Antibiotic Resistance: Causes, Consequences & Local Scene

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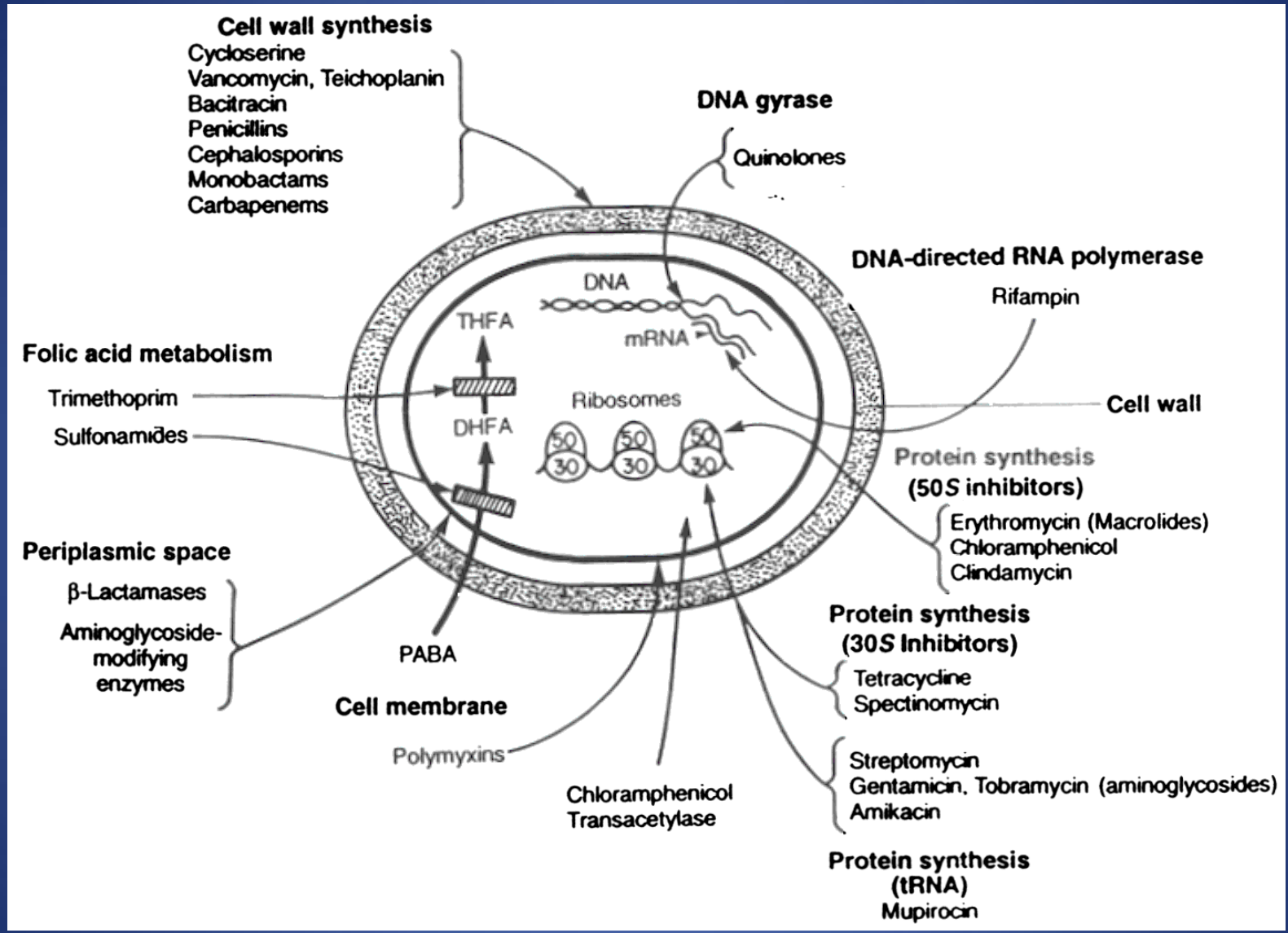
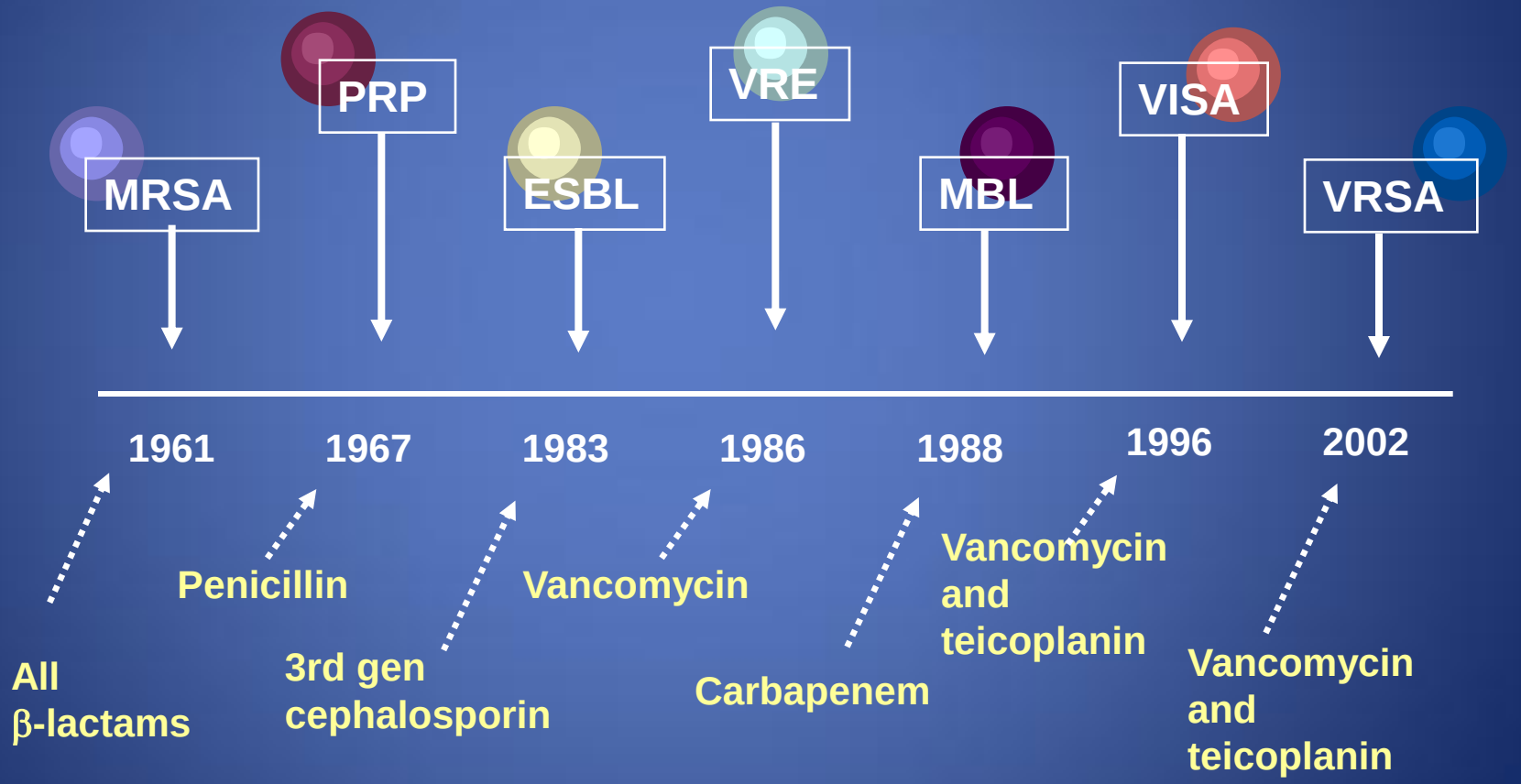


Neu HC. Science 1992; 257:1064-73

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.

