Acquisition of Antimicrobial resistance

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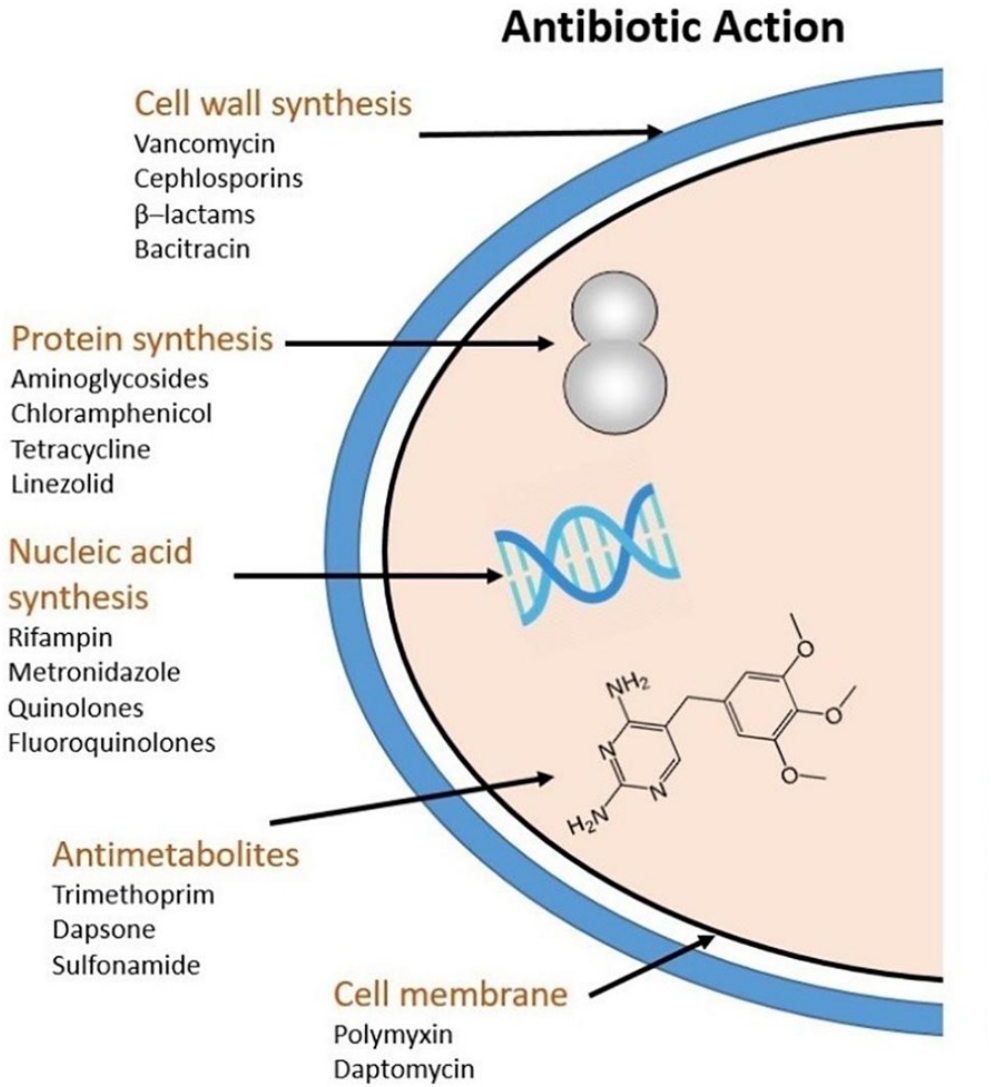
Overview

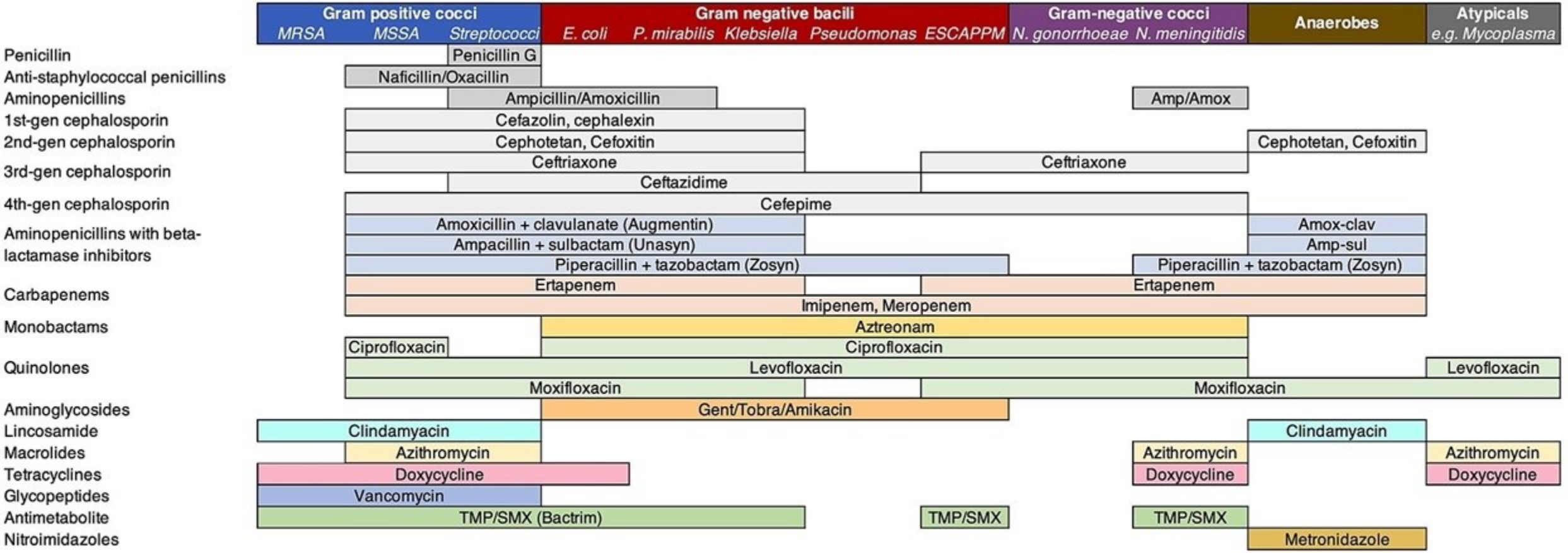
- Antibiotics – mechanism of action, spectrum
- AMR – Causes, History, Resistance mechanisms
- Acquisition of AMR – Role of MGEs and HGT
- What to look for in ACORN target pathogens?



