# 多重抗藥性細菌之抗藥機轉

主講人：盛望徽醫師

台大醫院 內科部 感染科

# 課程大綱

1.抗生素對細菌之作用機轉

2.細菌抗藥性機轉之演進

3.抗藥性革蘭氏陽性菌之抗藥機轉

4.抗藥性革蘭氏陰性菌之抗藥機轉

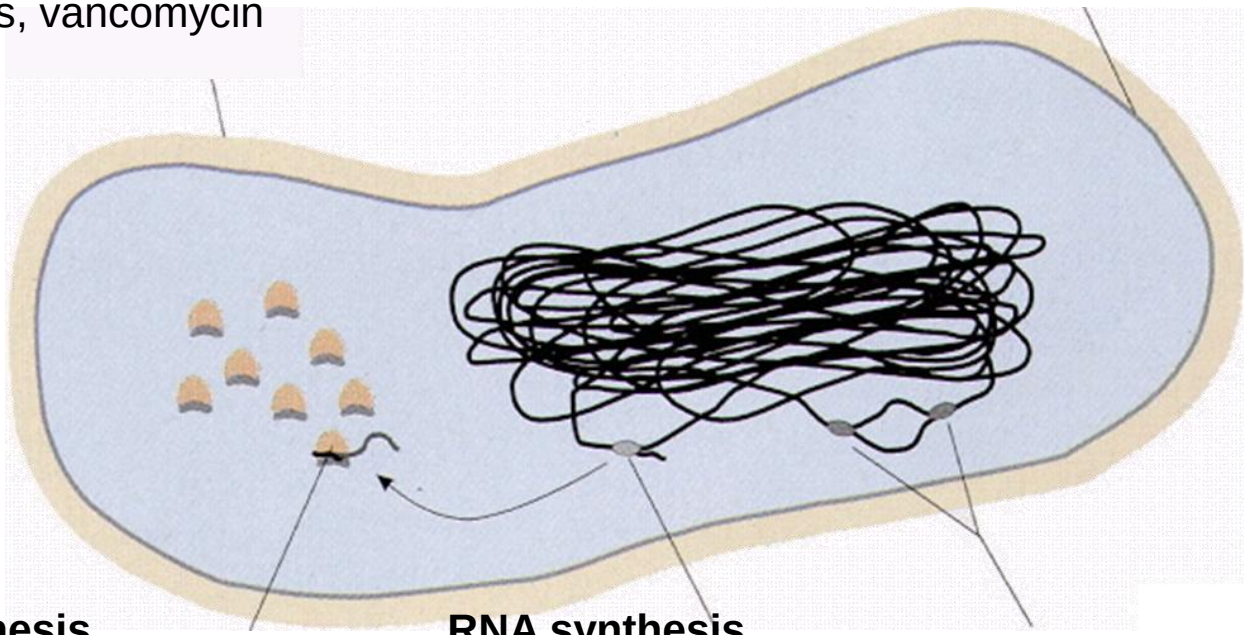
5.結論

# 1. 抗生素對細菌之作用機轉

# 細菌的結構

**Peptidoglycan cell wall**
Some antibiotics weaken the wall, causing the cell to rupture-penicillins, cephalosporins, vancomycin

**Plasma membrane**
Some antibiotics make the membrane leaky, allowing essential small molecules to leak out of the cell-polymyxins



**Protein synthesis**
Some antibiotics inhibit ribosomes which synthesise the proteins required by the cell-aminoglycosides, tetracyclines, macrolides

**RNA synthesis**
Some antibiotics inhibit synthesis of the RNA molecules that carry the genetic code between the DNA and the ribosomes-rifampicin

**DNA synthesis**
Some antibiotics inhibit replication of the genetic code-quinolones, novobiocin

# 抗微生物製劑（抗生素）作用機轉

| | |
|---|---|
| 抑制細胞壁合成 | • Penicillins, cephalosporins, glycopeptides, carbapenems |
| 抑制蛋白質合成 | • Aminoglycoside, macrolides, clindamycin, tetracyclines |
| 抑制核酸合成 | • Quinolones, rifampin |
| 抑制細胞膜功能 | • Polymyxins, daptomycin |
| 抑制營養代謝及生長 | • Sulfonamide |

