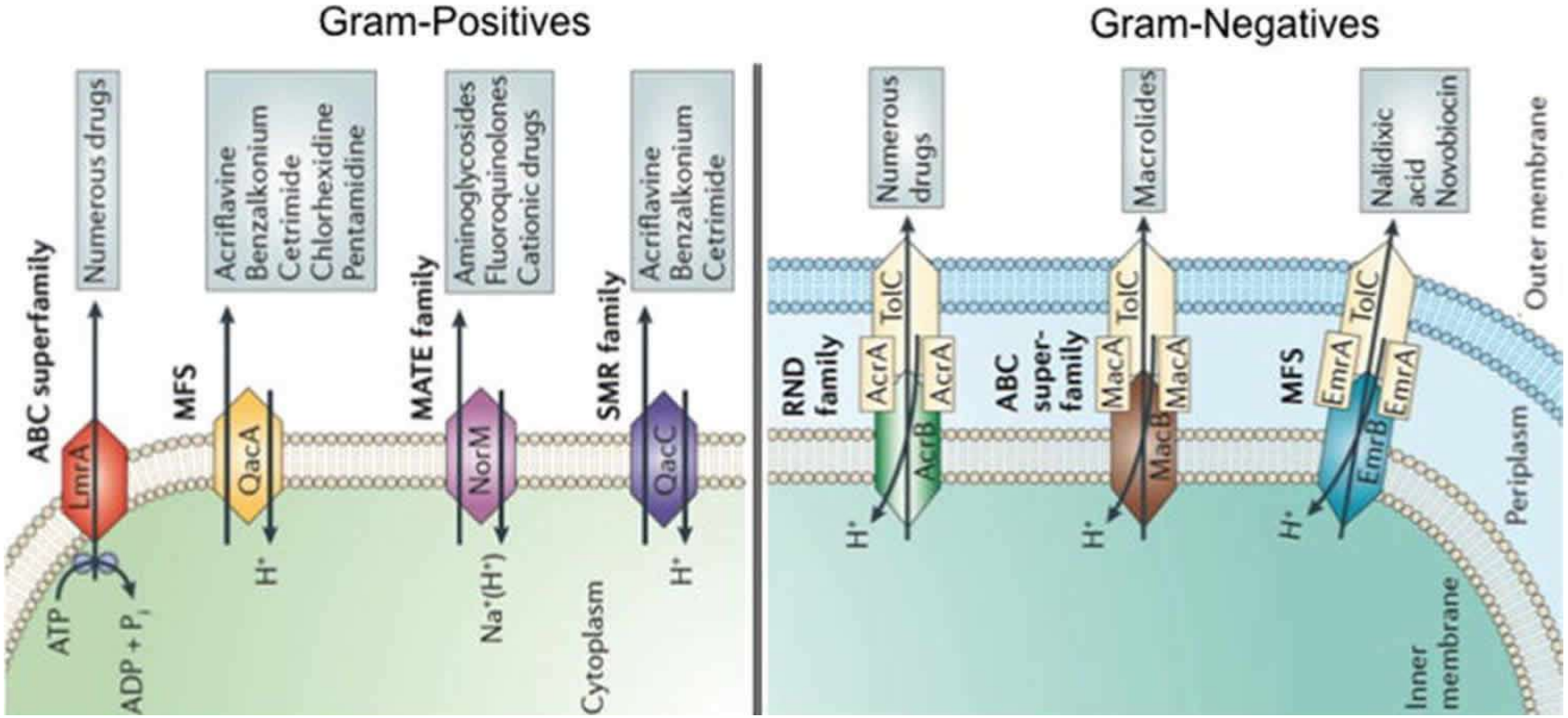


Ref: https://slideplayer.com/slide/12663654/

4. MECHANISMS OF ANTIBIOTIC EFFLUX

- **Specific or multidrug resistance mechanisms decreasing effective concentration of ATB in the bacterial cell**
- **Tetracyclines:** the **most commonly in enteric pathogens** (e.g. *E. coli*, *Shigella*…)
- Energy dependent proces (membrane transporter system)
- The genes (*tet*) located on the **chromosome, plasmids or transposable elements**
- **Macrolides, Streptogramins, Azalides (azithromycin)**: Efflux mechanism mediated by ***mef*** **(in Streptococci)** and ***msrA*** **(in Staphylococci)** are responsible for the resistence
- **Betalactams:** multidrug efflux pump in inner and outer membrane is known in **P. aeruginosa**
- **Fluorochinolones: detected in enteric bacteria and staphylococci, determining by a specific quinolone efflux pump (e.g. EmrAB, AcrAB)**