Mechanisms of Action of Antibiotics

Wright, 2010

Spectrum of Antibiotics



See github.com/aetherist/antibiogram for details. For educational purposes only. Consult your local antibiogram for clinical use.

TMP/SMX = Trimethoprim-sulfamethoxazole, MRSA = Methicillin-resistant Staphylococcus aureus, MSSA = Methicillin-sensitive Staphylococcus aureus, ESCAPPM = Enterobacter spp., Serratia spp., Citrobacter freundii, Aeromonas spp., Proteus spp., Providencia spp. and Morganella morganii.

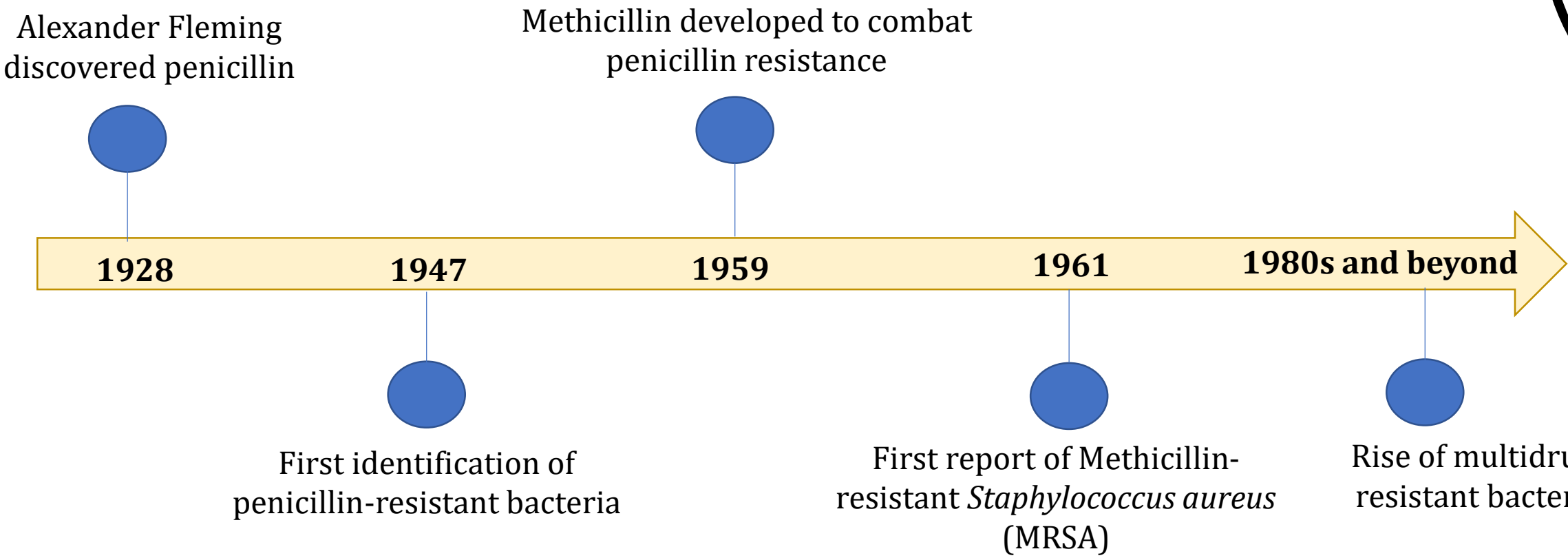
https://commons.wikimedia.org/wiki/File:2023-12-12_Antibiotics_Coverage_Diagram.jpg

Antimicrobial resistance (AMR)