WHO factsheet on Antimicrobial resistance

Resistance to antibacterial agents

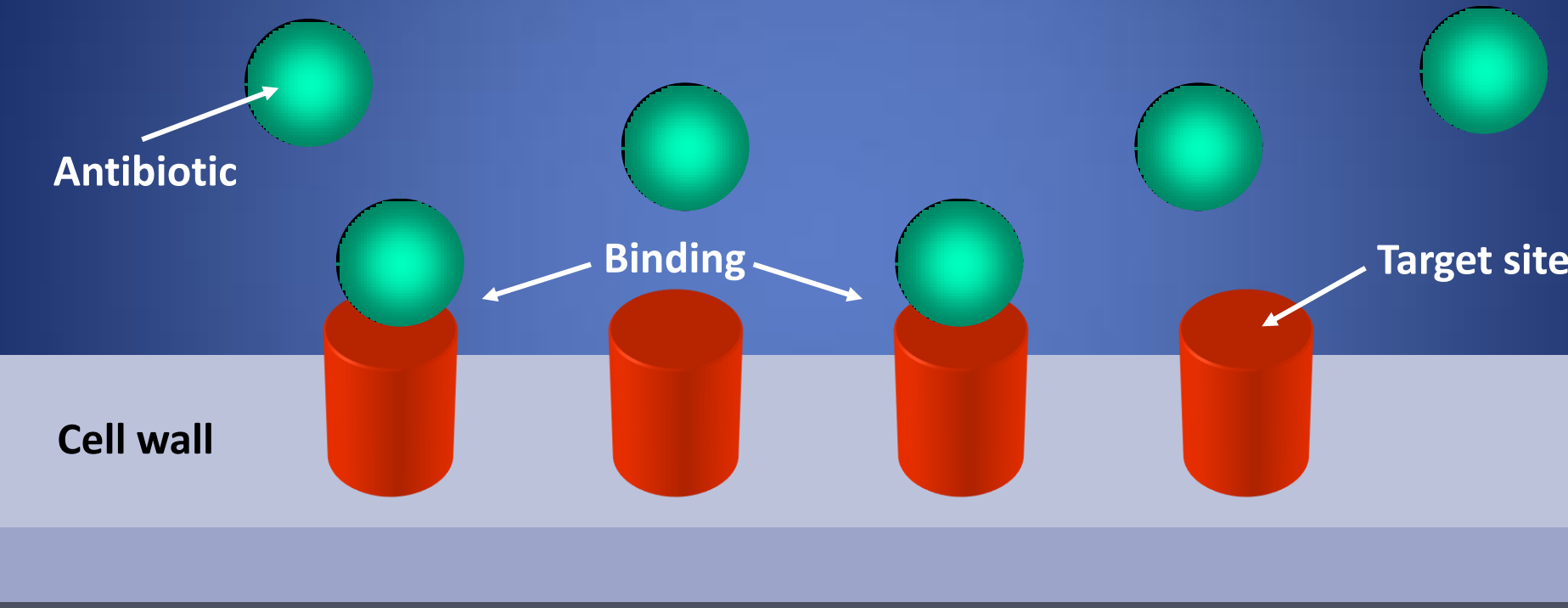
- Antibiotic resistance either arises as a result of innate consequences or is acquired from other sources
- Bacteria acquire resistance by:
  - mutation: spontaneous single or multiple changes in bacterial DNA
  - addition of new DNA: usually via plasmids, which can transfer genes from one bacterium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

Mechanisms of antibacterial resistance (1)

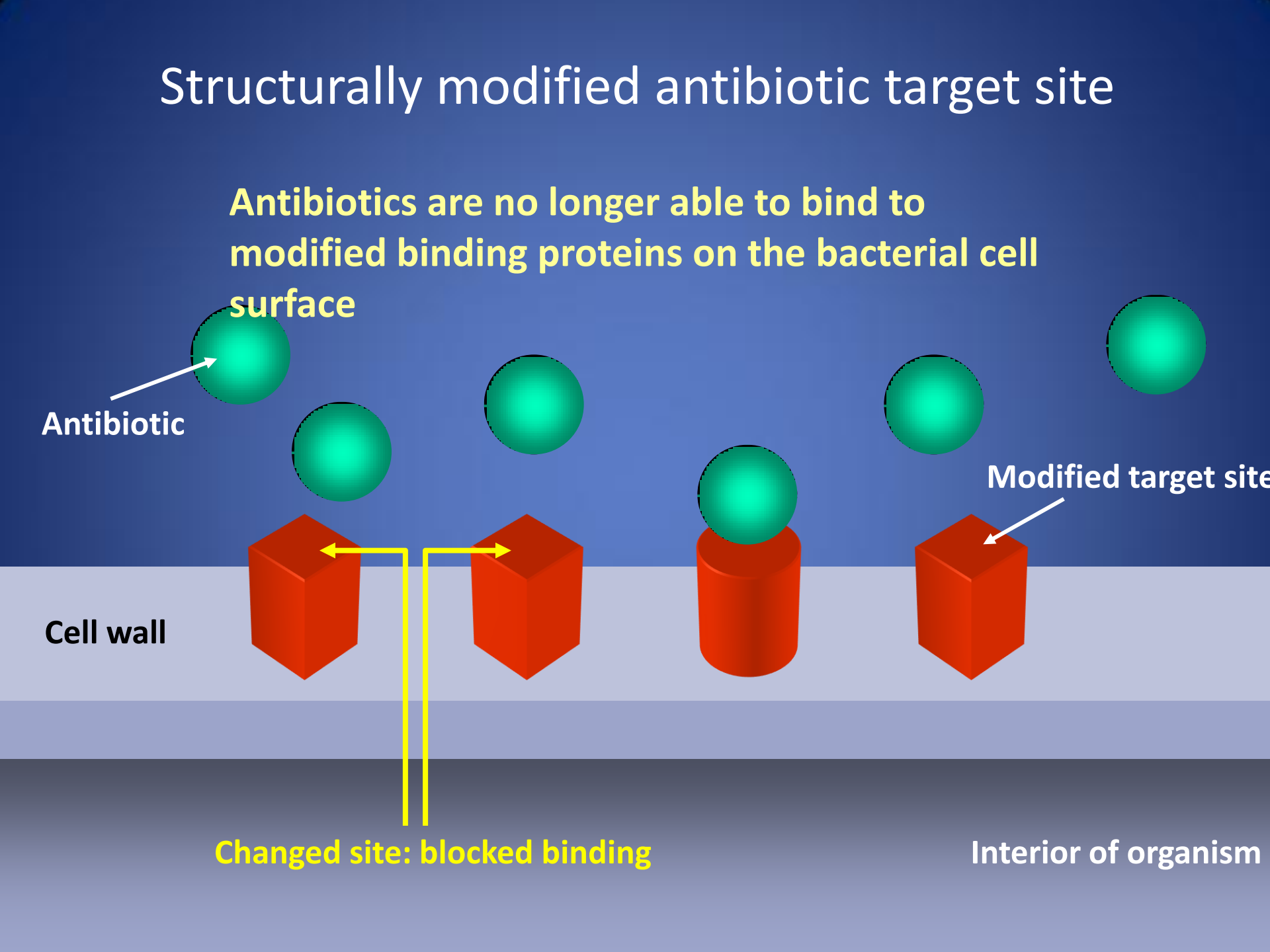
- Structurally modified antibiotic target site, resulting in:
  - reduced antibiotic binding
  - formation of a new metabolic pathway preventing metabolism of the antibiotic