Representation of different types of efflux pumps in Gram-positive and Gram-negative bacteria



Ref: https://healthjade.net/antibiotic-resistance/

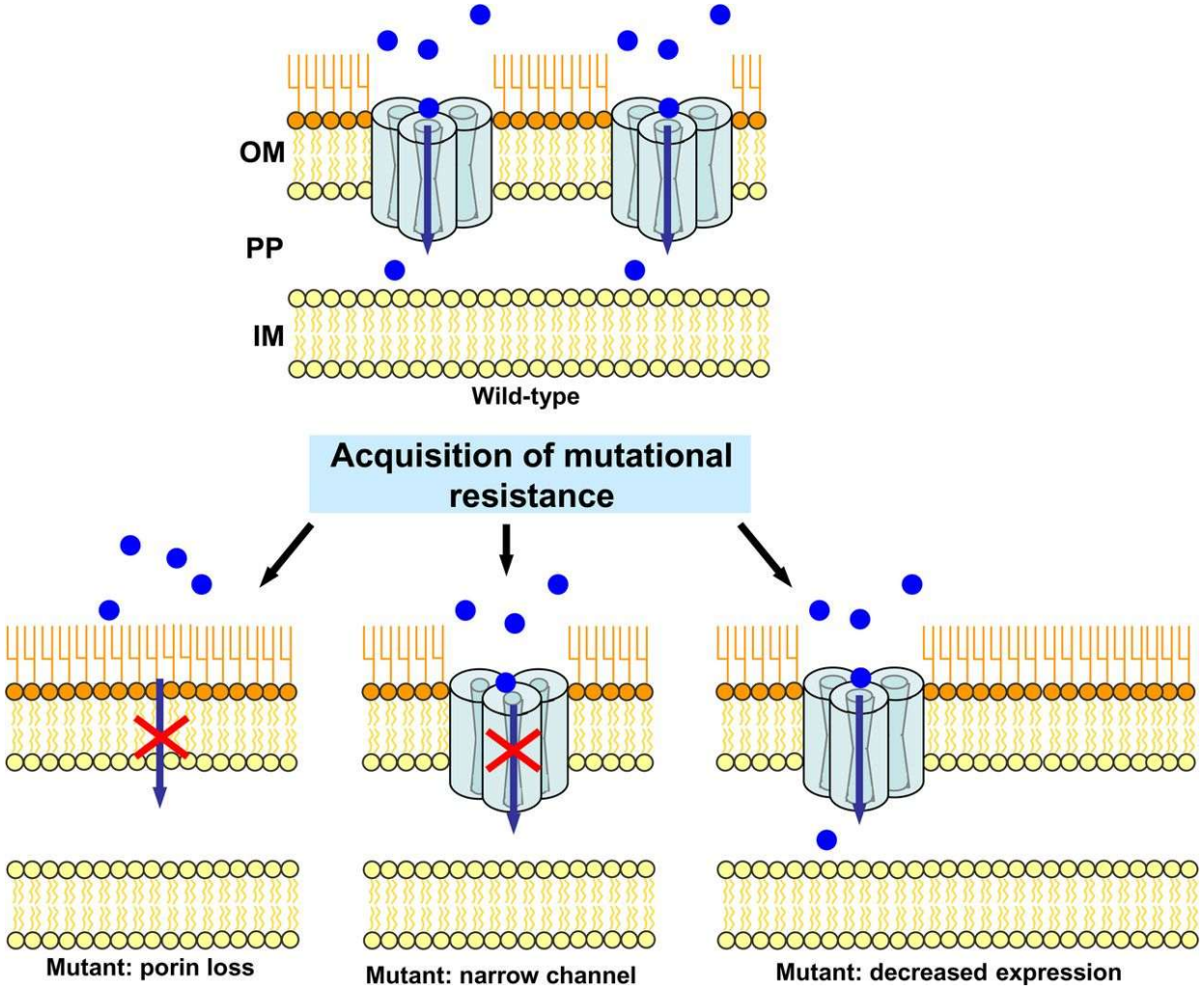
5. DECREASED PERMEABILTY OF BACTERIAL MEMBRANES

- Outer or inner membrane permeability: bacteria can regulate **size** and **number of the porins**