# 抑制細胞壁合成

- Cell wall polymer - peptidoglycan inhibitors
  β-lactams : penicillins 青黴素
  cephalosporins 頭孢子素
  carbapenems 碳氫黴烯

- Block cross-linking of peptidoglycan
  Glycopeptides : vancomycin萬古黴素
  teicoplanin; bacitracin

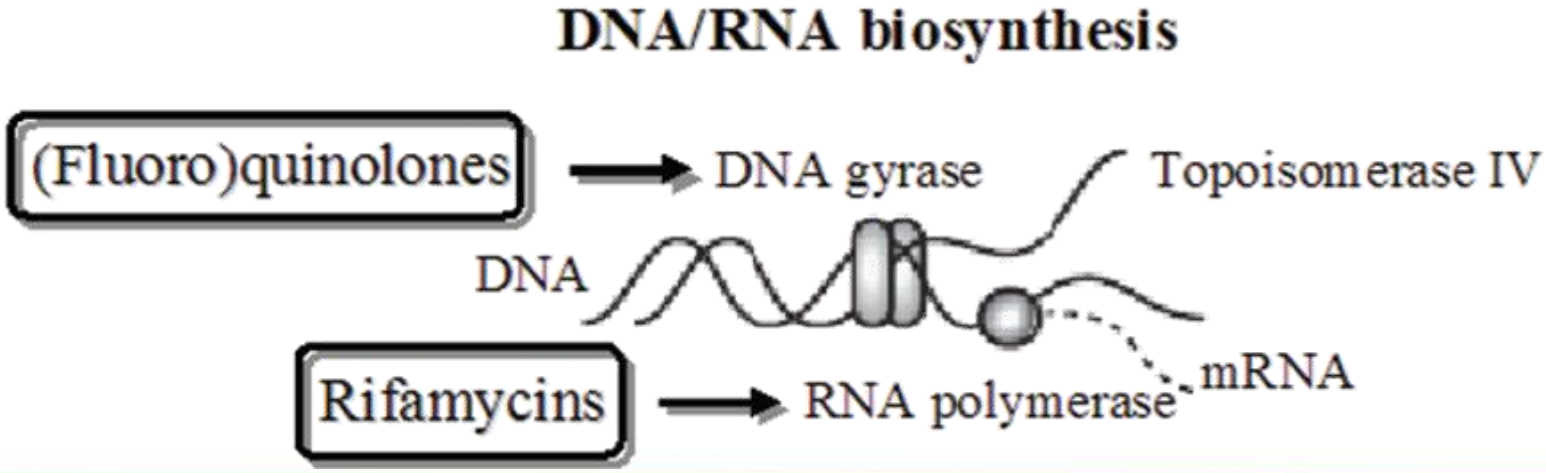
- Fosfomycin : inhibit MurA biogenesis

# 抑制蛋白質合成

- 抑制30S核醣體蛋白質合成(30s ribosome)
  Aminoglycosides : gentamicin, tobramycin, amikacin, streptomycin
- 抑制50S核醣體蛋白質合成(50s ribosome)
  Macrolides : erythromycin, clarithromycin, azithromycin, clindamycin, chloramphenicol
- 抑制70S複合體形成(70s initiation complex)
  Linezolid

# 抑制核酸合成

- 抑制DNA合成(抑制DNA gyrase)
  Quinolones: nalidixic acid, ofloxacin, ciprofloxacin, levofloxacin, moxifloxacin, gemifloxacin
- 抑制RNA合成：Rifampicin