Structurally modified antibiotic target site

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



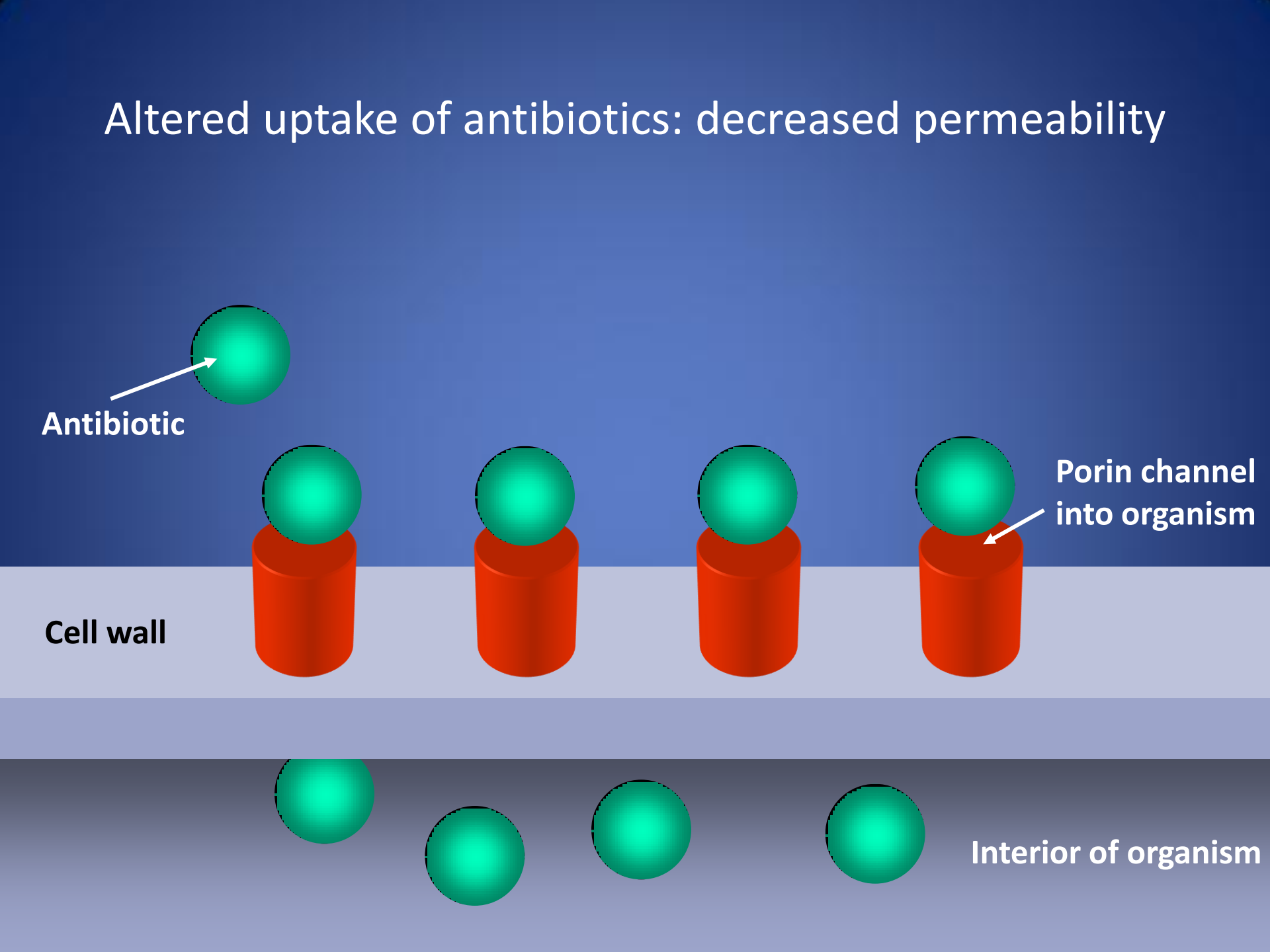
Structurally modified antibiotic target site



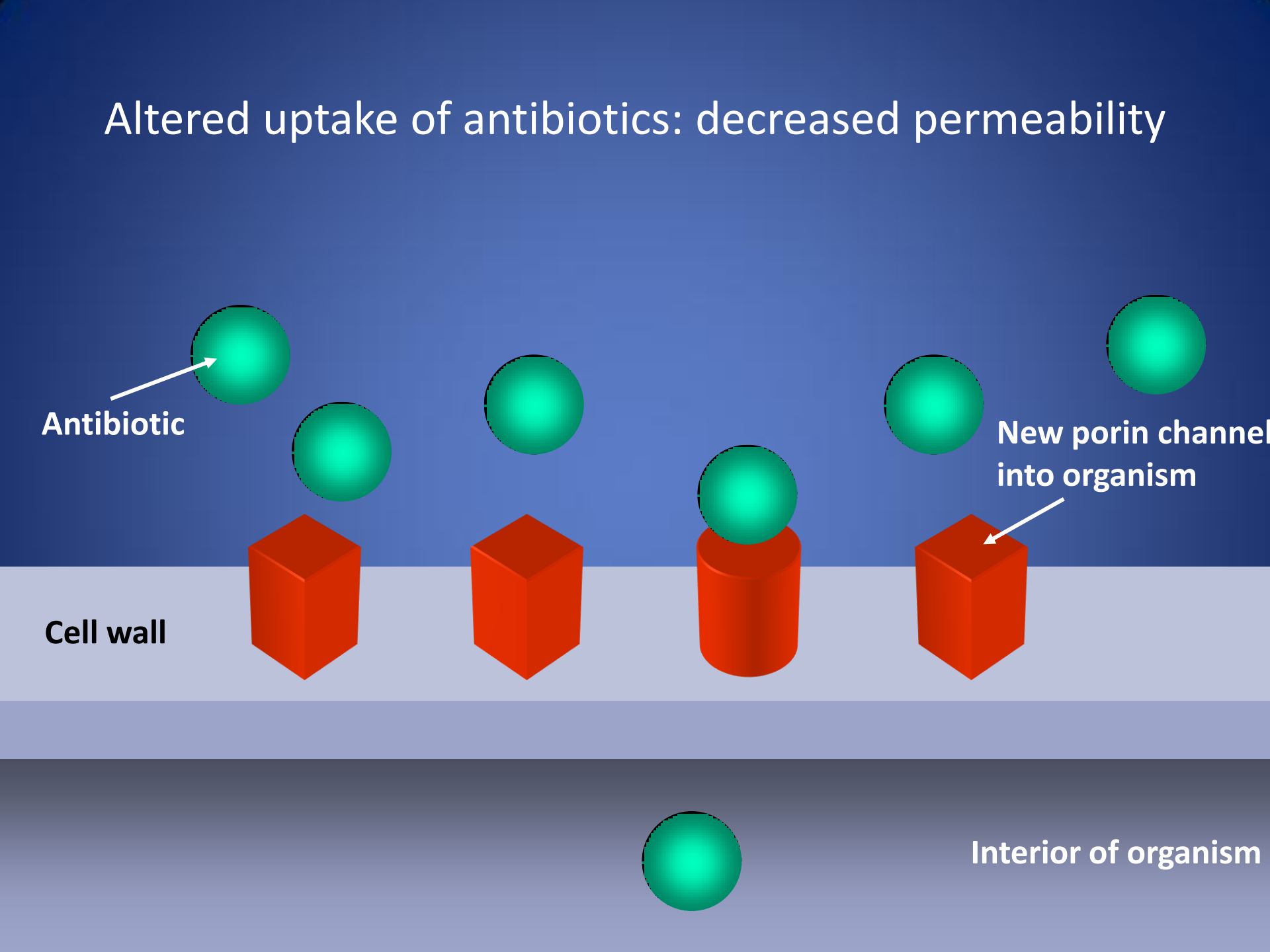
Mechanisms of antibacterial resistance (2)

