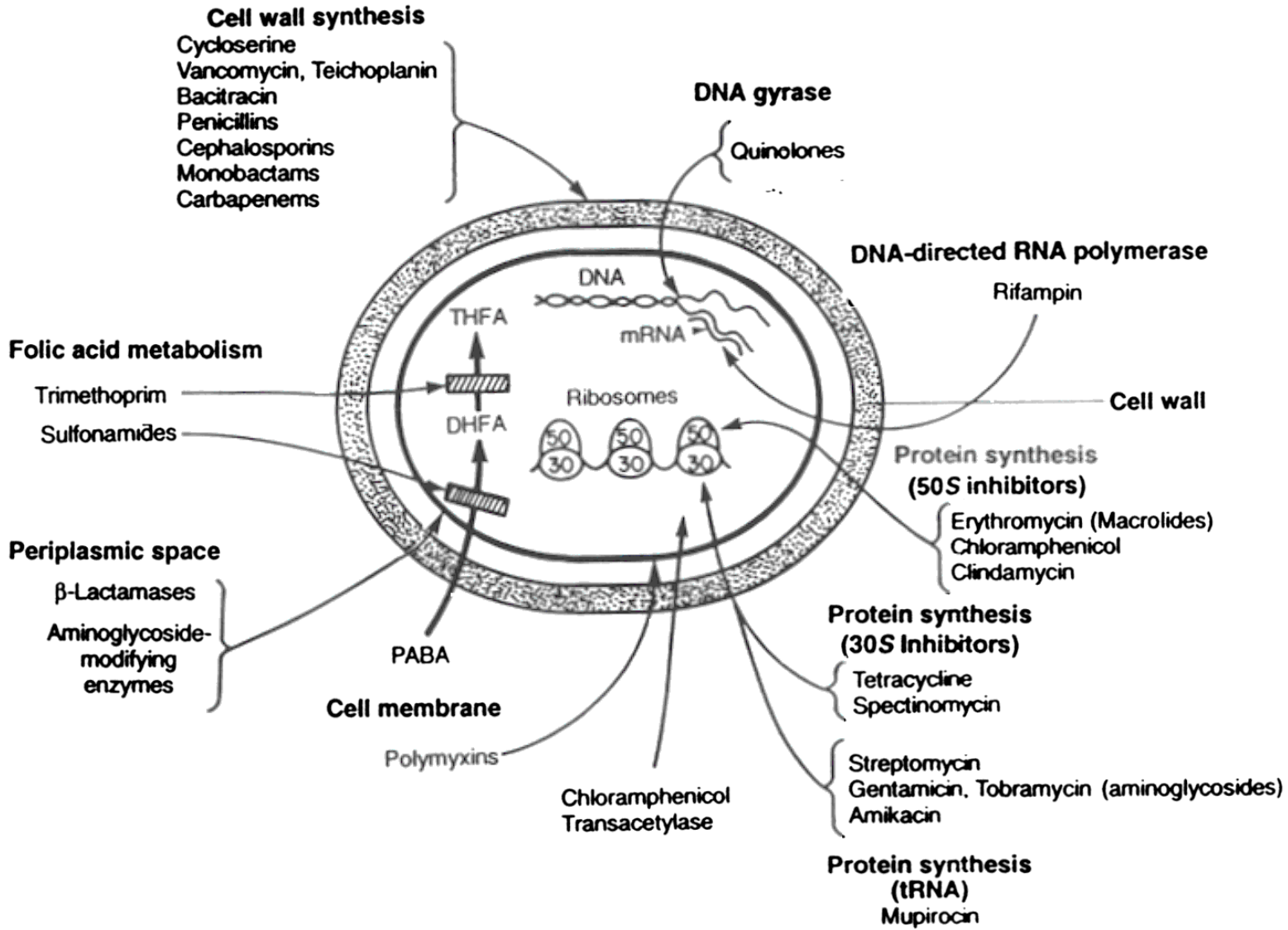


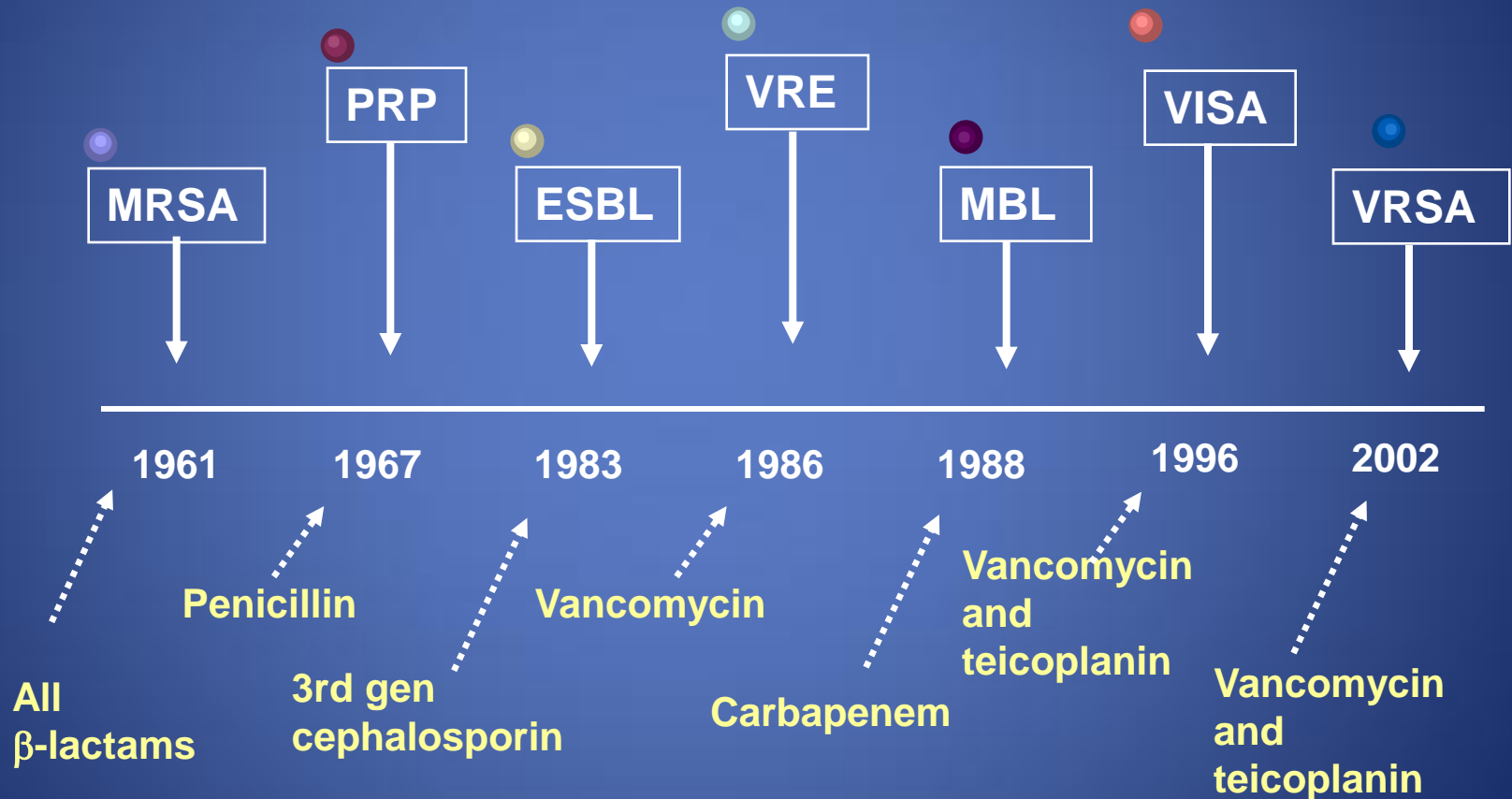
Antibiotic Resistance: Causes, Consequences & Local Scene



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Antibiotic Resistance – A Global Problem



Driving force for antibiotic resistance

- Inadequate national commitment to a comprehensive and coordinated response, ill-defined accountability and insufficient engagement of communities;
- Weak or absent surveillance and monitoring systems;
- Inadequate systems to ensure quality and uninterrupted supply of medicines;
- Inappropriate and irrational use of medicines, including in animal husbandry;
- Poor infection prevention and control practices;
- Depleted arsenals of diagnostics, medicines and vaccines as well as insufficient research and development on new products.