# 抑制細胞膜功能

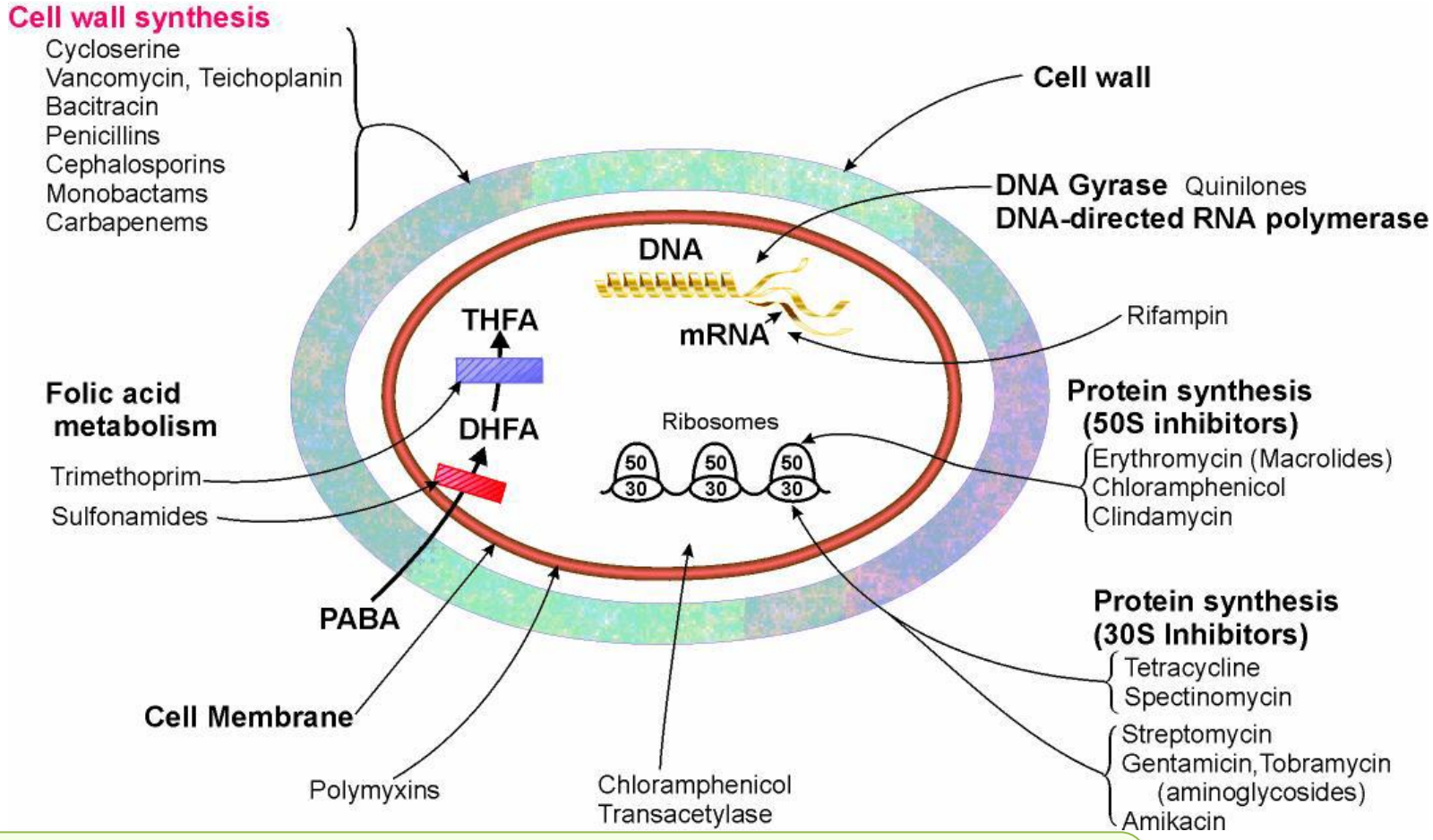
- Polymyxins: Polycation molecule binds to membrane and change membranous electric charges