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

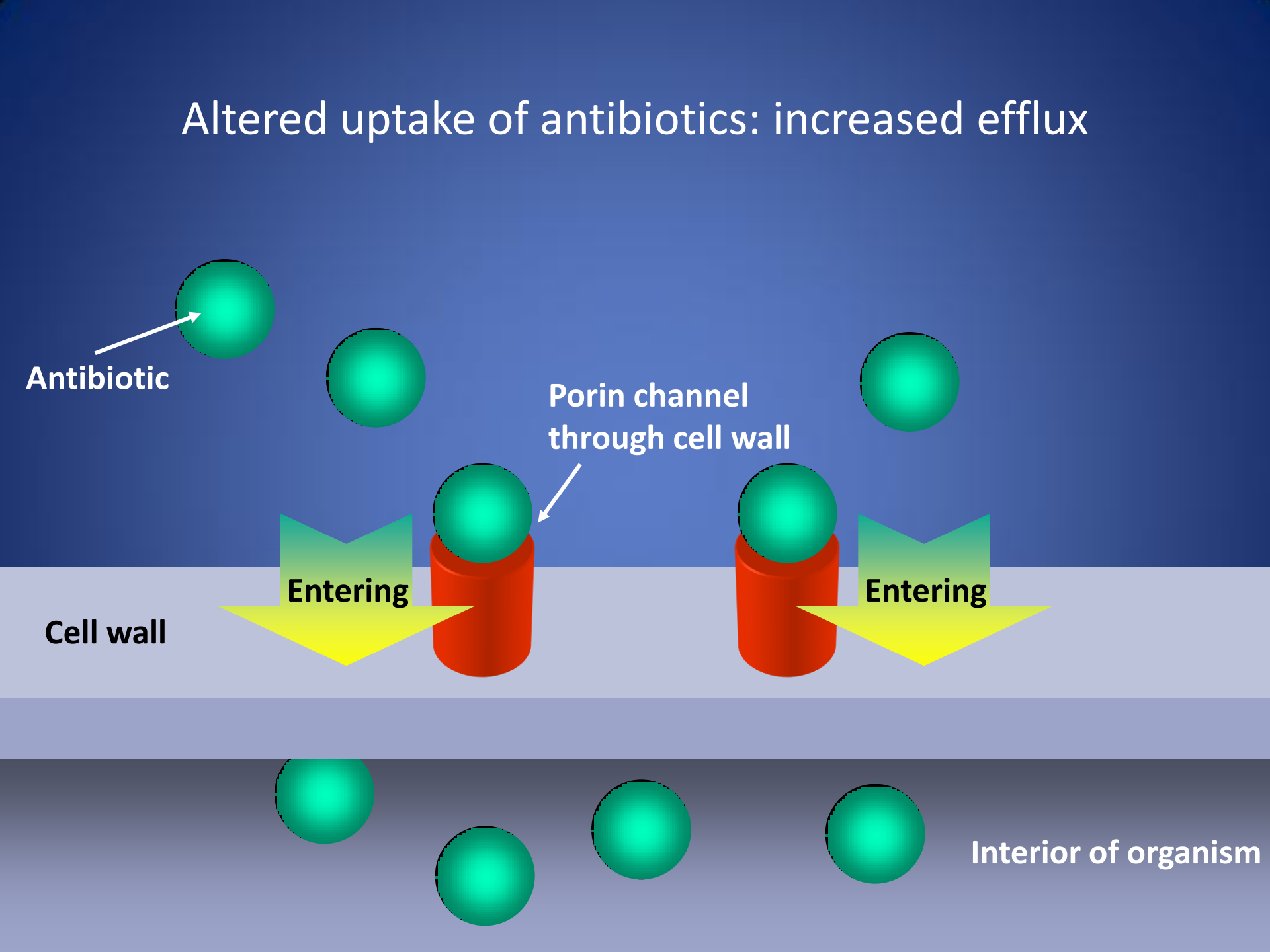
Altered uptake of antibiotics: decreased permeability