- Relativelly **quickly emerged** (during a particular patient treatment, e.g. imipenem/*P.aeruginosa*)

- **The most known in *P. aeruginosa*** determining rersistance to aminoglycosides, carbapenems

Modification, reduction and loss of porins

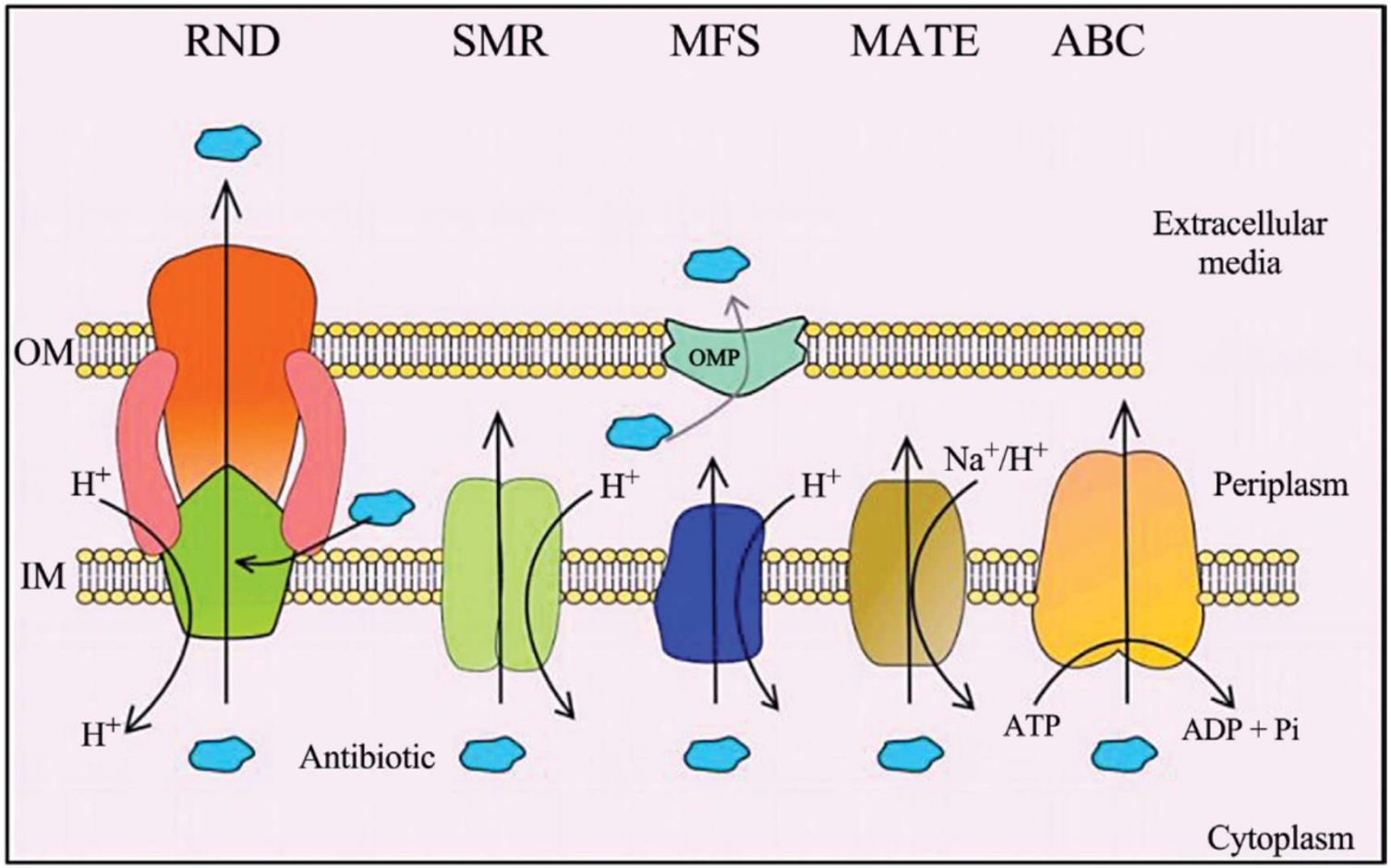


Multidrug-resistence mechanisms among bacteria

- Bacterial pathogen can express **more than 1 resistance mechanism** leding to **multidrug-resistance** or even **pan-resistence**
- In general, **resistance in Gramnegative bacteria starts** with limited outer **membrane permeability coupled with the overexpression of MDR efflux pumps**
- **It may alowe to survive bacterial pathogen facilitating the accumulation of new antibiotic-resistrance mutations**
- **Clinically important efflux pumps: RND, MFS, SMR** (staphylococcal multiresistance), **MATE family – such pumps are widespread** among procaryotes responsible for the export of toxic substances and allowing survival in noxious environment
- **Ussually sequentially transfered by multiple-resistant determinants located on mobile genetic elements** (e.g. conjugative transpozon Tn916 conferring resistance to tetracycline na chloramphenicol among bacterial species)