- Daptomycin: Insert phosphatidyl glycerol and depolarization

# 抑制營養代謝及生長

- Sulfonamides: inhibit folic acid synthesis

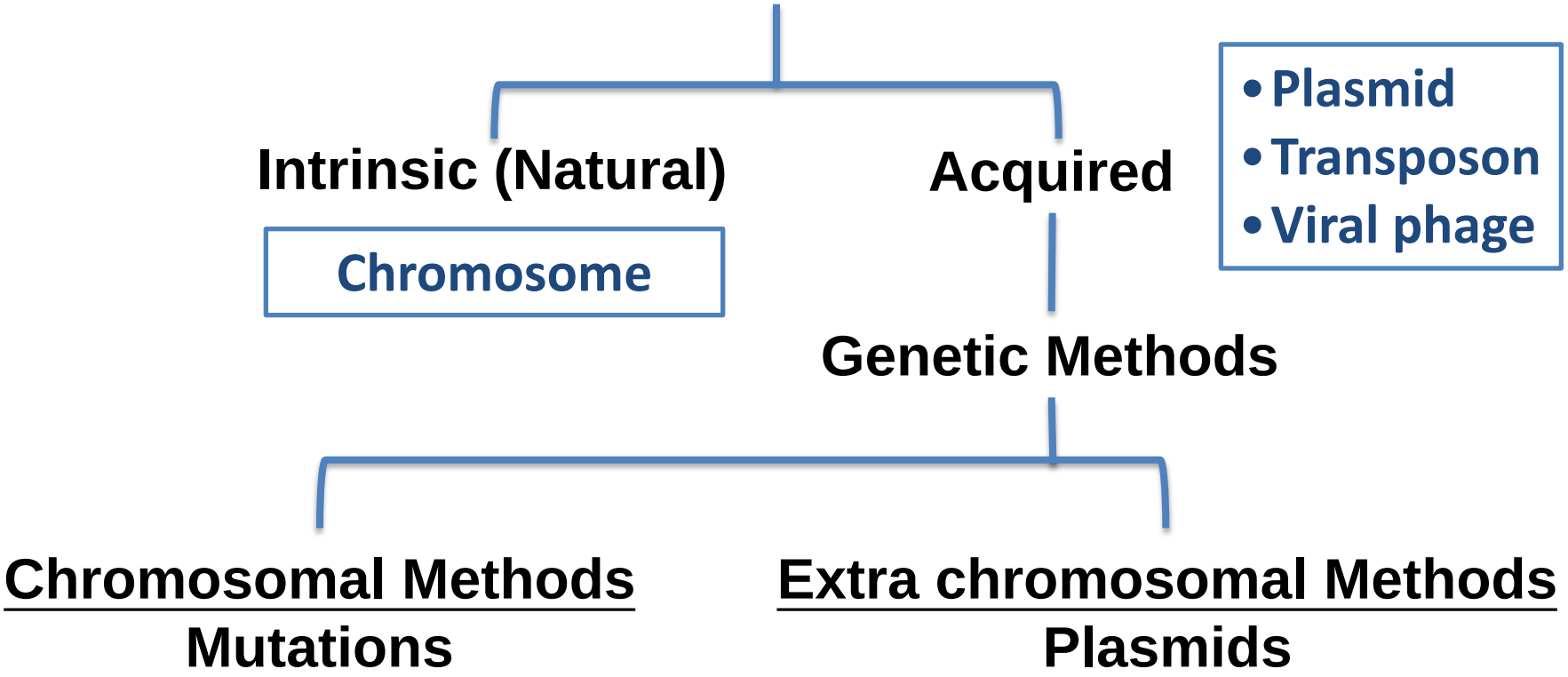
# Bacterial Targets for Current Antibiotics Used in the Clinic




資料來源：Dyner, L. (2009). Antibiotic deployment and resistance observed. [Chart from Slideshow]. Stanford University. Retrieved from Slideshow from http://peds.stanford.edu/Tools/documents/AntibioticResistanceLLD.pdf