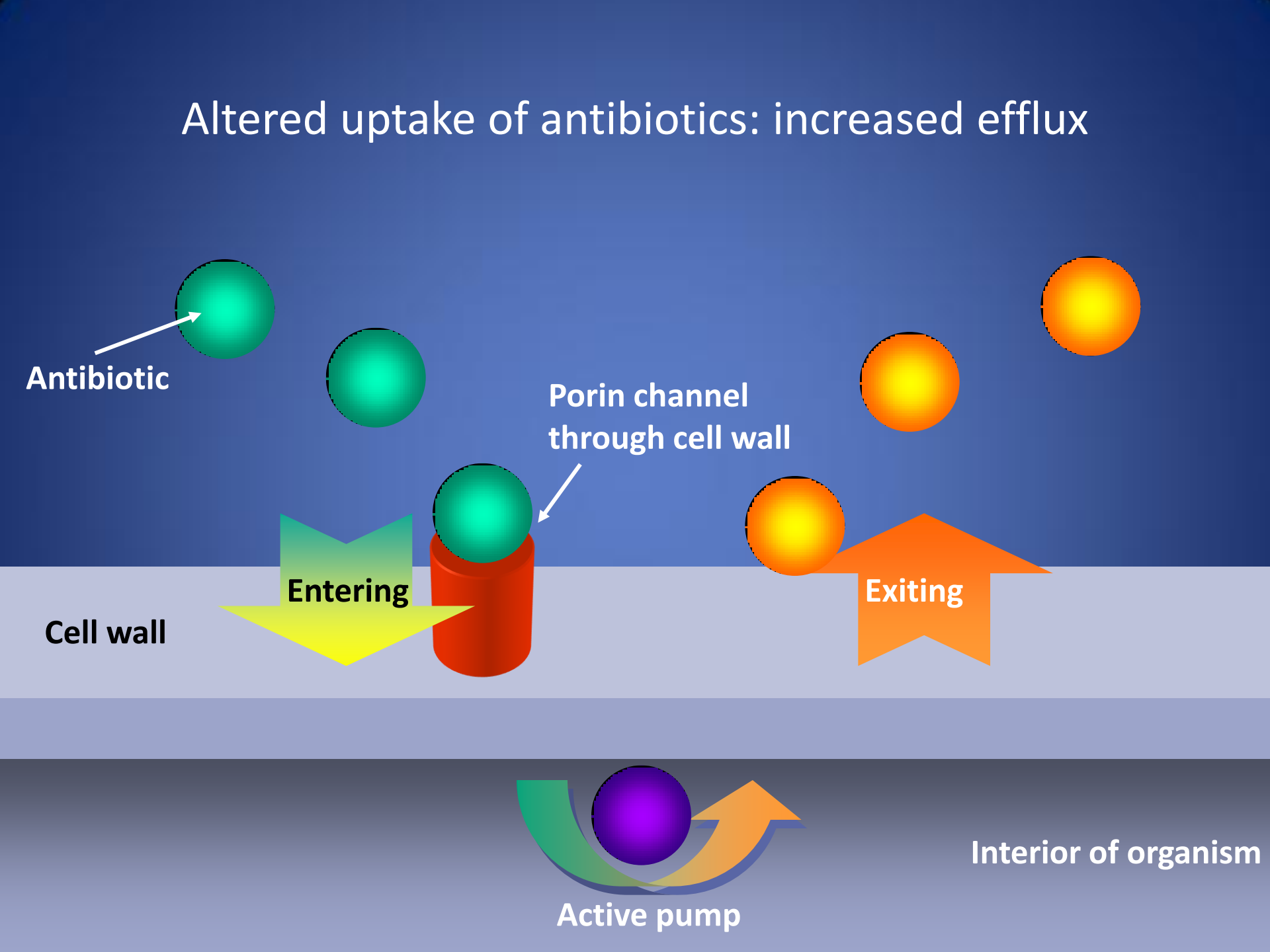
Altered uptake of antibiotics: decreased permeability



Altered uptake of antibiotics: increased efflux



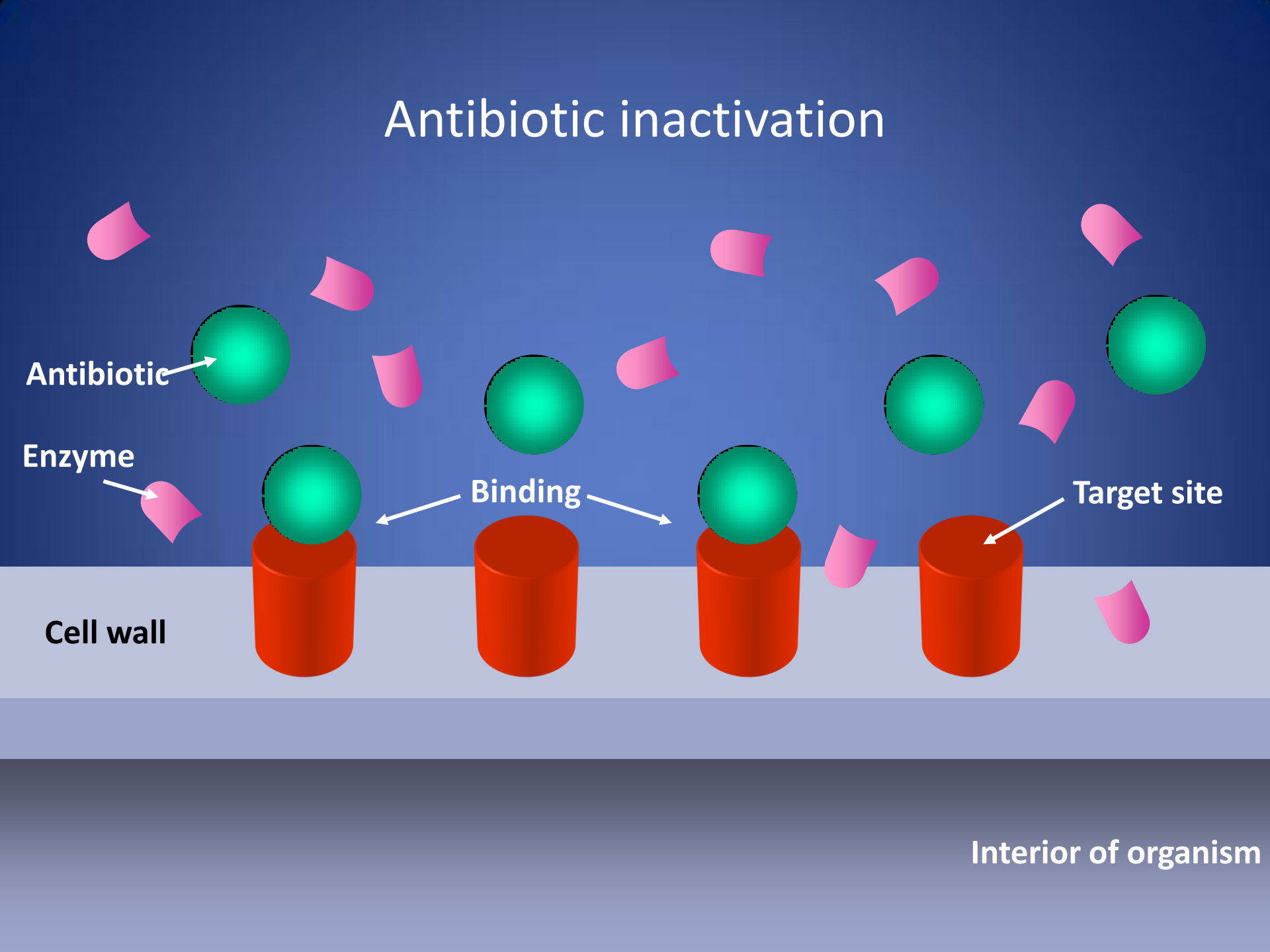
Altered uptake of antibiotics: increased efflux