- **Integrons usually capture multiple antibiotic resistance genes,** which can insert **resistence gene cassetes** into their attI integration site and are **often found on transposons carried on plasmids, with seemingly endless recombinant potential**

Ref: Mandell G.L., Bennett J.E., Dolin R. Principles and Practice of Infectious Diseases

Sructure of significant ATB Efflux pumps



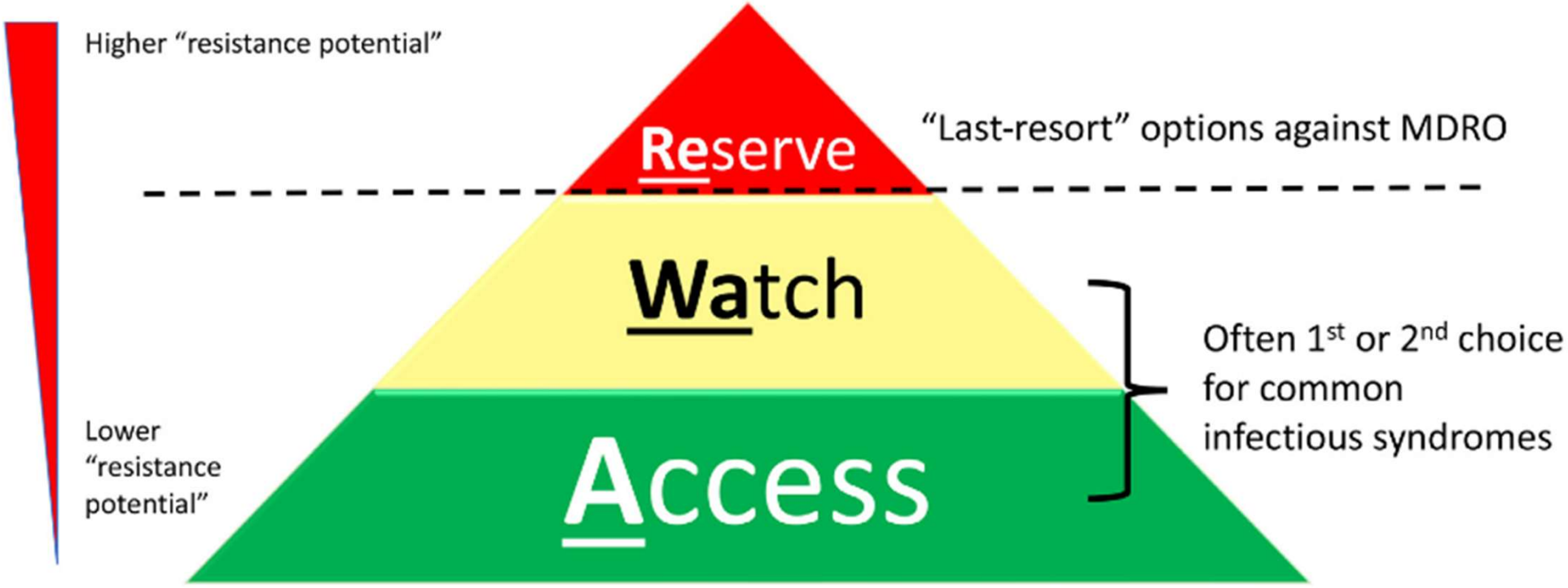
AWaRe classification of antibiotics for evaluation and monitoring of use, 2023

- The **AWaRe classification** of antibiotics was **developed** in 2017 **by the WHO Expert Committee on Selection and Use of Essential Medicines** as a **tool to support antibiotic stewardship** efforts **at local, national and global levels.**
- Antibiotics are classified into three **groups**, **Access**, **Watch** and **Reserve**, taking into account the **impact** of different antibiotics and antibiotic classes **on antimicrobial resistance,** to **emphasize the importance of their appropriate use**. It is updated every 2 years.