Resistance to antibacterial agents

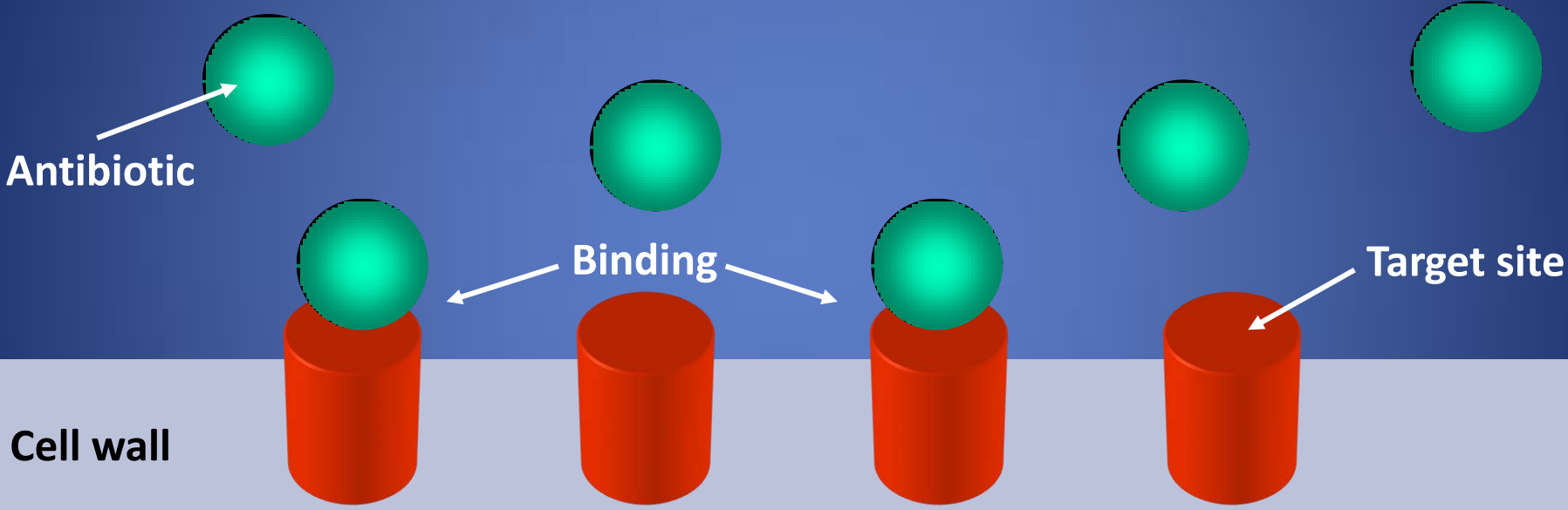
- Antibiotic resistance either arises as a result of innate consequences or is acquired from other sources
- Bacteria acquire resistance by:
 - mutation: spontaneous single or multiple changes in bacterial DNA
 - addition of new DNA: usually via plasmids, which can transfer genes from one bacterium to another
 - transposons: short, specialised sequences of DNA that can insert into plasmids or bacterial chromosomes

Mechanisms of antibacterial resistance (1)

- Structurally modified antibiotic target site, resulting in:
 - reduced antibiotic binding
 - formation of a new metabolic pathway preventing metabolism of the antibiotic

Structurally modified antibiotic target site

Antibiotics normally bind to specific binding proteins on the bacterial cell surface