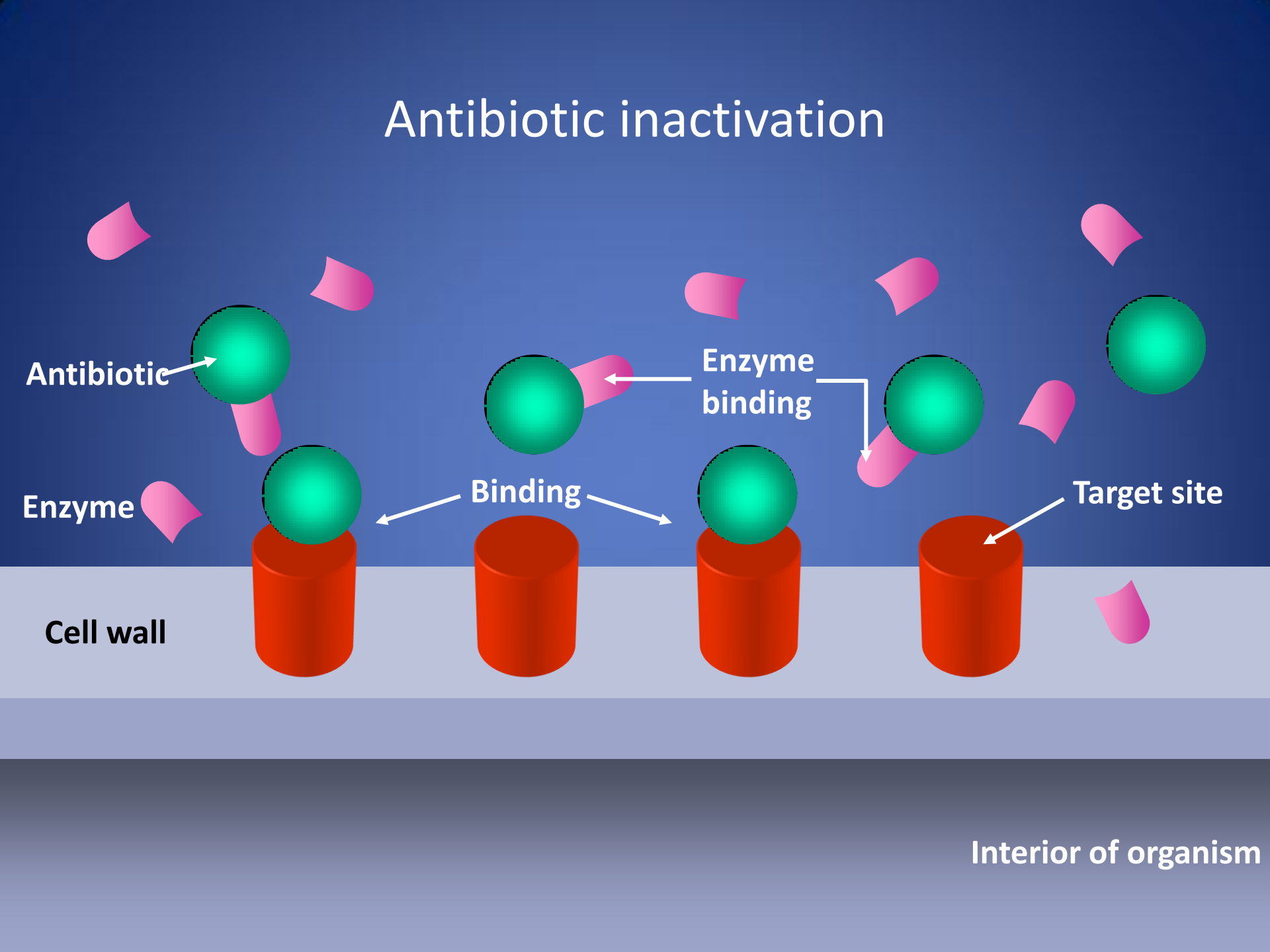
Mechanisms of antibacterial resistance (3)