* The AWaRe classification **monitoring the effects of stewardship policies that aim to optimize antibiotic use** is intended as a tool for **monitoring antibiotic consumption**, defining targets and and curb antimicrobial resistance. The WHO 13th General Programme of Work 2019–2023 includes a country-level target of at least 60% of total antibiotic consumption being Access group antibiotics.

AWaRe : Antibiotics are categorized into three groups

Essential Access, Watch and Reserve antibiotics need to be equally accessible and affordable for those who need them



ACCESS

GROUP

[bez názvu]

- first or second choice antibiotics
- offer the best therapeutic value, while minimizing the potential for resistance

WATCH

GROUP

- first or second choice antibiotics
- only indicated for specific, limited number of infective syndromes
- more prone to be a target of antibiotic resistance and thus prioritized as targets of stewardship programs and monitoring

RESERVE

GROUP

- “last resort”
- highly selected patients (life-threatening infections due to multi-drug resistant bacteria)
- closely monitored and prioritized as targets of stewardship programs to ensure their continued effectiveness

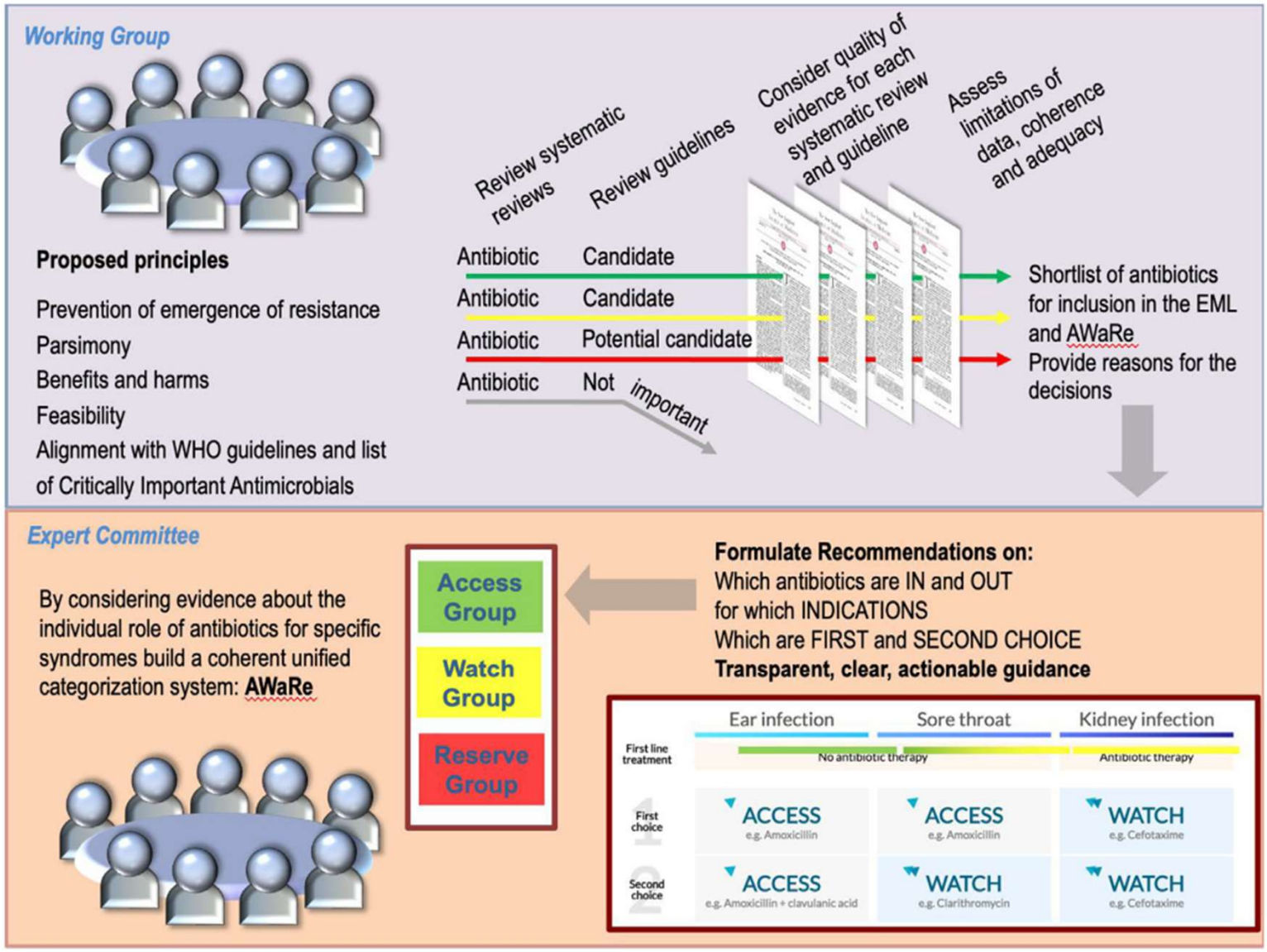


Fig. 1. Roles and tasks of the Working Group and the Expert Committee and their relationship.

References: Moja et al. WHO's essential medicines and AWaRe: recommendations on first- and second-choice antibiotics for empiric treatment of clinical infections, Clinical Microbiology and Infection, 2024

ACCESS

Aminocyclitols:
Spectinomycin

Aminoglycosides:
Amikacin
Gentamicin

Amphenicols:
Chloramphenicol
Thiamphenicol

Beta-lactam/ beta-lactamase-inhibitor:
Amoxicillin/clavulanic-acid
Ampicillin/sulbactam
Sultamicillin

Beta-lactamase-inhibitors:
Sulbactam

First-generation-cephalosporins:
Cefacetrile
Cefadroxil
Cefalexin
Cefaloridine
Cefalotin
Cefapirin
Cefatrizine
Cefazedone
Cefazolin
Cefradine
Cefroxadine
Ceftezole

Imidazoles:
Metronidazole_IV
Metronidazole_oral
Ornidazole_IV
Ornidazole_oral
Secnidazole
Tinidazole_IV
Tinidazole_oral

Lincosamides:
Clindamycin

Nitrofuran derivatives:
Furazidin
Nifurtoinol

Nitrofuran-derivatives:
Nitrofurantoin

Sulfonamide-trimethoprim combinations:
Sulfadiazine/tetroxoprim
Sulfadiazine/trimethoprim
Sulfadimidine/trimethoprim
Sulfamerazine/trimethoprim
Sulfamethoxazole/trimethoprim
Sulfametrole/trimethoprim
Sulfamoxole/trimethoprim

Penicillins:
Amoxicillin
Ampicillin
Azidocillin
Bacampicillin
Benzathine-benzylpenicillin
Benzylpenicillin
Clometocillin
Cloxacillin
Dicloxacillin
Epicillin
Flucloxacillin
Hetacillin
Mecillinam
Metampicillin
Meticillin
Nafcillin
Oxacillin
Penamecillin
Phenoxymethylpenicillin
Pivampicillin
Pivmecillinam
Procaine-benzylpenicillin
Propicillin
Talampicillin

Sulfonamides:
Sulfadiazine
Sulfadimethoxine
Sulfadimidine
Sulfafurazole
Sulfaisodimidine
Sulfalene
Sulfamazone
Sulfamerazine
Sulfamethizole
Sulfamethoxazole
Sulfamethoxypyridazine
Sulfametomidine
Sulfametoxydiazine
Sulfamoxole
Sulfanilamide
Sulfaperin
Sulfaphenazole
Sulfapyridine
Sulfathiazole
Sulfathiourea

Tetracyclines:
Doxycycline
Tetracycline

Trimethoprim-derivatives:
Brodimoprim
Trimethoprim

WATCH

Aminoglycosides:
Arbekacin
Bekanamycin
Dibekacin
Isepamicin
Kanamycin_IV
Kanamycin_oral
Micronomicin
Neomycin_IV
Neomycin_oral
Netilmicin
Ribostamycin
Sisomicin
Streptoduocin
Streptomycin_IV
Streptomycin_oral
Tobramycin