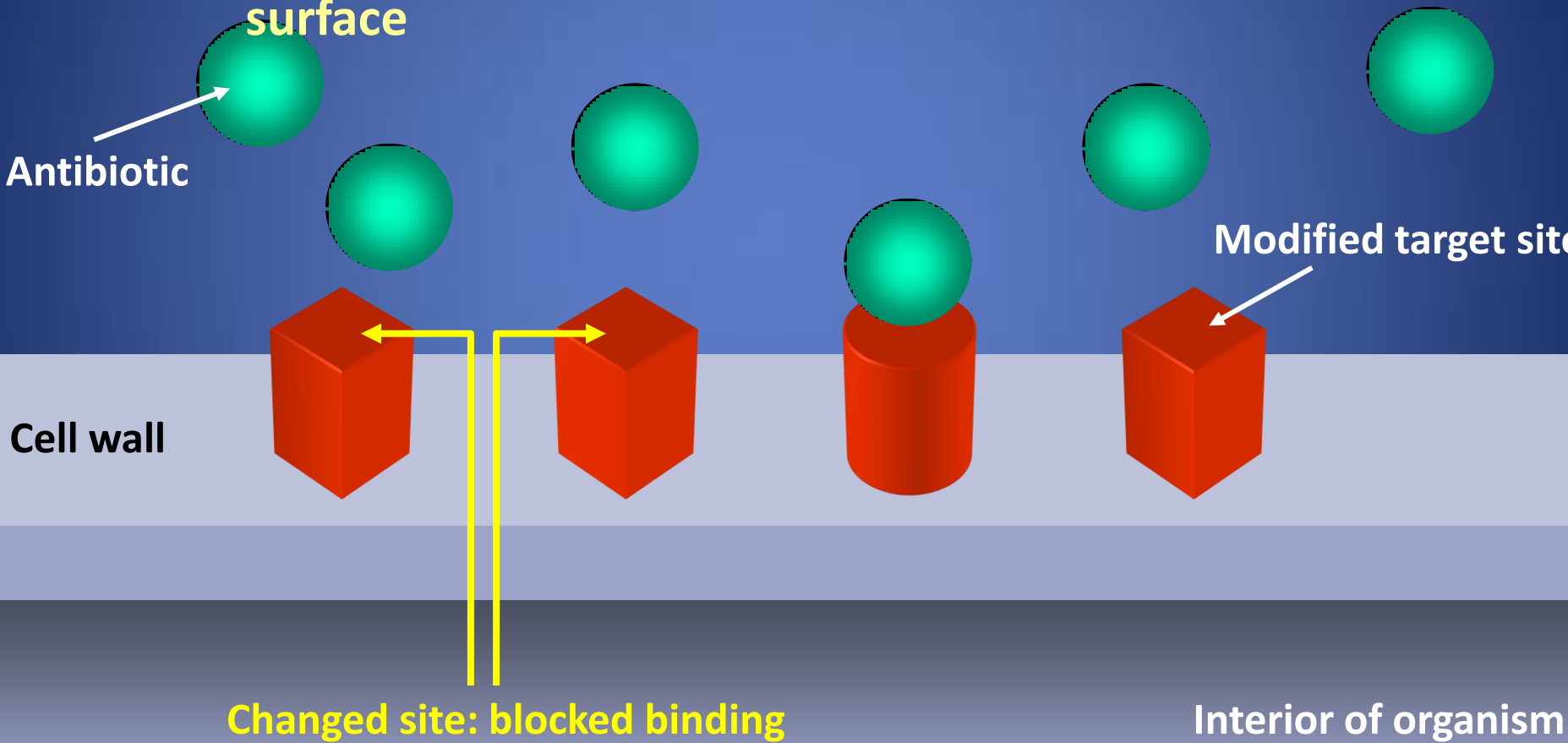


Cell wall

Interior of organism

Structurally modified antibiotic target site

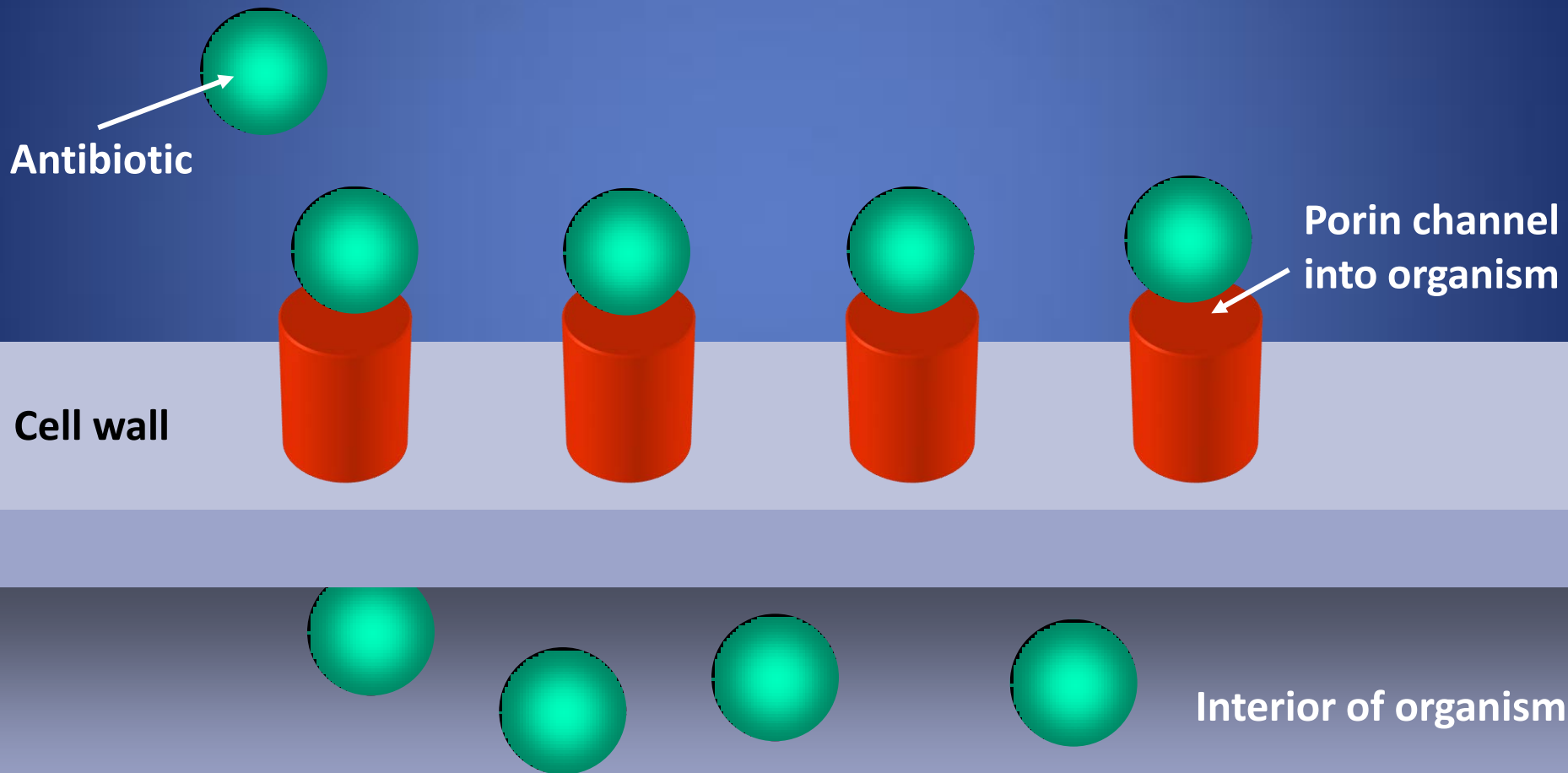
Antibiotics are no longer able to bind to modified binding proteins on the bacterial cell surface



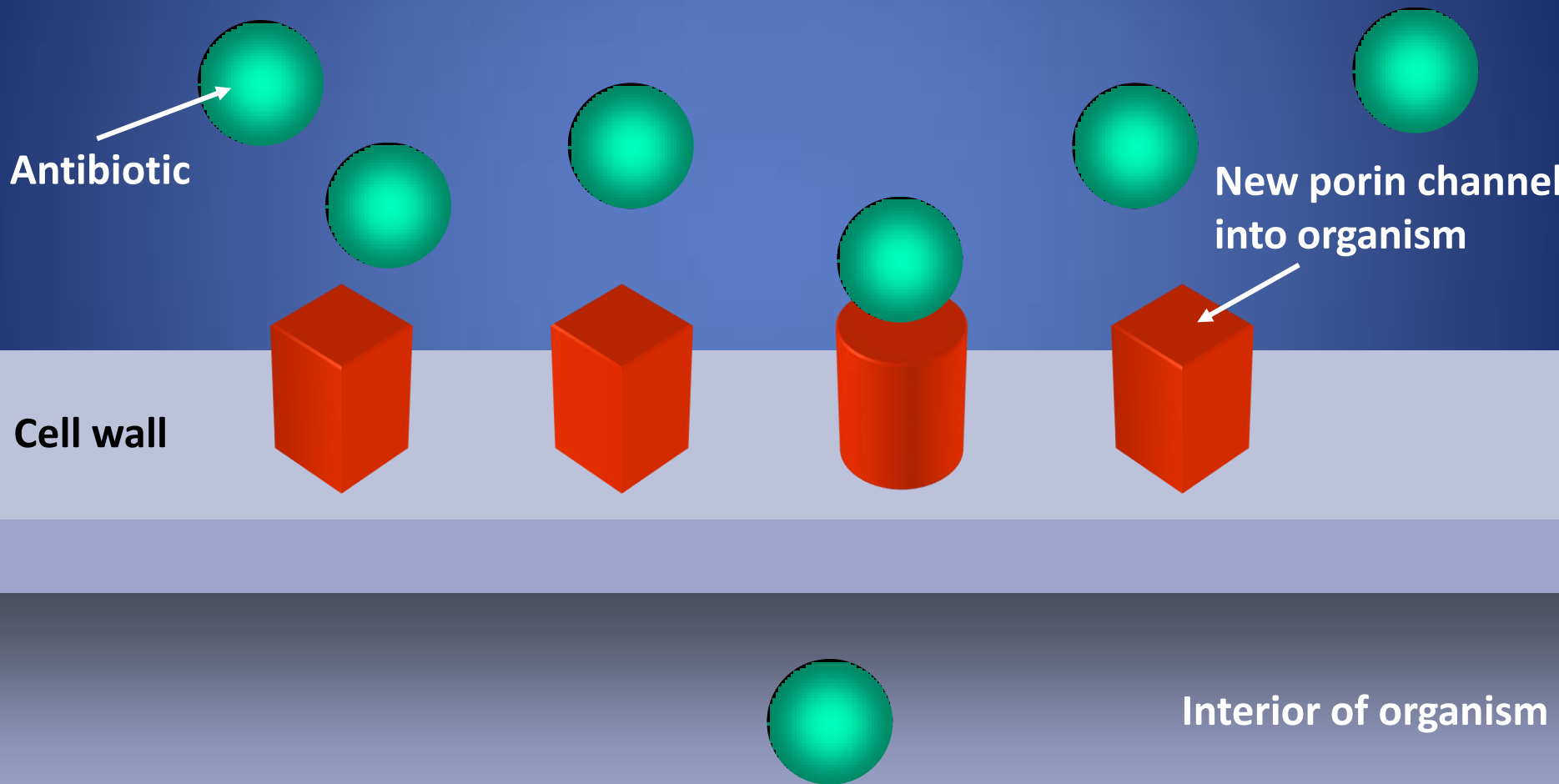
Mechanisms of antibacterial resistance (2)

- Altered uptake of antibiotics, resulting in:
 - decreased permeability
 - increased efflux