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

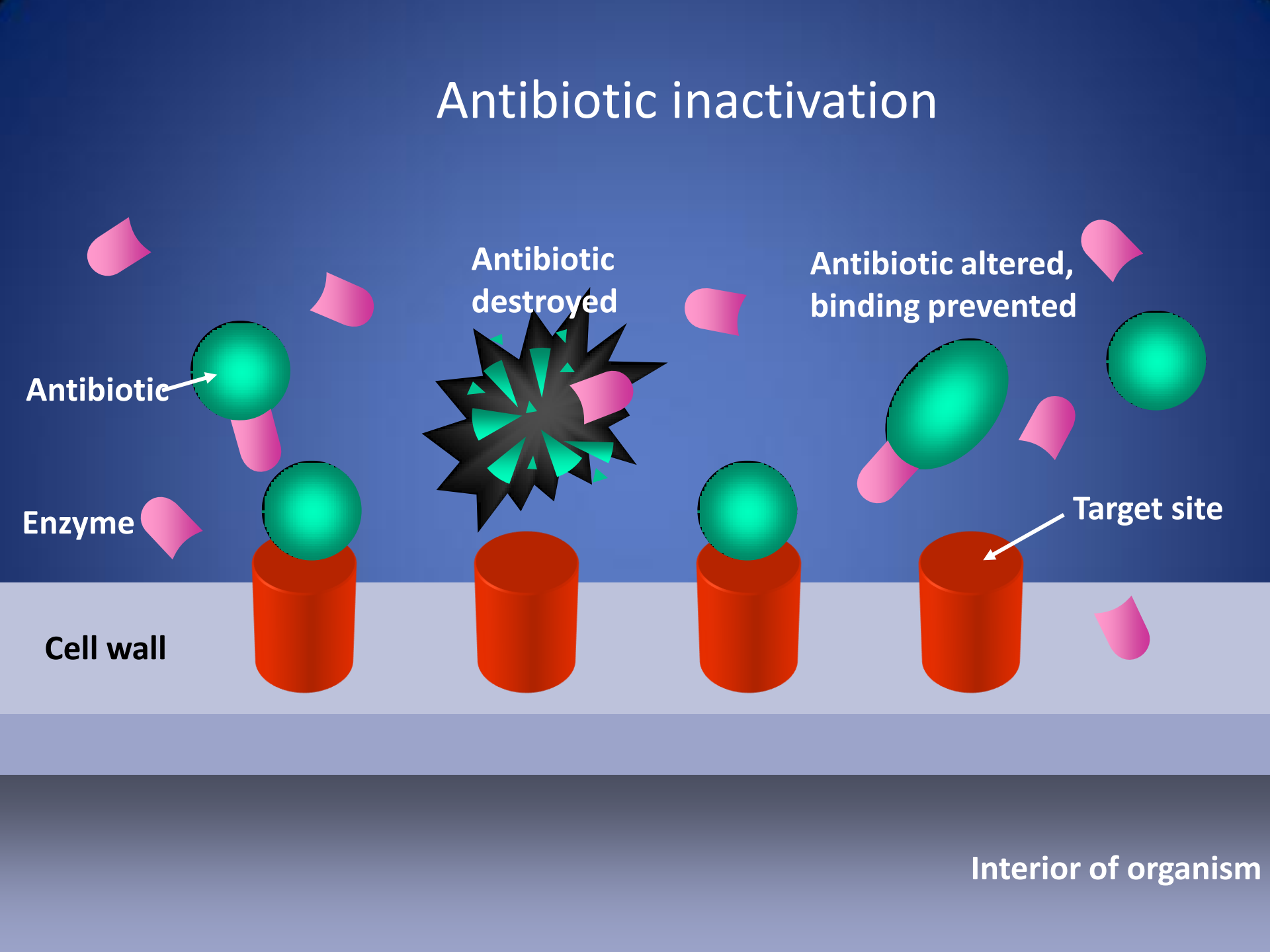
Antibiotic inactivation



Antibiotic inactivation



Antibiotic inactivation

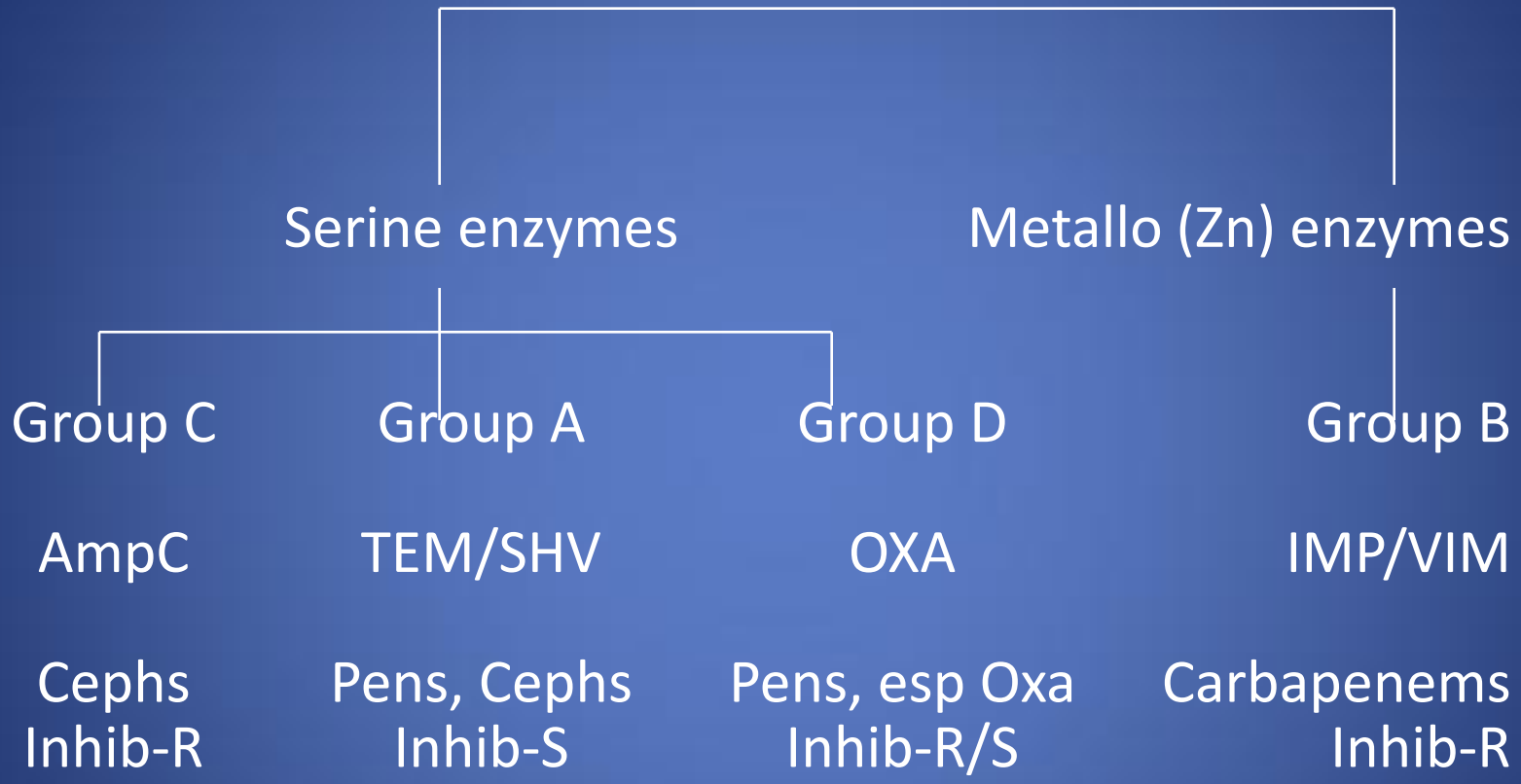


Major classes of antibiotics & resistance mechanisms

Antibiotic	Mechanism of action	Major resistance mechanisms
β-Lactams	Inactivate PBPs (peptidoglycan synthesis)	• β-lactamases • Low affinity PBPs • Efflux pumps
Glycopeptides	Bind to precursor of peptidoglycan	• Modification of precursor
Aminoglycosides	Inhibit protein synthesis (bind to 30S subunit)	• Modifying enzymes (add adenyl or Phosphate)
Macrolides	Inhibit protein synthesis (bind to 50S subunit)	• Methylation of rRNA • Efflux pumps
(Fluoro)Quinolones	Inhibit topoisomerases (DNA synthesis)	• Altered target enzyme • Efflux pumps

PBPs penicillin-binding proteins

β-Lactamases: Classification



Bush. Rev Inf Dis 1987;10:681; Bush et al. Antimicrob Agents Chemother 1995;39:12; Bush. Curr Opin Investig Drugs 2002;3:1284

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.	*S.aureus*
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 *P. vulgaris*, CepA *B. fragilis*.
2f	Carbapenemase	A	Clav.	IMI-1, NmcA, Sme 1-3
3	Metallo-enzyme	B	-	*S.maltophilia*
4	Penicillinase	-	-	*B.cepacia*

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)

Livermore & Woodford. Curr Opin Microbiol 2000;3:489–495

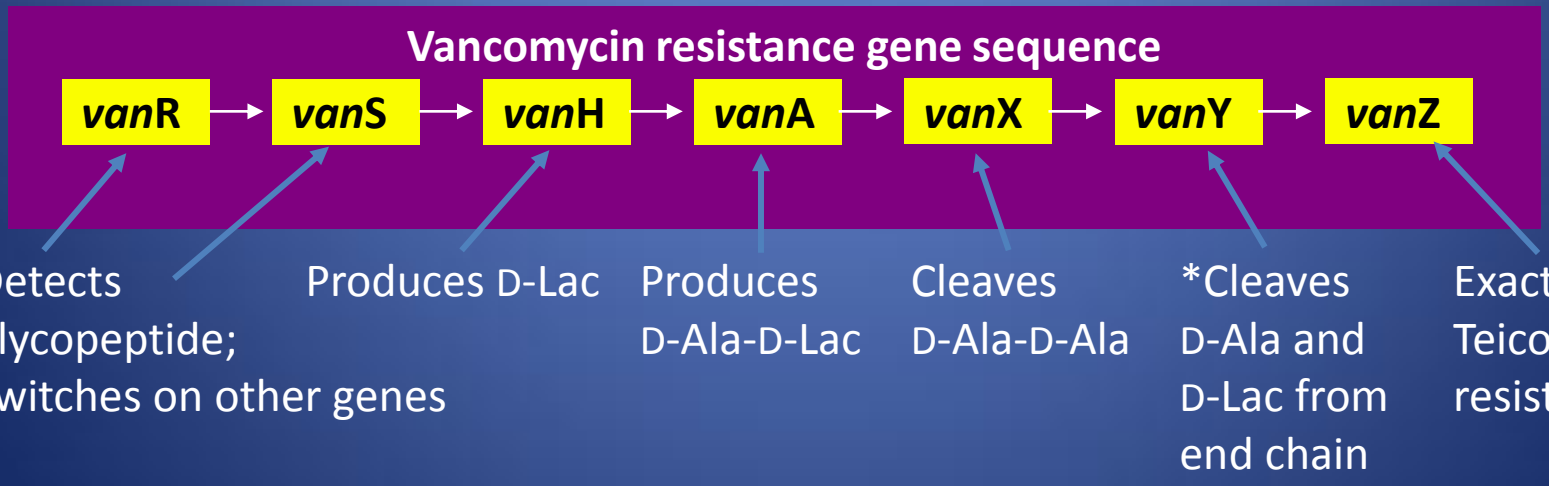
Antimicrobial features of MRSA

- Mechanism involves altered target site
  - new penicillin-binding protein — PBP 2' (PBP 2a)
  - encoded by chromosomally located *mec*A 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*)