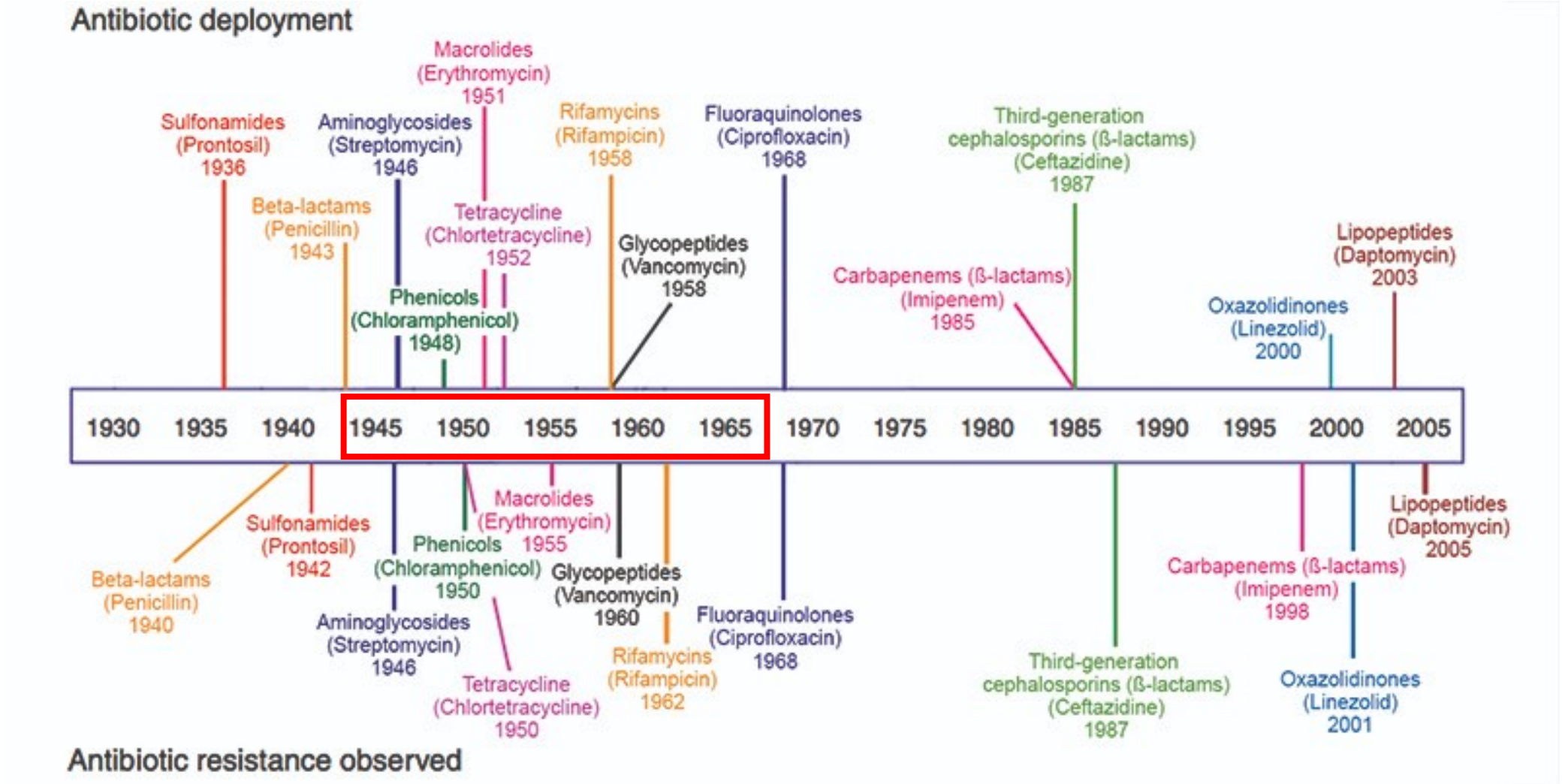
- Ability of bacteria to resist the effects of antibiotics, a type of drug - such as penicillin or ciprofloxacin - that kills or stops the growth of bacteria

- Bacteria employ a variety of strategies to modify a bacterial component or process so that antibiotics can no longer stop their growth or kill them

The History of Antibiotic Resistance



Timeline of antibiotics and emergence of AMR



https://www.open.edu/openlearn/mod/oucontent/view.php?id=75701&extra=thumbnailfigure_idm259