# 2.細菌抗藥性機轉之演進

# Mechanism of Antibiotic Resistance



# Intrinsic/Acquired Resistance

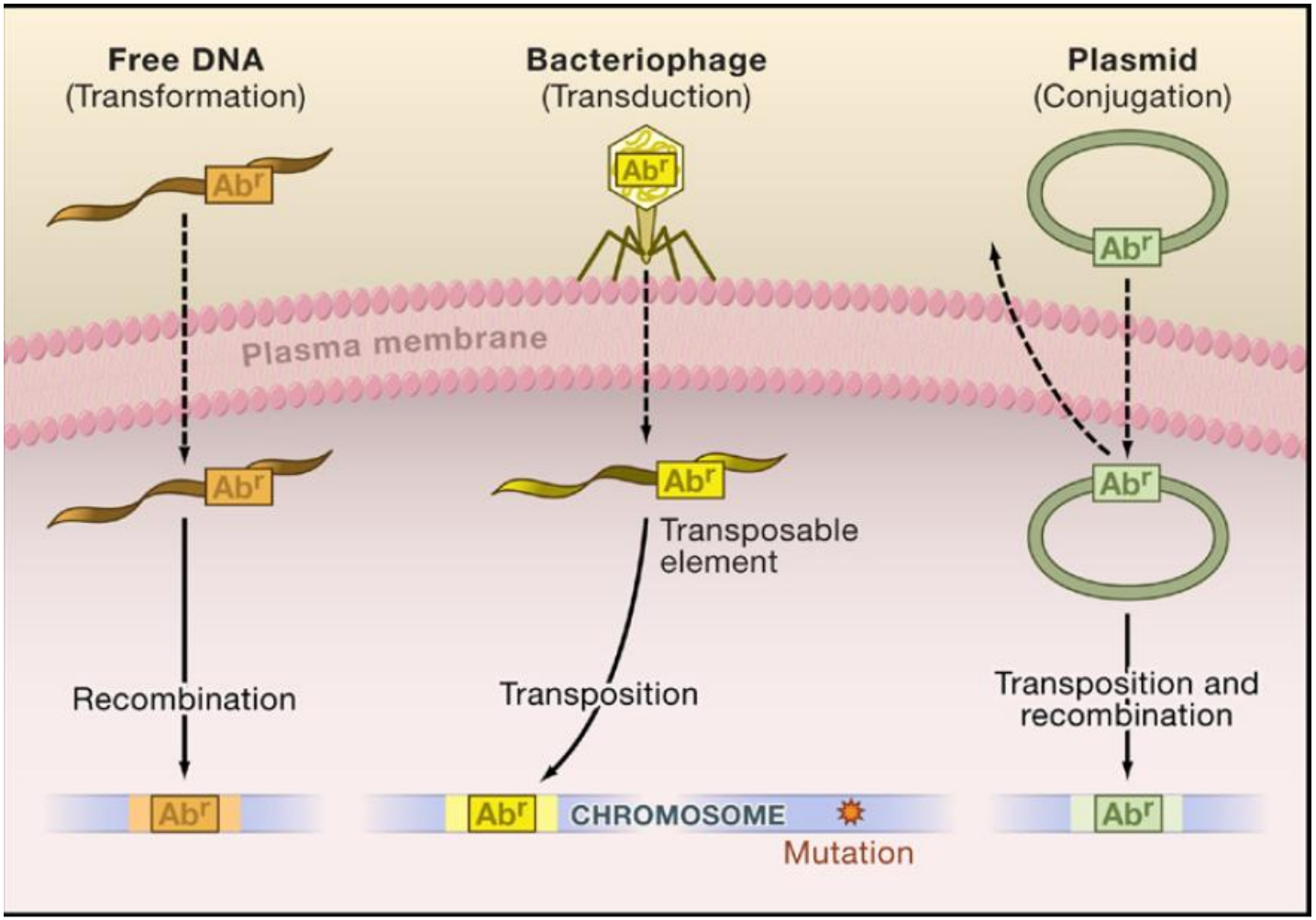
## Example: *Enterococcus*

Intrinsic resistance
- β-Lactams (particularly cephalosporins and penicillinase-resistant penicillins)
- Low concentrations of aminoglycosides
- Clindamycin
- Fluoroquinolones
- Trimethoprim–sulfamethoxazole

Acquired resistance
- High concentrations of β-lactams, through penicillin-binding proteins or β-lactamase
- High concentrations of aminoglycosides
- Glycopeptides (vancomycin and teicoplanin)
- Tetracycline
- Erythromycin
- Fluoroquinolones