Hiramatsu et al. Trends Microbiol 2001;9:486–493
Berger-Bachi & Rohrer. Arch Microbiol 2002;178:165–171

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 *van*A 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

Courtesy of CICO Office, HA

- *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
- *Nisseria gonorrhoeae:*
  - Established fluoroquinolone rersistance

    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%

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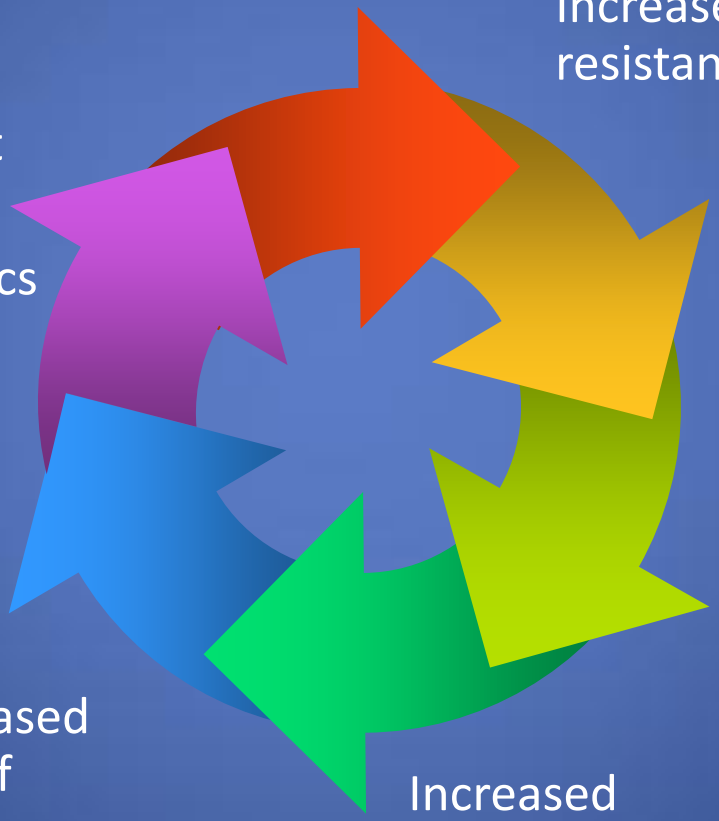
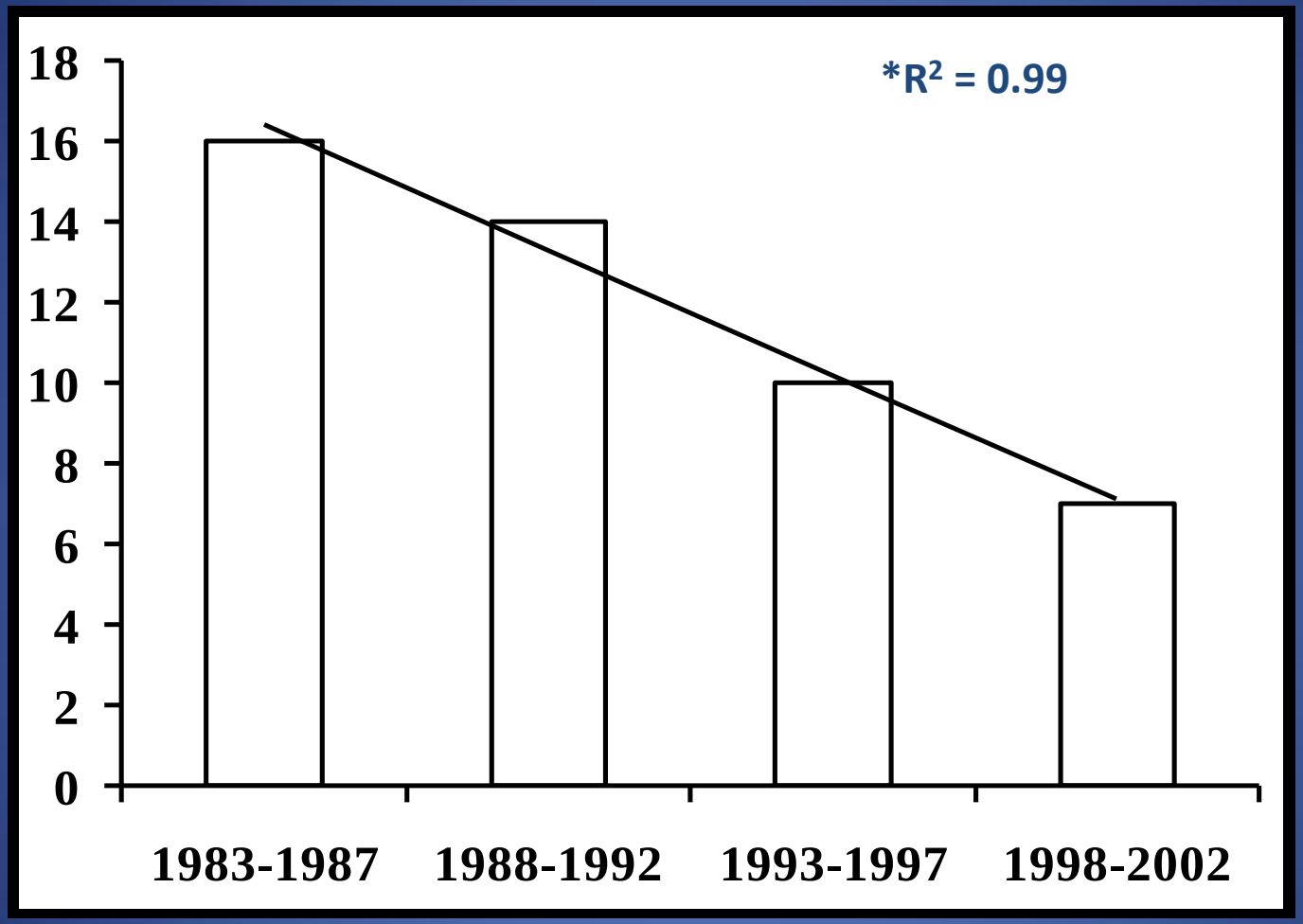
Antibiotic use, resistance, treatment failure and healthcare burden: a vicious circle



Trends in Development of New Antibacterials



*p = 0.007 by linear regression

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

Edwards J, *ICAAC*, 2003

Bad Bugs, No Drugs

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

IDSA
Infectious Diseases Society of America

July 2004

Table of Contents

Tables

Charts

Bad Bugs Need Drugs

10x'20

Ten new ANTIBIOTICS by 2020