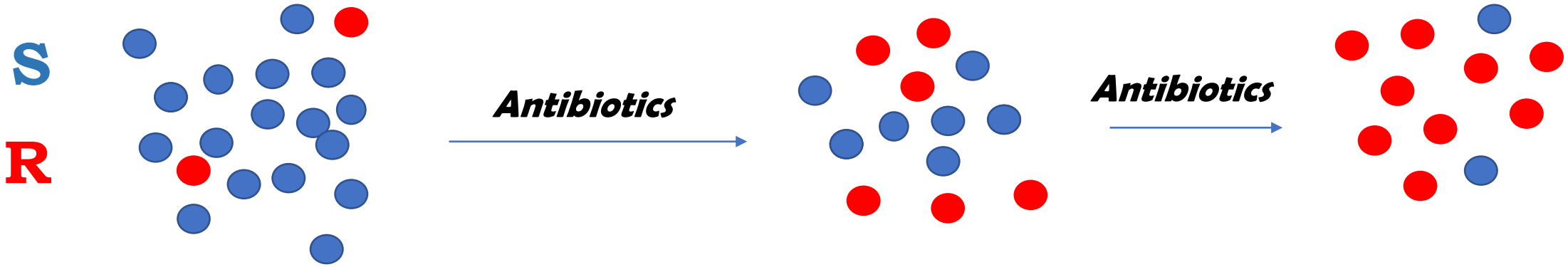
Causes of antibiotic resistance

AMR is a natural process that occurs

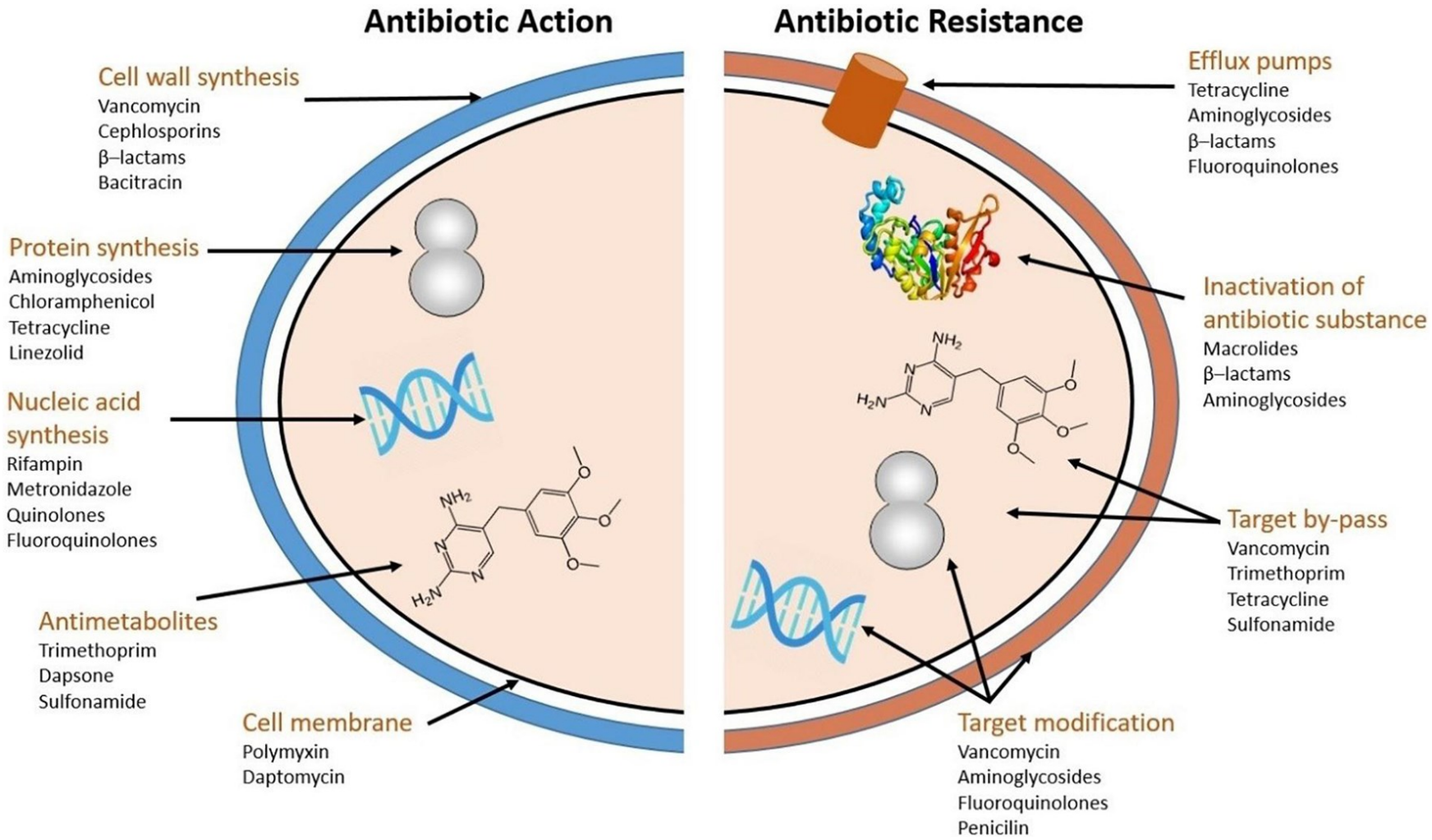
- due to genetic changes in the bacteria

However, antibiotic resistance is being accelerated

- through the overuse and misuse of antibiotics
- overuse of antibiotics - can kill off the drug-sensitive bacteria and allow the resistant bacteria to remain and flourish