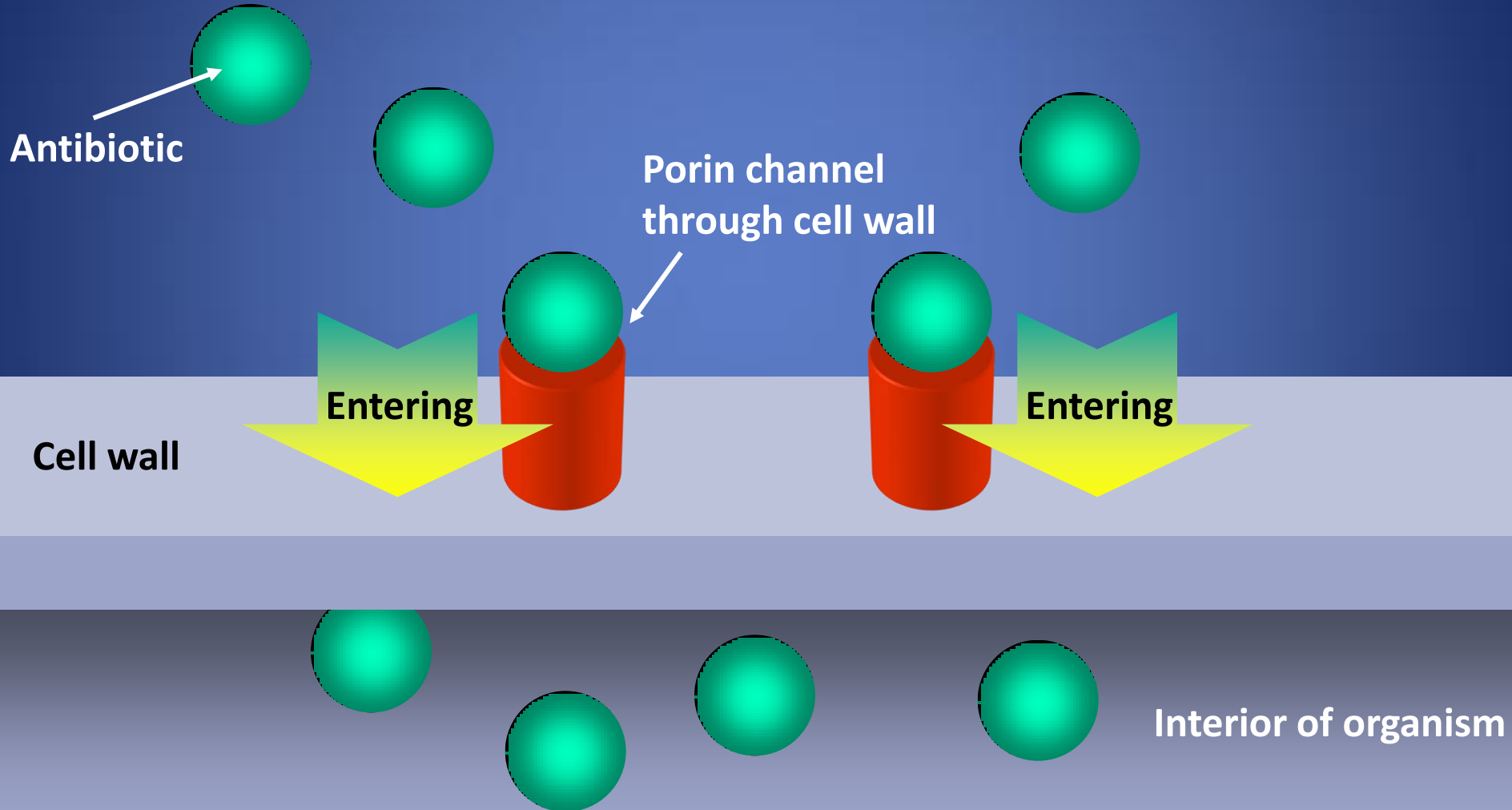
Altered uptake of antibiotics: decreased permeability



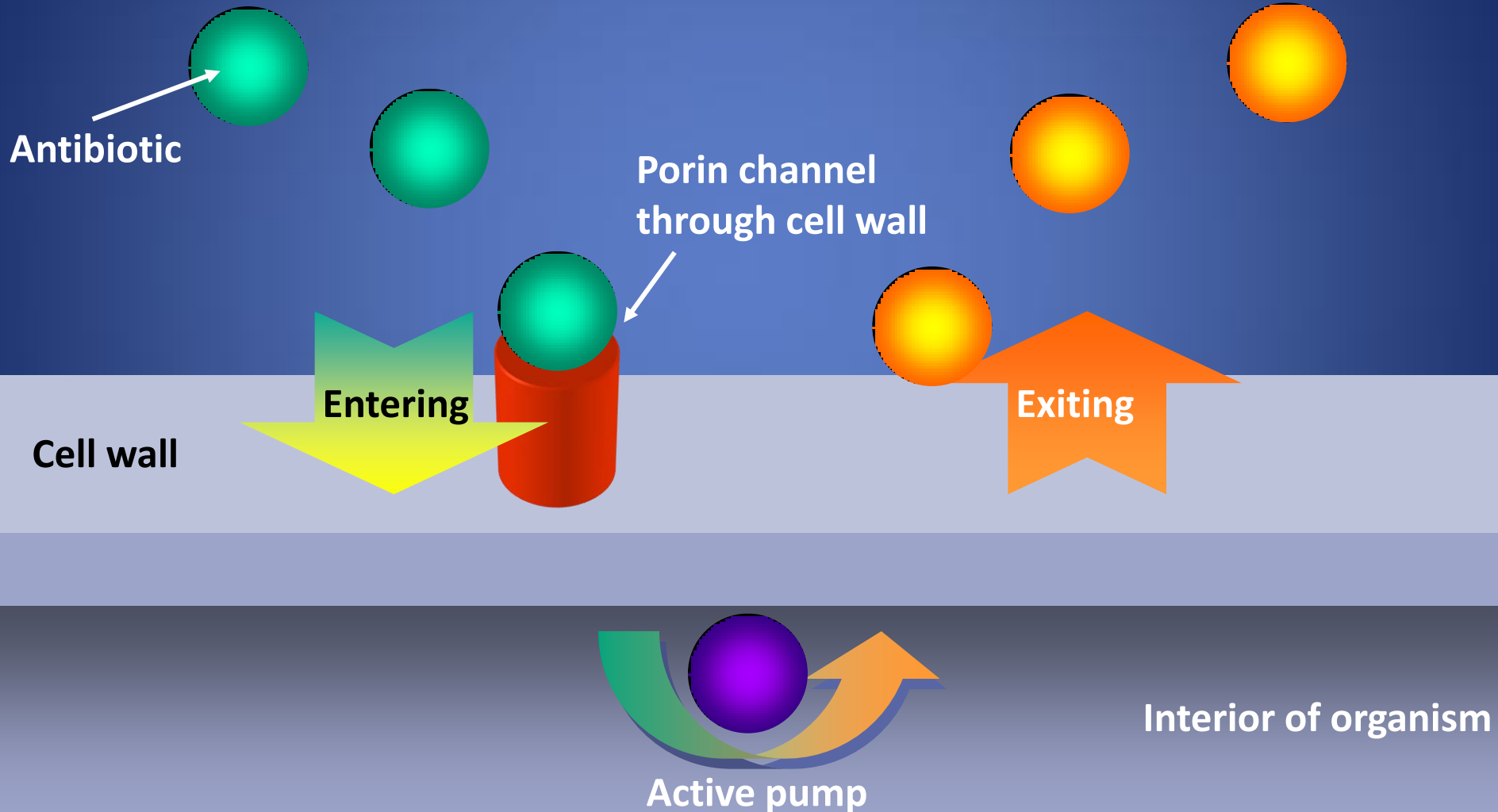
Altered uptake of antibiotics: decreased permeability