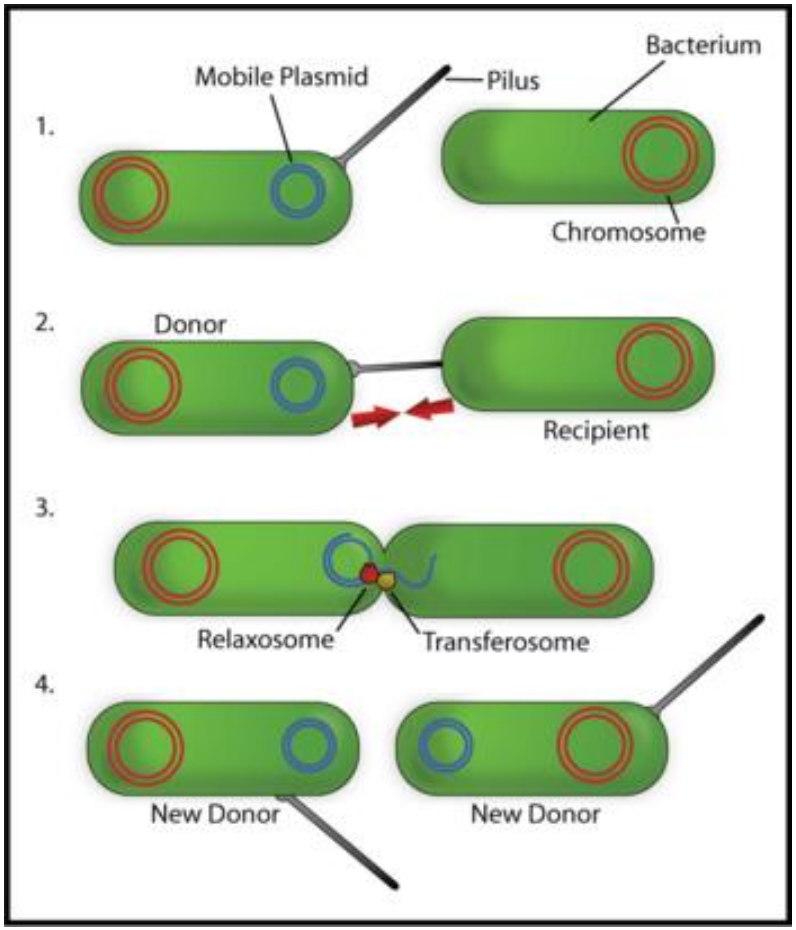
資料來源：Gold HS. N Engl J Med 1996; 335:1445:53

# Acquisition of Antibiotic Resistance



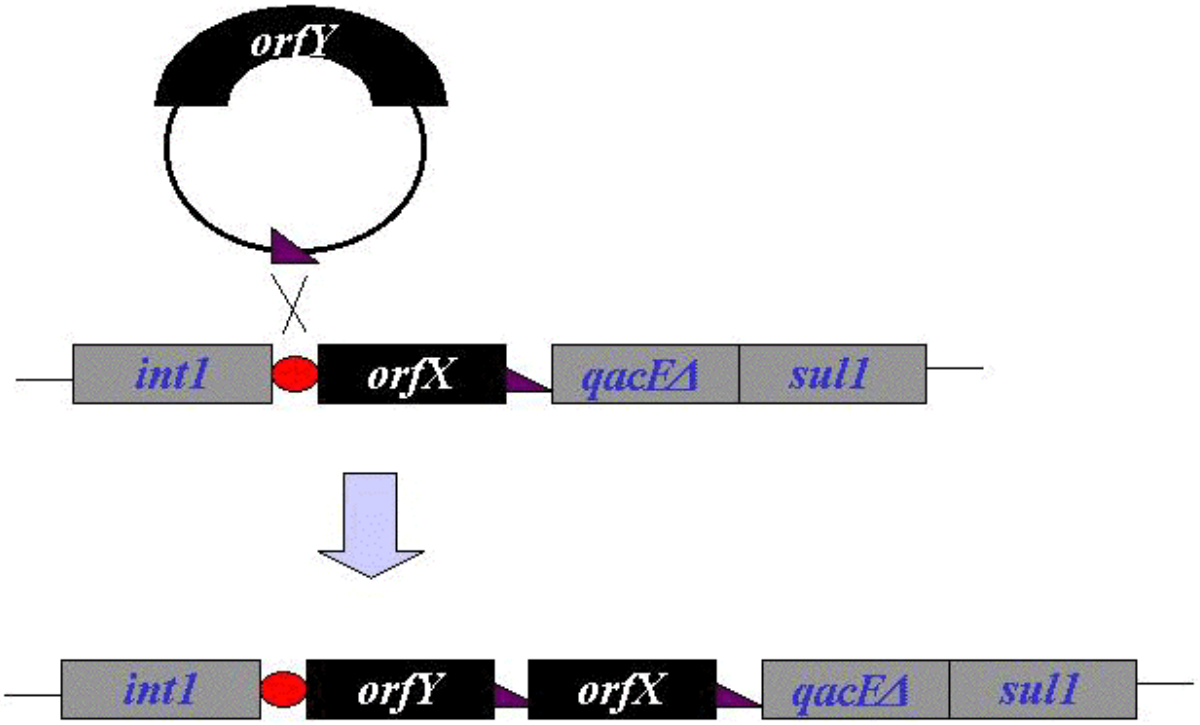
# Horizontal Spreads of Antibiotic Resistance Genes(1/2)