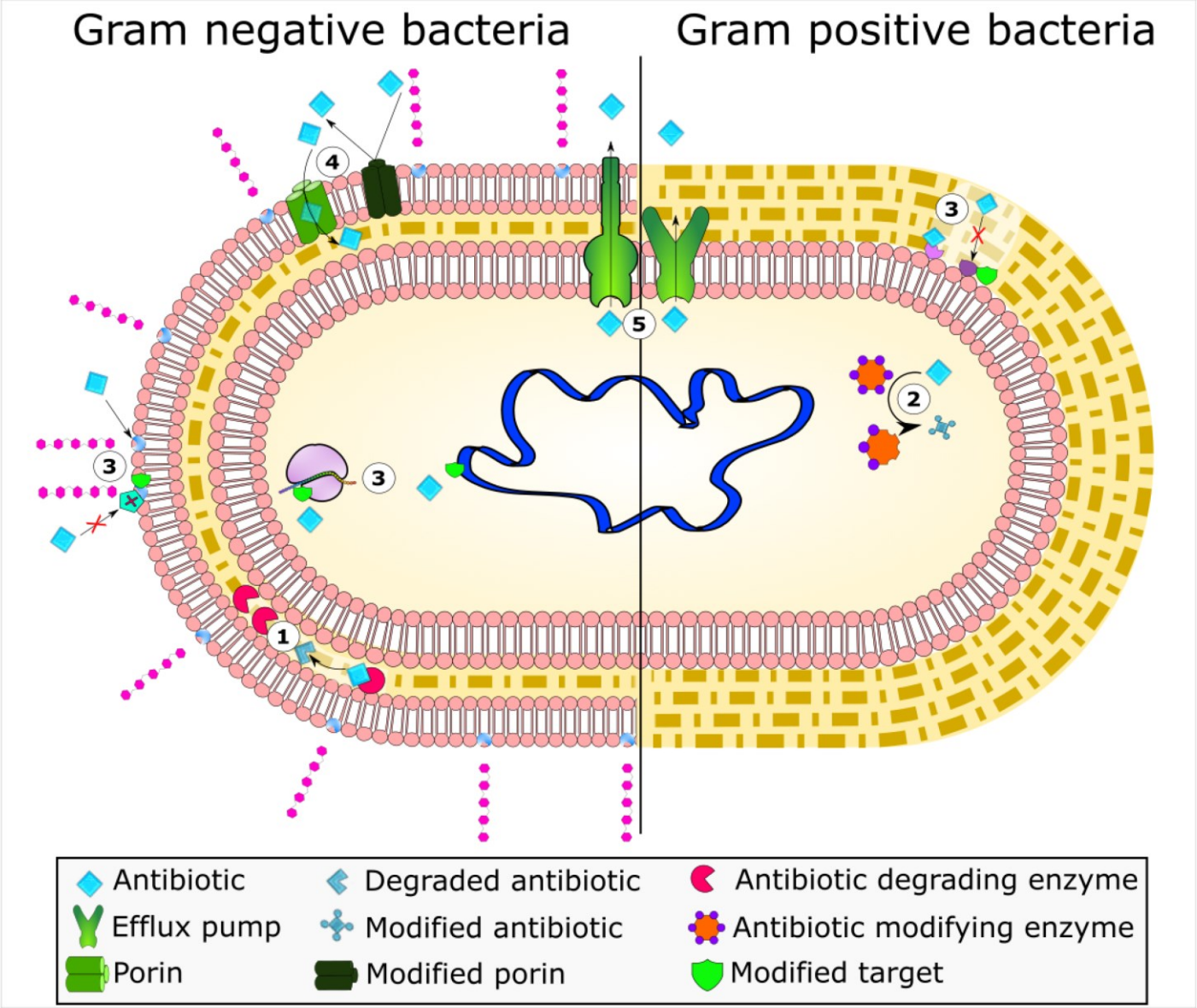
Mechanisms of Antimicrobial Resistance



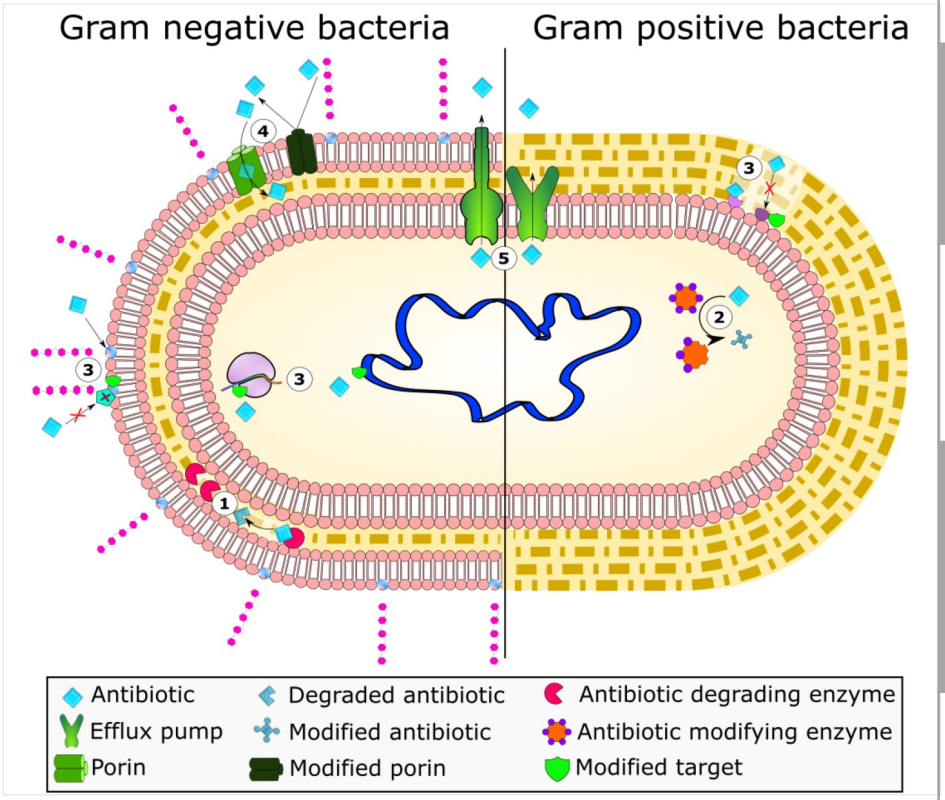
Wright, 2010

AMR Resistance mechanisms

1. Enzymatic hydrolysis
2. Enzymatic modifications
3. Modifications of antibiotic targets
4. Reduced permeability to antibiotics by modifications of porins
5. Active extrusion of antibiotics by membrane efflux pumps



by Manuel F. Varela et al., 2021
PMID: 34067579



Enzymatic hydrolysis	*Beta-lactamases*
Enzymatic modifications	*Aminoglycoside modifying enzymes*
Modifications of antibiotic targets	*QRDR mutations*
Reduced permeability to antibiotics by modifications of porins	*ompK -Kpn*
Active extrusion of antibiotics by membrane efflux pumps	*Mex-Pseudomonas*

by Manuel F. Varela et al., 2021
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Types of resistance

Intrinsic Resistance

- ***Chromosomal***

Resistance to an antimicrobial agent that is natural to a genus/species/group of bacteria

Mechanisms:

1. Absence of Target
2. Low affinity target
3. Innate Efflux pumps
4. Drug inactivation
5. Permeability barrier

Examples: Colistin resistance in Gram-positives, SPICE organisms, blaSHV-K. pneumoniae

Acquired Resistance

- ***Extra chromosomal (ARGs)***
- ***Chromosomal***

Mutation occurs due to alteration in the site of antibiotic action

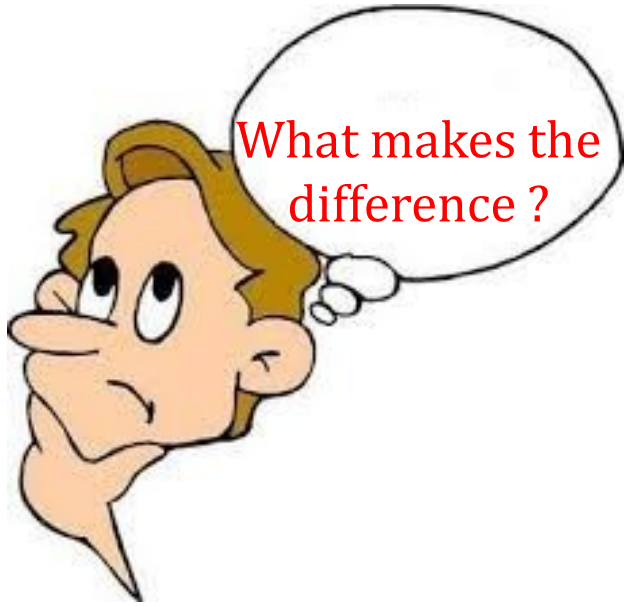
Mechanisms:

1. Drug inactivation
2. Drug hydrolysis
3. Alteration of drug target
4. Innate Efflux pumps
5. Permeability barrier

Examples: Beta-lactamases, AMEs, 16S RMTases etc., QRDR mutations

Though they all are bacterial pathogens…

- *E. coli*
- *K. pneumoniae*
- *Acinetobacter spp*
- *S. aureus*



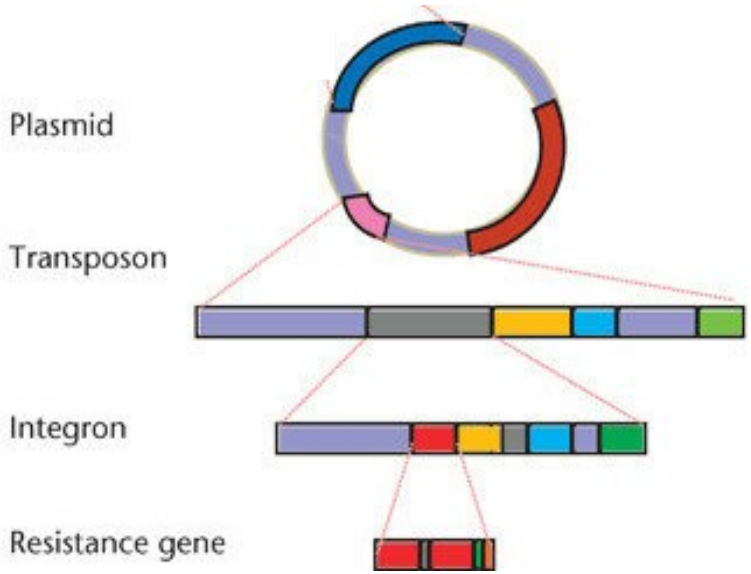
Diverse resistance mechanisms

Mobile genetic elements (MGEs)/ Transposable elements (Tes)

- ✓ Plasmids
- ✓ Transposons
- ✓ Integrons
- ✓ Integrative conjugative elements
- ✓ Resistance Islands
- ✓ Genomic Islands
- ✓ Transposable bacteriophages

Martinez et al., 2009

Mobile genetic elements (MGEs)/ Transposable elements (TEs)



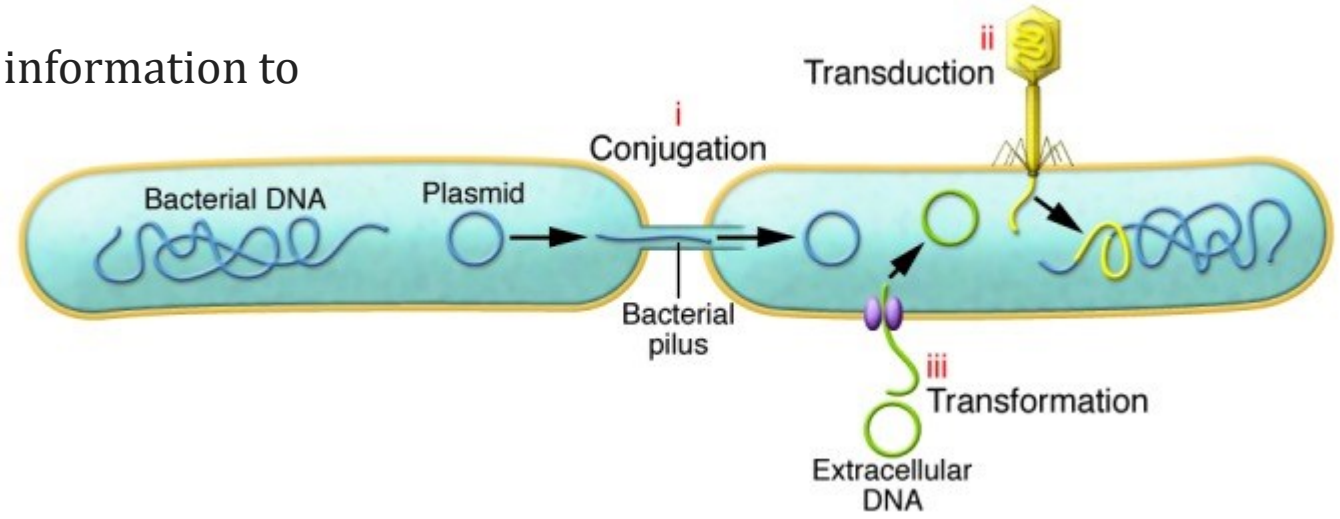
Plasmid	Transposon (jumping genes)	Integrons
It is a small circular and double-stranded form of extrachromosomal DNA ***Inc group - Enterobacteriaceae***	It is a DNA segment that can translocate within the genome	Genetic elements that contain a site-specific recombination system able to integrate, express and exchange specific DNA elements, called gene cassettes
It can replicate independently	It is not a self-replicative DNA segment	It lacks mobility-related functions on its own

Martinez et al., 2009

Mechanisms of horizontal gene transfer (HGT)

Bacteria are capable of transferring genetic information to one another using the horizontal routes