Altered uptake of antibiotics: increased efflux



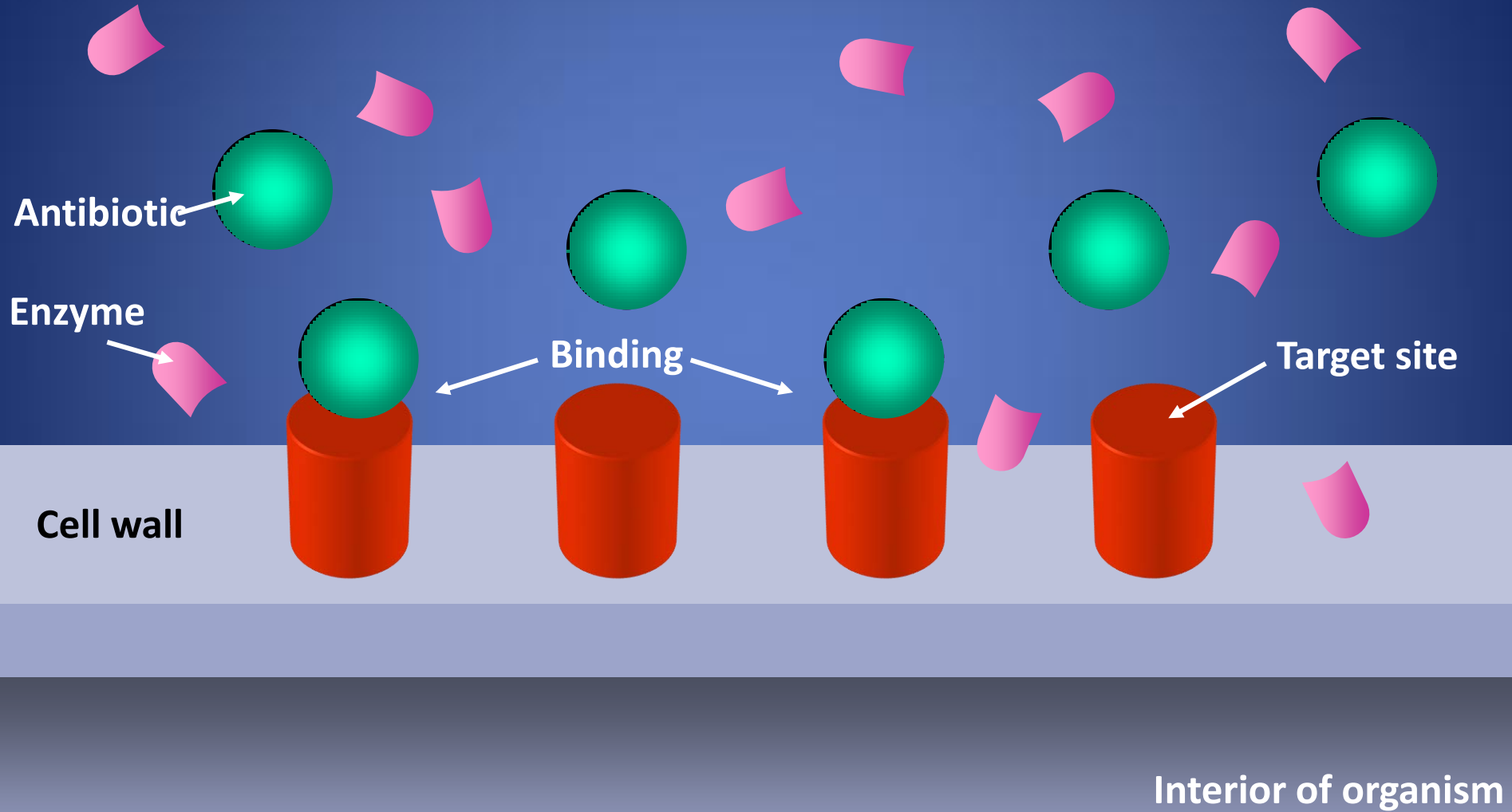
Altered uptake of antibiotics: increased efflux



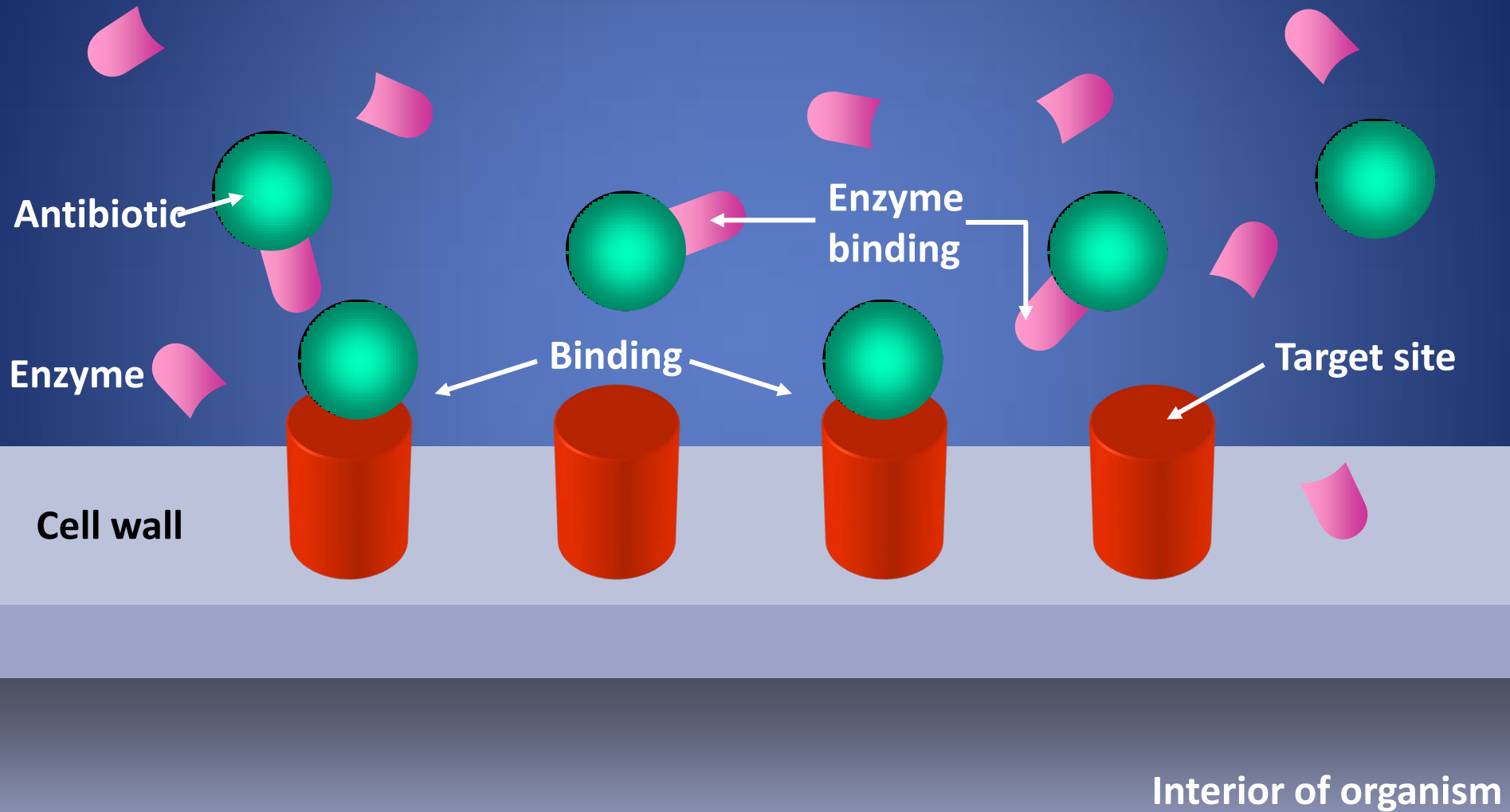
Mechanisms of antibacterial resistance (3)

- Antibiotic inactivation
 - bacteria acquire genes encoding enzymes that inactivate antibiotics
- Examples include:
 - β -lactamases
 - aminoglycoside-modifying enzymes
 - chloramphenicol acetyl transferase