Beta-lactam/beta-lactamase-inhibitor_anti-pseudomonal:
Piperacillin/tazobactam

Beta-lactamase-inhibitors:
Tazobactam

Carbapenems:
Biapenem
Doripenem
Ertapenem
Imipenem/cilastatin
Meropenem
Panipenem
Tebipenem

Fluoroquinolones:
Ciprofloxacin
Delafloxacin
Enoxacin
Fleroxacin
Garenoxacin
Gatifloxacin
Gemifloxacin
Grepafloxacin
Lascufloxacin
Levofloxacin
Levonadifloxacin
Lomefloxacin
Moxifloxacin
Norfloxacin
Ofloxacin
Pazufloxacin
Pefloxacin
Prulifloxacin
Rufloxacin
Sitafloxacin
Sparfloxacin
Temafloxacin
Tosufloxacin
Trovafloxacin

Fourth-generation-cephalosporins:
Cefepime
Cefosolis
Cefozopran
Cefpirome

Glycopeptides:
Teicoplanin
Vancomycin_IV
Vancomycin_oral

Lincosamides:
Lincomycin

Macrolides:
Azithromycin
Clarithromycin
Dirithromycin
Erythromycin
Fidaxomicin
Flurithromycin
Josamycin
Midecamycin
Miocamycin
Oleandomycin
Rokitamycin
Roxithromycin
Solithromycin
Spiramycin
Telithromycin
Troleandomycin

Penicillins:
Aspoxicillin
Azlocillin
Carbenicillin
Carindacillin
Mezlocillin
Pheneticillin
Piperacillin
Sulbenicillin
Temocillin
Ticarcillin

Phenol derivatives:
Clofoctol

Phosphonics:
Fosfomycin_oral

Quinolones:
Cinoxacin
Flumequine
Nemonoxacin
Oxolinic-acid
Pipemidic-acid
Piromidic-acid
Rosoxacin

Rifamycins:
Rifabutin
Rifampicin
Rifamycin_IV
Rifamycin_oral
Rifaximin

Second-generation-cephalosporins:
Cefaclor
Cefamandole
Cefbuperazone
Cefmetazole
Cefminox
Cefonicid
Ceforanide
Cefotetan
Cefotiam
Cefoxitin
Cefprozil
Cefuroxime
Flomoxef
Loracarbef

Steroid antibacterials:
Fusidic-acid

Streptogramins:
Pristinamycin

Tetracyclines:
Chlortetracycline
Clomocycline
Demeclocycline
Lymecycline
Metacycline
Minocycline_oral
Oxytetracycline
Penimepicycline
Rolitetracycline
Sarecycline

Third-generation-cephalosporins:
Cefcapene-pivoxil
Cefdinir
Cefditoren-pivoxil
Cefetamet-pivoxil
Cefixime
Cefmenoxime
Cefodizime
Cefoperazone
Cefotaxime
Cefpiramide
Cefpodoxime-proxetil
Cefsulodin
Ceftazidime
Cefteram-pivoxil
Ceftibuten
Ceftizoxime
Ceftriaxone
Latamoxef

RESERVE

Aminoglycosides:
Plazomicin

Carbapenems:
Imipenem/cilastatin/relebactam
Meropenem/vaborbactam

Fifth-generation cephalosporins:
Ceftaroline-fosamil
Ceftobiprole-medocaril
Ceftolozane/tazobactam

Glycopeptides:
Dalbavancin
Oritavancin
Telavancin

Glycylcyclines:
Tigecycline

Lipopeptides:
Daptomycin

Monobactams:
Aztreonam
Carumonam

Other-cephalosporins:
Cefiderocol

Oxazolidinones:
Linezolid
Tedizolid

Penems:
Faropenem

Phosphonics:
Fosfomycin_IV

Pleuromutilin:
Lefamulin

Polymyxins:
Colistin_IV
Colistin_oral
Polymyxin-B_IV
Polymyxin-B_oral

Streptogramins:
Dalfopristin/quinupristin

Tetracyclines:
Eravacycline
Minocycline_IV
Omadacycline

Third-generation-cephalosporins:
Ceftazidime/avibactam

Trimethoprim-derivatives:
Iclaprim