- ✓ conjugation,
- ✓ phage transduction, and
- ✓ natural transformation

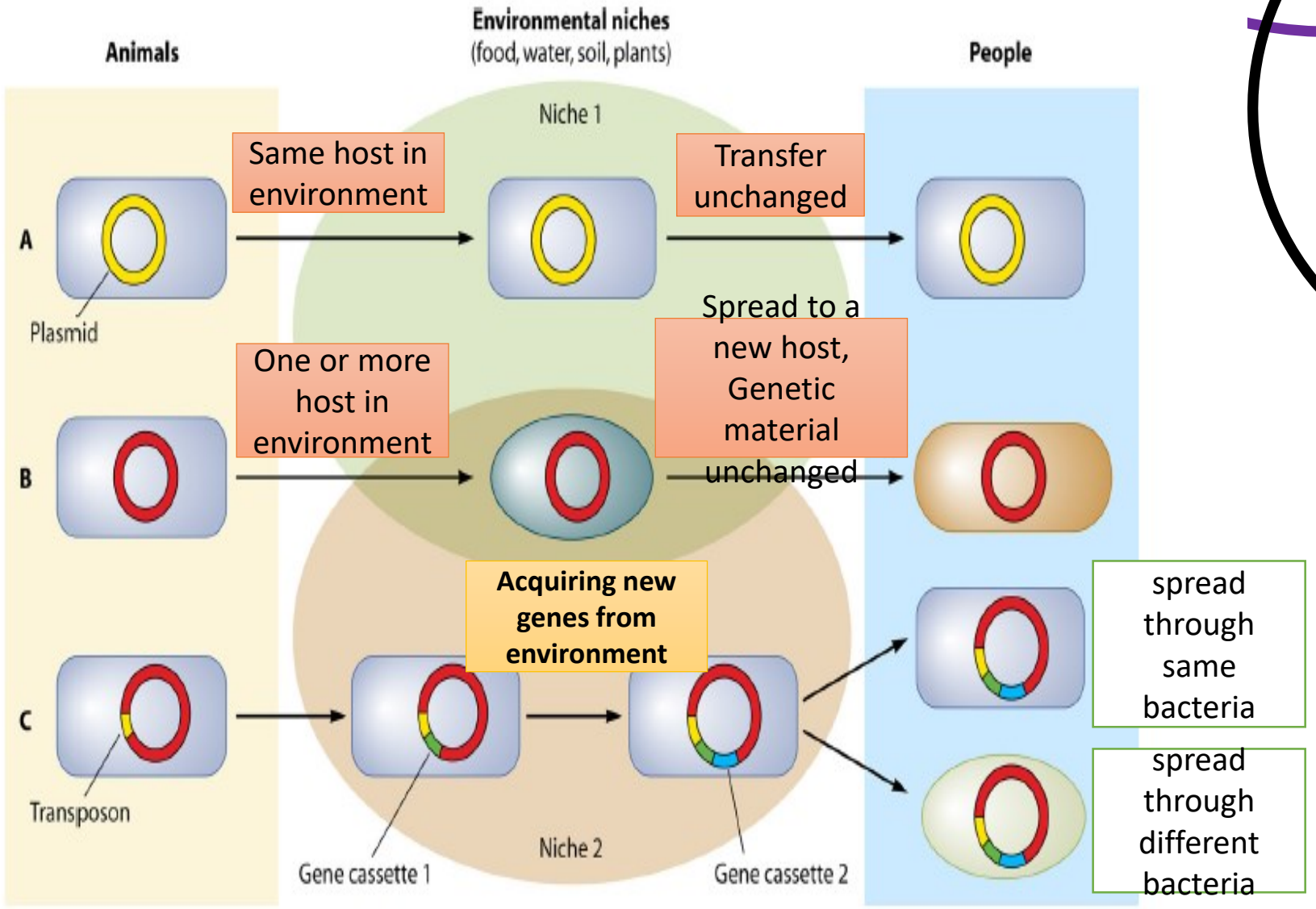


1. Donor and recipient cells are physically connected - the formation of a transient bridge (pilus)
2. DNA transfer of bacterial DNA between a donor cell and a recipient cell mediated by phages
3. Certain bacterial species can take up free DNA from the environment using membrane protein complexes

Sheetal R. Modi wt al., 2014

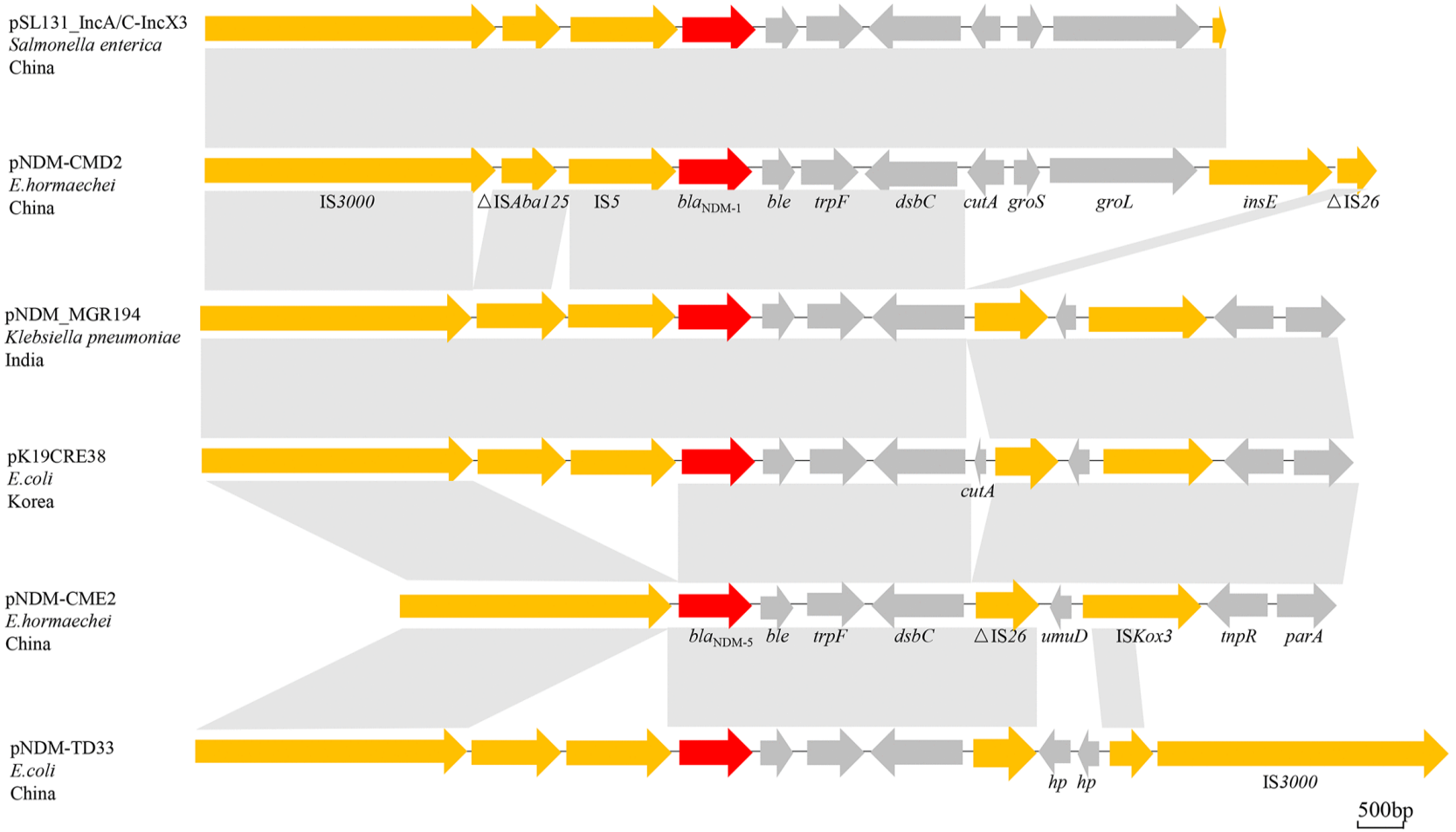
Where and how the exchange happen?