- Plasmid
- Transposon



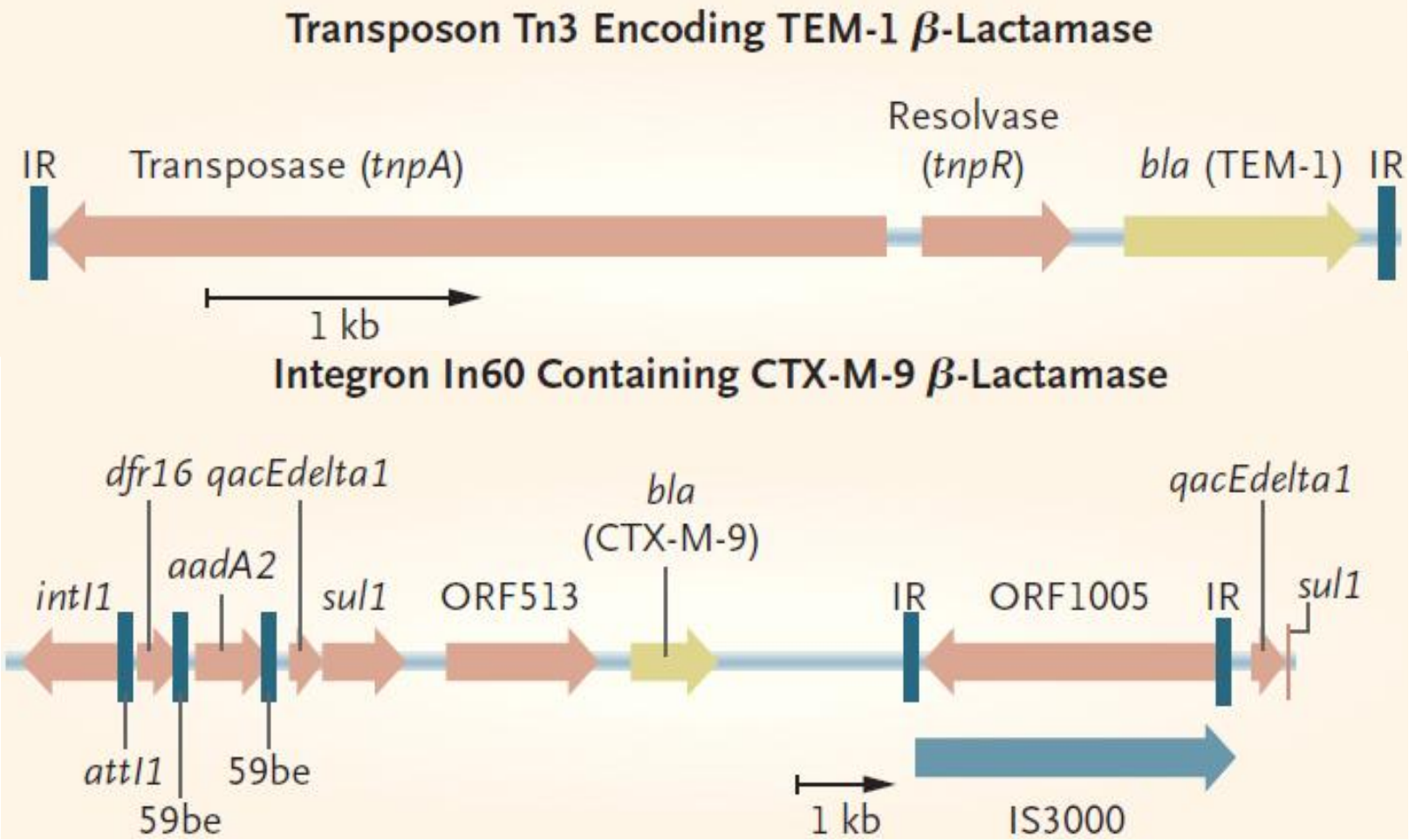
# Horizontal Spreads of Antibiotic Resistance Genes(2/2)