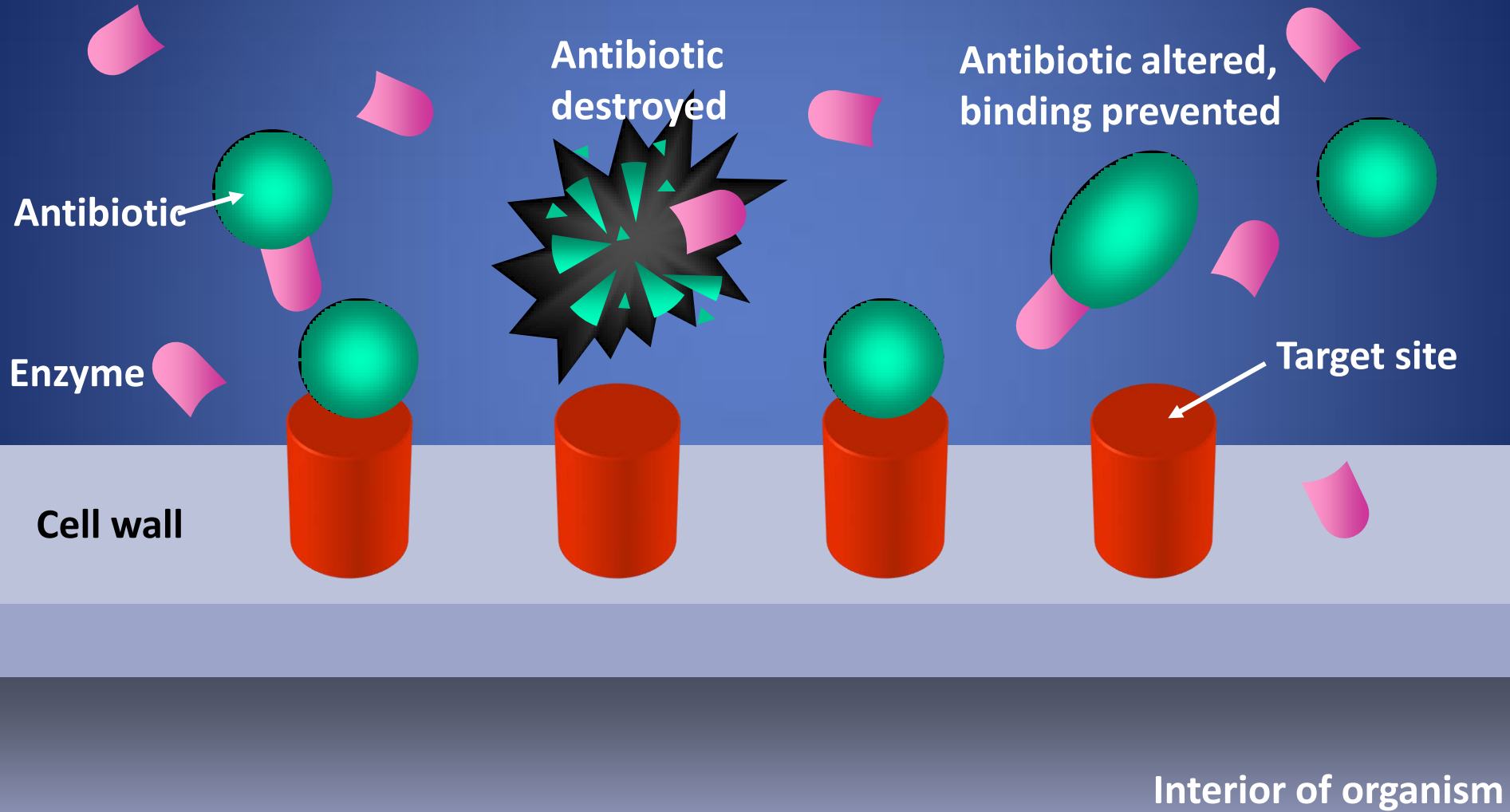
Antibiotic inactivation



Antibiotic inactivation



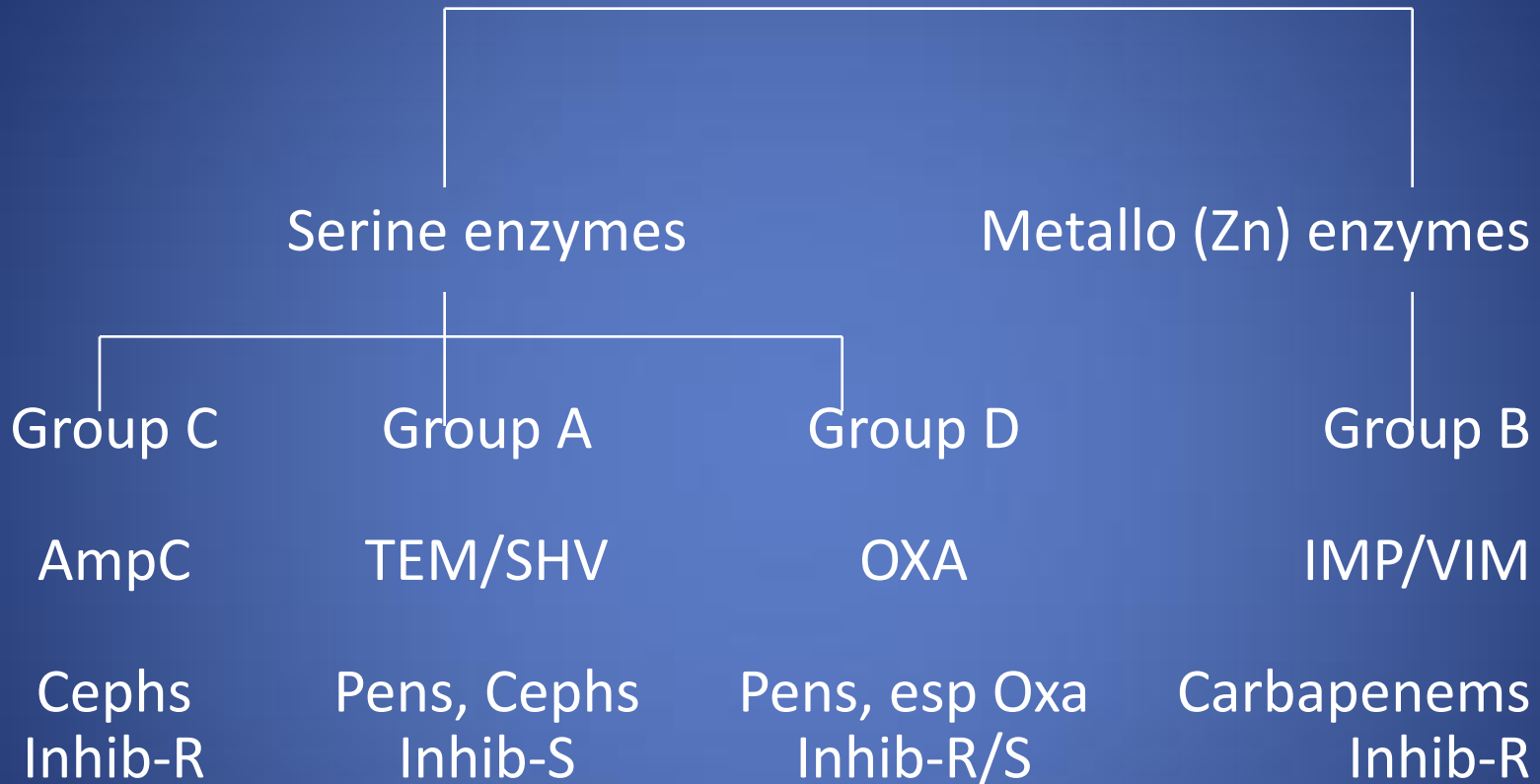
Antibiotic inactivation



Major classes of antibiotics & resistance mechanisms

Antibiotic	Mechanism of action	Major resistance mechanisms
β -Lactams	Inactivate PBPs (peptidoglycan synthesis)	<ul style="list-style-type: none">• β-lactamases• Low affinity PBPs• Efflux pumps
Glycopeptides	Bind to precursor of peptidoglycan	<ul style="list-style-type: none">• Modification of precursor
Aminoglycosides	Inhibit protein synthesis (bind to 30S subunit)	<ul style="list-style-type: none">• Modifying enzymes (add adenylyl or Phosphate)
Macrolides	Inhibit protein synthesis (bind to 50S subunit)	<ul style="list-style-type: none">• Methylation of rRNA• Efflux pumps
(Fluoro)Quinolones	Inhibit topoisomerases (DNA synthesis)	<ul style="list-style-type: none">• Altered target enzyme• Efflux pumps