- **Different genetic backgrounds**



Marshall et al., 2011

Genetic environment of *blaNDM-1* and *blaNDM-5*



Ding et al., 2021

Beta-lactamases…The Big problem…!

	Enterobacterales		***Non Fermenters***
	E. coli	***K. pneumoniae***	***Acinetobacter spp***
Carbapenemase	Class B (MBL): **NDM** Class D: Oxa-48 like	Class A: **KPC** Class B (MBL): **NDM** Class D: **Oxa-48 like**	Class B (MBL): SPM,VIM,IMP,**NDM** Class D: **Oxa-23, 24, 51, 58**

HGT-mediated resistance mechanisms

Gram-negatives

Beta-lactamases

- ESBLs (CTX-M), Carbapenemase (NDM), AmpCs (CMY)

Aminoglycosides

- AMEs (AAD, ANT, APH), 16S RMTases (armA, rmtA)

Tetracyclines

- Tet-A,B,C

Sulfonamides, trimethoprim

- Sul1/2, Dfr

Colistin

- MCR

Gram-positives

Penicillin

- Penicillinase

Aminoglycosides

- AMEs (AAD, ANT, APH)

Glycopeptides

- Van genes (VanA-E, VanG)

Macrolides

- mefA, msrA,

Ding et al., 2021
Kakoullis et al., 2021

ACORN target pathogens

S. aureus

- Oxacillin – MSSA/MRSA
- Inducible clindamycin –R
- Aminoglycosides – R
- Macrolides – R
- Vancomycin – R

E. coli ***K. pneumoniae*** ***Acinetobacter spp***

Beta-lactams

Cephalosporins (3rd gen –ESBL, Ampc)

Carbapenems (carbapenemases-MBL, Oxa's)

Aminoglycosides (AMEs & 16S rRNA methyl transferases)

Colistin (chromosomal and plasmid-MCR)

ACORN target pathogens – What to look for?

S. aureus

- Plasmids
- SCCmec elements - mecA
- PBP mutations
- Chromosomal mutations
- Efflux pumps

E. coli

- Plasmids
- Transposons
- Integrons
- ICEs

- Chromosomal mutations

K. pneumoniae

- Plasmids
- Transposons
- Integrons
- ICEs

- Chromosomal mutations
- Porins

Acinetobacter spp

- Genomic Islands/
- Resistance Islands
- Plasmids
- Transposons
- Integrons
- ICEs

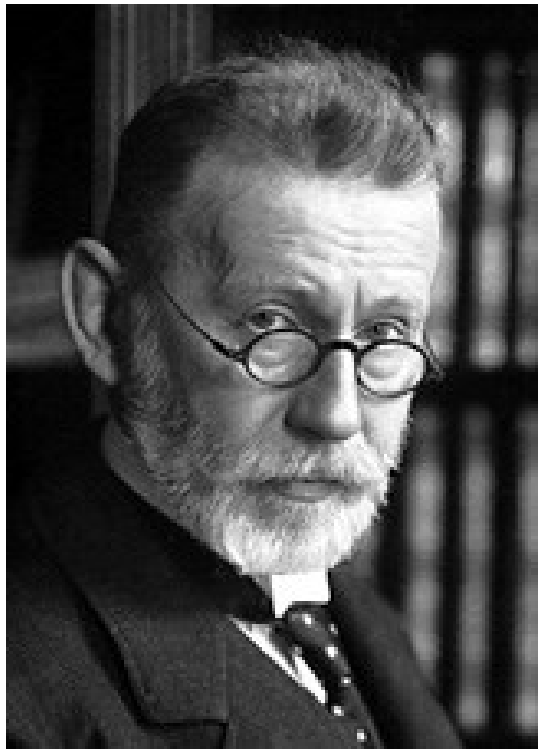
- Chromosomal mutations
- Porins
- Efflux pumps

Extrachromosomal
Chromosomal

Key Message – AMR acquisition

- ✓ Antibiotic spectrum – Gram negative vs. Gram positive
- ✓ Antibiotic selection pressure – select out resistant population
- ✓ Type of resistance – against a specific antibiotic (beta-lactams: beta-lactamases, PBP mutations, porins, efflux)
- ✓ Beware of the intrinsic resistance mechanisms – target pathogen being analyzed (internal QC)
- ✓ AMR mechanisms – diverse; however, pathogen specific
- ✓ Drivers of AMR – Role of MGEs – plasmids, transposons, IS elements, resistance/genome islands, ICEs, etc., - differs with each pathogen based on the genomic characteristics - One size doesn't fit all.
- ✓ Not all organisms can acquire MGEs – resistance mechanisms in place to overcome the burden of maintaining the acquired plasmid

Every organism is a different personality…!
Know your organism – to analyze them…!



Thank you…!!!

"Drug resistance follows the drug like a faithful shadow"

- Paul Erhlich (1854-1915)