β -Lactamases: Classification



Modified Bush–Jacoby–Medeiros Classification of β –Lactamases

Functional Group	Substrate profile	Molecular Class	Inhibitor	Example
1	Cephalosporinase	C	Oxa	AmpC, MIR-1
2a	Penicillinase	A	Clav.	<i>S.aureus</i>
2b	Broad spectrum	A	Clav.	TEM-1/2, SHV-1
2be	Extended spectrum	A	Clav.	TEM 3-29, TEM46-104 SHV2-28, CTX-M types
2br	Inhibition resistant	A	-	TEM 30-41 (IRT1-12)
2c	Carbenicillinase	A	Clav.	PSE-1
2d	Oxacillinase	D	(Clav.)	OXA-1 (OXA-2 &-10 derived ESBL)
2e	Cephalosporinase	A	Clav.	FPM-1 <i>P. vulgaris</i> , CepA <i>B. fragilis</i> .
2f	Carbapenemase	A	Clav.	IMI-1, Nmca, Sme 1-3
3	Metallo-enzyme	B	-	<i>S.maltophilia</i>
4	Penicillinase	-	-	<i>B.cepacia</i>

Antimicrobial features of ESBLs

- Inhibited by β -lactamase inhibitors
- Usually confer resistance to:
 - first-, second- and third-generation cephalosporins (eg ceftazidime)
 - monobactams (eg aztreonam)
 - carboxypenicillins (eg carbenicillin)
- Varied susceptibility to piperacillin/tazobactam
- Typically susceptible to carbapenems
- Often clinically and/or microbiologically non-susceptible to fourth-generation cephalosporins

Antimicrobial features of carbapenem resistance

- Natural resistance is chromosomally mediated
 - naturally occurring carbapenemases
- Acquired resistance is plasmid-mediated, involving various mechanisms
 - most commonly by carbapenemases (especially in Gram-negative bacteria)
 - reduced affinity of target PBPs
 - decreased membrane permeability (Gram-negative bacteria)
 - active efflux pumps
- Mechanisms can co-exist and vary by pathogen

Antimicrobial features of carbapenem resistance: carbapenemases

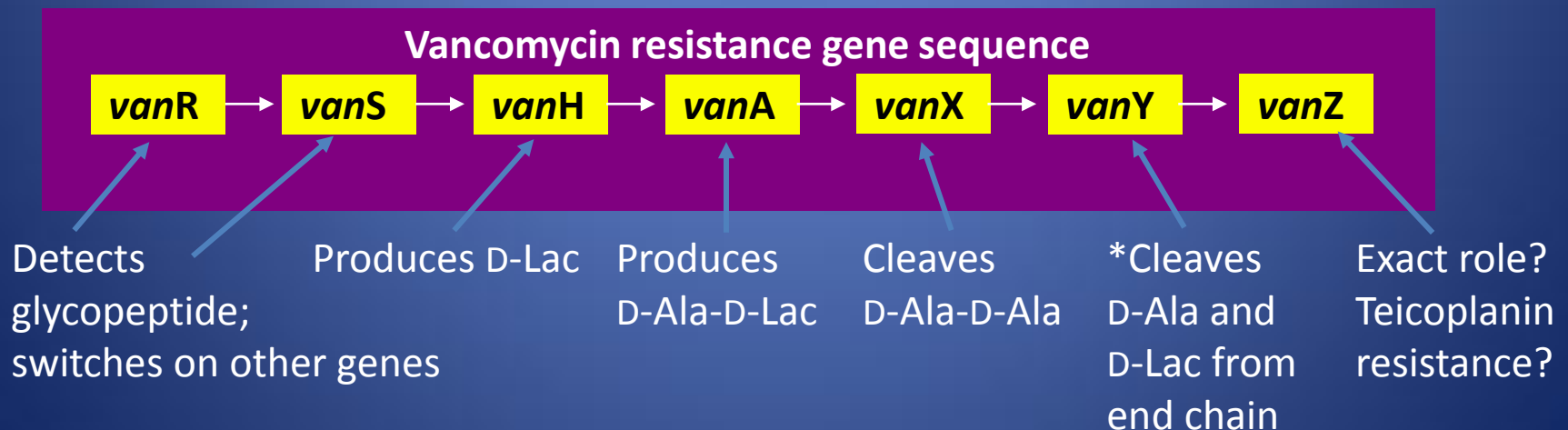
- Carbapenemases are a major source of acquired resistance in Gram-negative bacteria
- Belong to three different molecular classes of β -lactamases:
 - class B metallo-enzymes (eg IMP, VIM, NDM-1)
 - class D oxacillinases (OXA-23 to OXA-27)
 - class A clavulanic acid-inhibited enzymes (eg SME, NMC, IMI, KPC)

Antimicrobial features of MRSA

- Mechanism involves altered target site
 - new penicillin-binding protein — PBP 2' (PBP 2a)
 - encoded by chromosomally located *mecA* gene
- Confers resistance to all β -lactams
- Cross-resistance common with many other antibiotics
- Gene carried on a mobile genetic element — staphylococcal cassette chromosome *mec* (SCC*mec*)

Antimicrobial features of VRE

- Development is slow due to very complex gene mechanisms:
 - Alters pentapeptide precursor end sequence from D-alanyl-D-alanine to D-alanyl-D-x, where x is lactate, serine or other amino acid
 - Or produces (*vanY*) tetrapeptide that cannot bind vancomycin



Antimicrobial features of VISA

- Mechanism not fully understood, but a combination of:
 - increased quantities of PBPs causing extracellular trapping
 - altered cell wall proteins reducing permeability

Antimicrobial features of VRSA

- Mechanism due to acquisition by conjugative process of *vanA* from enterococci

MDRO situations in HA hospitals 2009 - 2010

Incidence	MRSA BSI	VRSA	VRE	ESBL+ NR	CRE/ CRE PCR +ve	CRA/ MDRA	CRPA/ MRPA
2009	0.17 /1000 acute bed days	No	0.2% Sporadic outbreaks in hospitals	20-25%	0.05 to 0.07% / NA	39% MDRA= 2.6 to 4%	4.75% MRPA= 0.1%
2010	0.15 / 1000 acute bed days	No	0.4% (3 outbreaks involved 28 patients)	20-25%	0.19% / 13 cases	? MDRA= 2.1%	4.62% MRPA= 0.1%
Trend	Decreasing (12%↓cf 2009; 21%↓ cf 2007)	No	Slightly increasing	stable	Low but increasing	MDRA: Slightly decreasing	stable

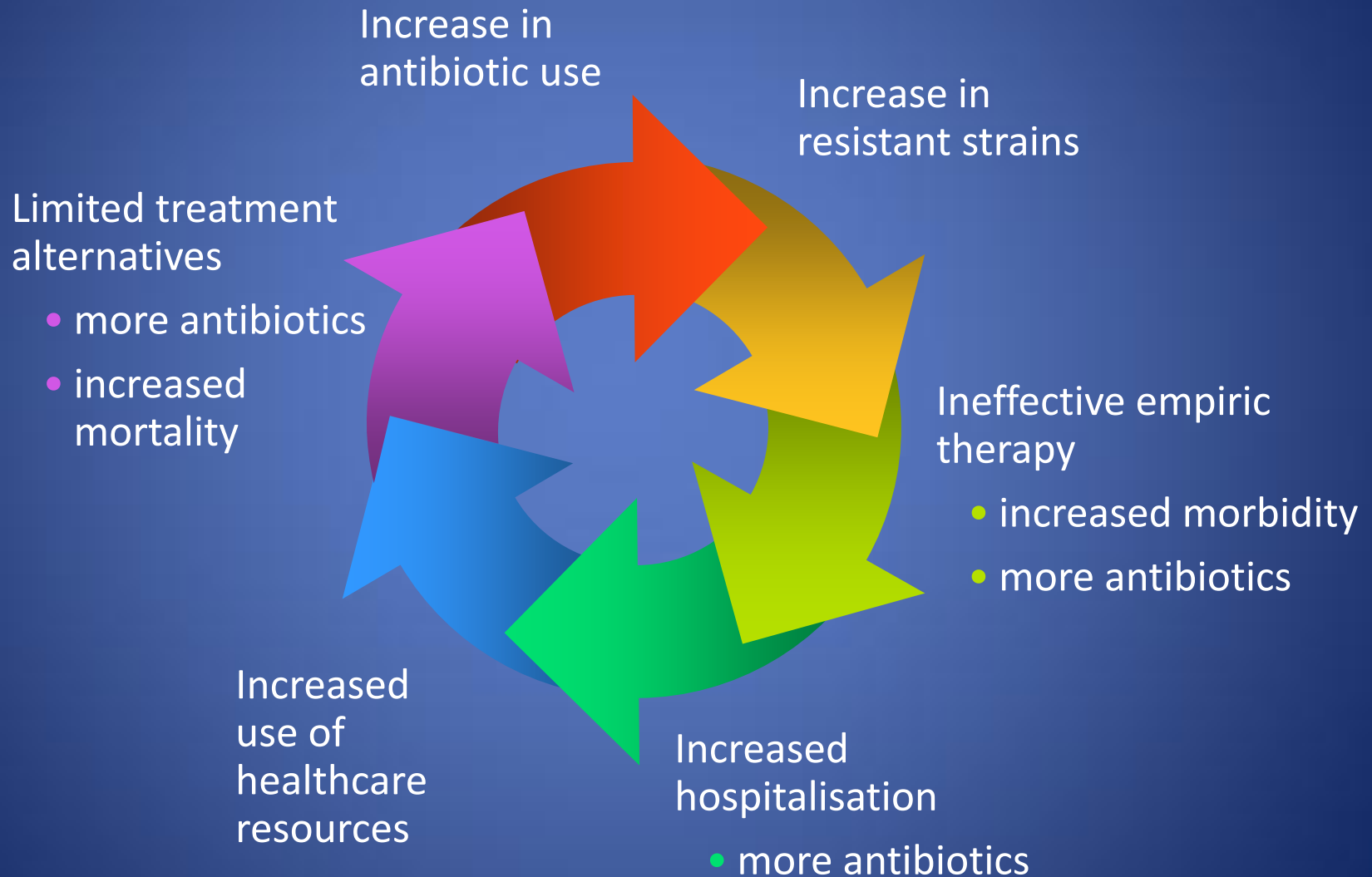
MRPA=concomitant R to Imipenem, Ceftazidime, Amikacin and Ciprofloxacin

MDRA= concomitant R to Fluoroquinolones, Aminoglycosides, Cephalosporins and BL/BLase inhibitor combinations

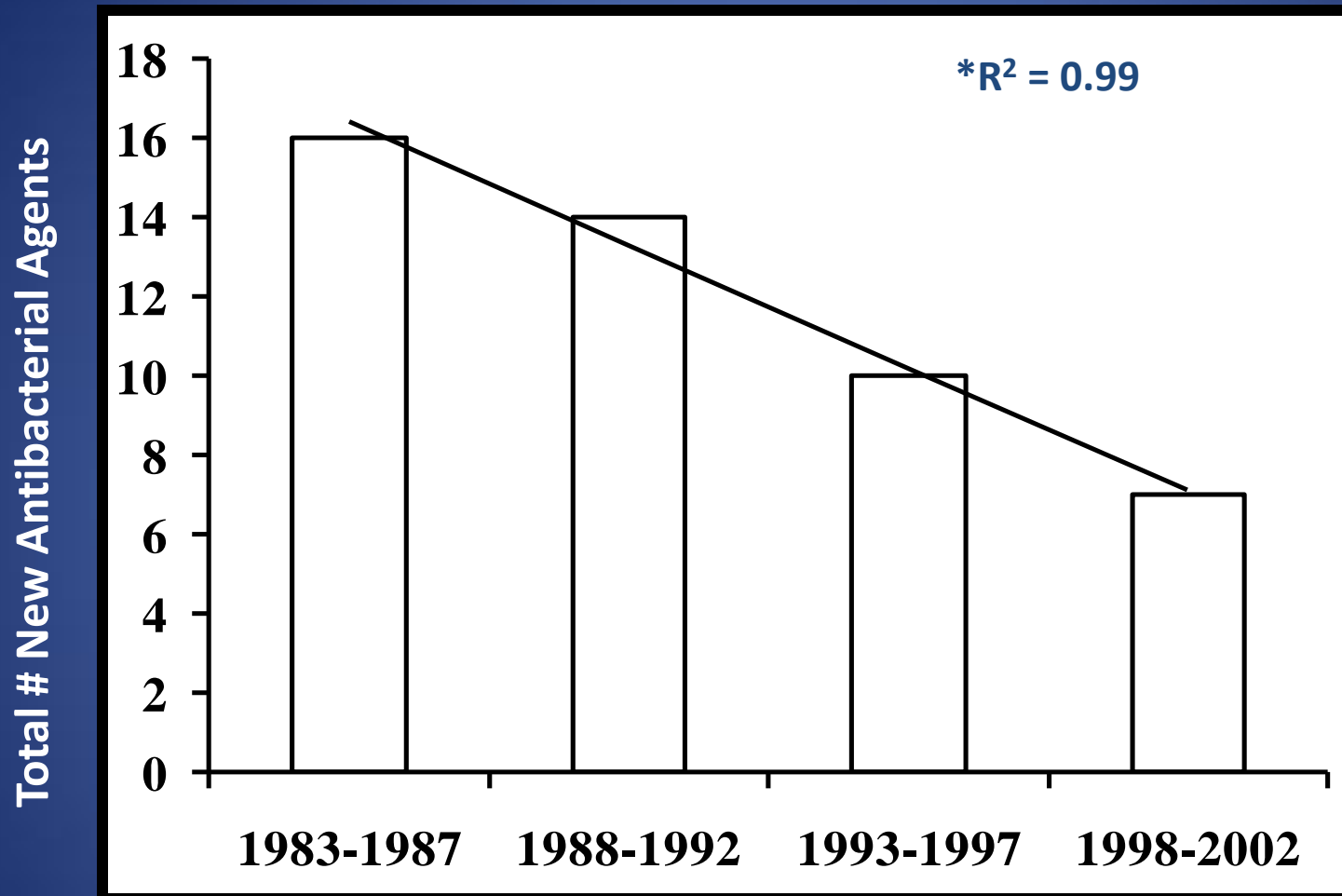
- ***Streptococcus pneumoniae***:
 - Penicillin intermediate susceptibility or resistance
Ip et al JCM 1999
 - Widespread macrolide resistance
Ip M et al. AAC 2001
 - Emerging fluoroquinolone resistance
Ho PL et al. JAC 2000
Ho PL et al. EID 2001
- ***Enterobacteriaceae***:
 - Up to 20% of *E. coli* and 9% of *Klebsiella* spp. from urine specimens at out-patient settings are ESBL producers
Data from PHLSB, CHP
- ***Neisseria gonorrhoeae***:
 - Established fluoroquinolone resistance
Kam KM et al. STD 1996
 - Emerging ceftibuten resistance
Lo JY et al. AAC 2008
- **TB**:
 - Annual rate ~ 90/100000 population
 - MDR-TB ~ 1%
 - XDR-TB ~ 0.1%

- TB:
 - Annual rate $\sim 90/100000$ population
 - MDR-TB $\sim 1\%$
 - XDR-TB $\sim 0.1\%$

Antibiotic use, resistance, treatment failure and healthcare burden: a vicious circle



Trends in Development of New Antibacterials



* $p = 0.007$ by linear regression

New antibacterial agent \equiv new molecular entity (NME) with antimicrobial properties, administered for systemic infection; topical agents, immunomodulators excluded

BAD BUGS, NO DRUGS

As Antibiotic Discovery Stagnates ...
A Public Health Crisis Brews



 **IDS**
Infectious Diseases Society of America

July 2004



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2



**Bad Bugs
Need Drugs**

10x '20

Ten new ANTIBIOTICS by 2020