- Gene cassette
- Integron




資料來源：http://www.brandigg.de/brand/INTEGRON

# Transposons and Integrons




資料來源：Jacoby GA, et al. N Engl J Med 2005; 352:380-91

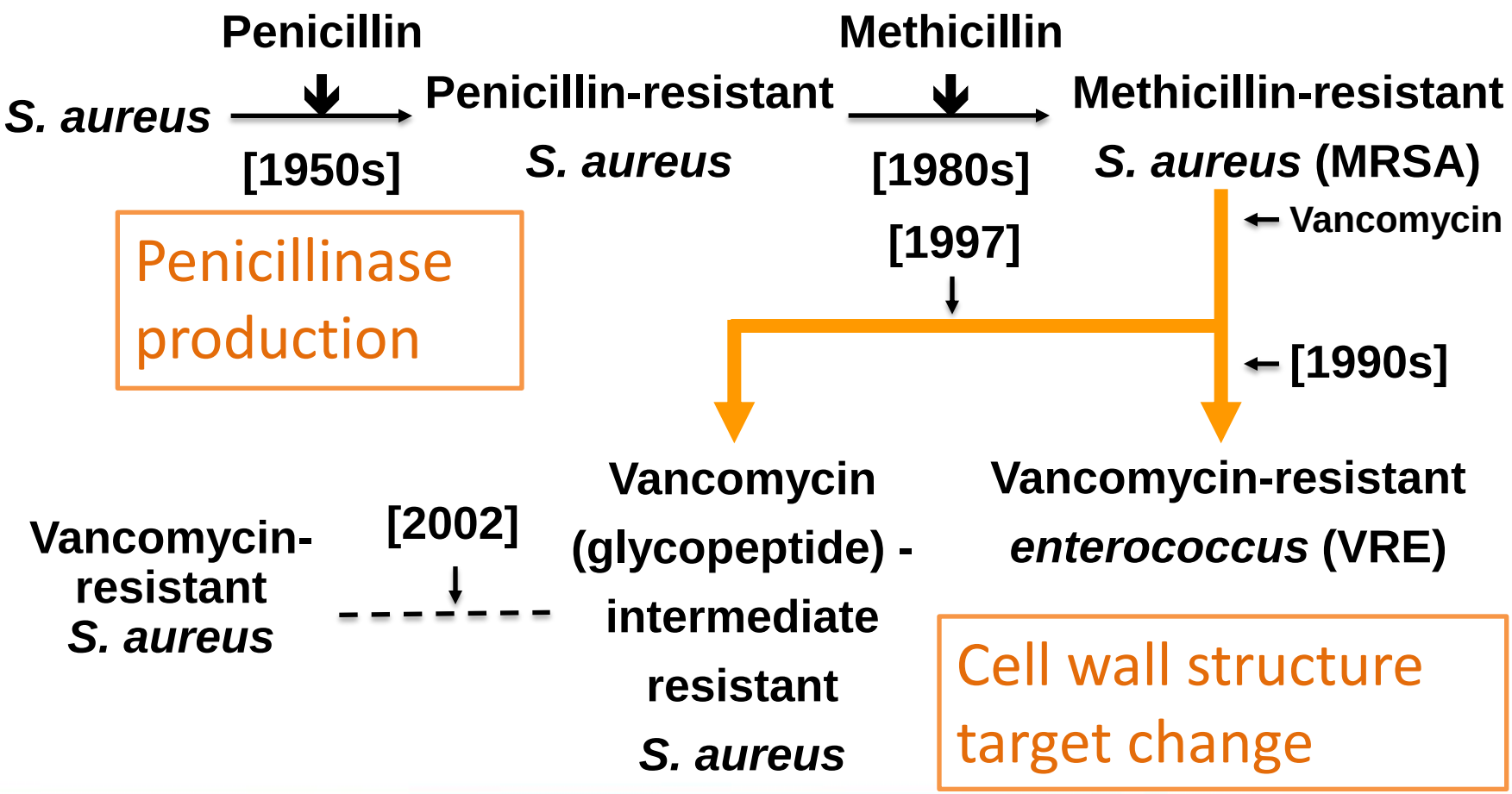
# 細菌發生抗藥性的步驟

**抗藥性基因之發生**
（基因本身自然突變；自其他生物獲得）

**環境選擇性壓力**(Selection pressure)
(Antibiotics use in human and animal)

**抗藥性細菌之散佈**
(Spread in the environment)
（未做好院內感控）

# 抗藥性機轉的演進
# 以金黃色葡萄球菌為例




資料來源：Enright MC, et al. Proc Natl Acad Sci U S A 2002; 99:7687–92

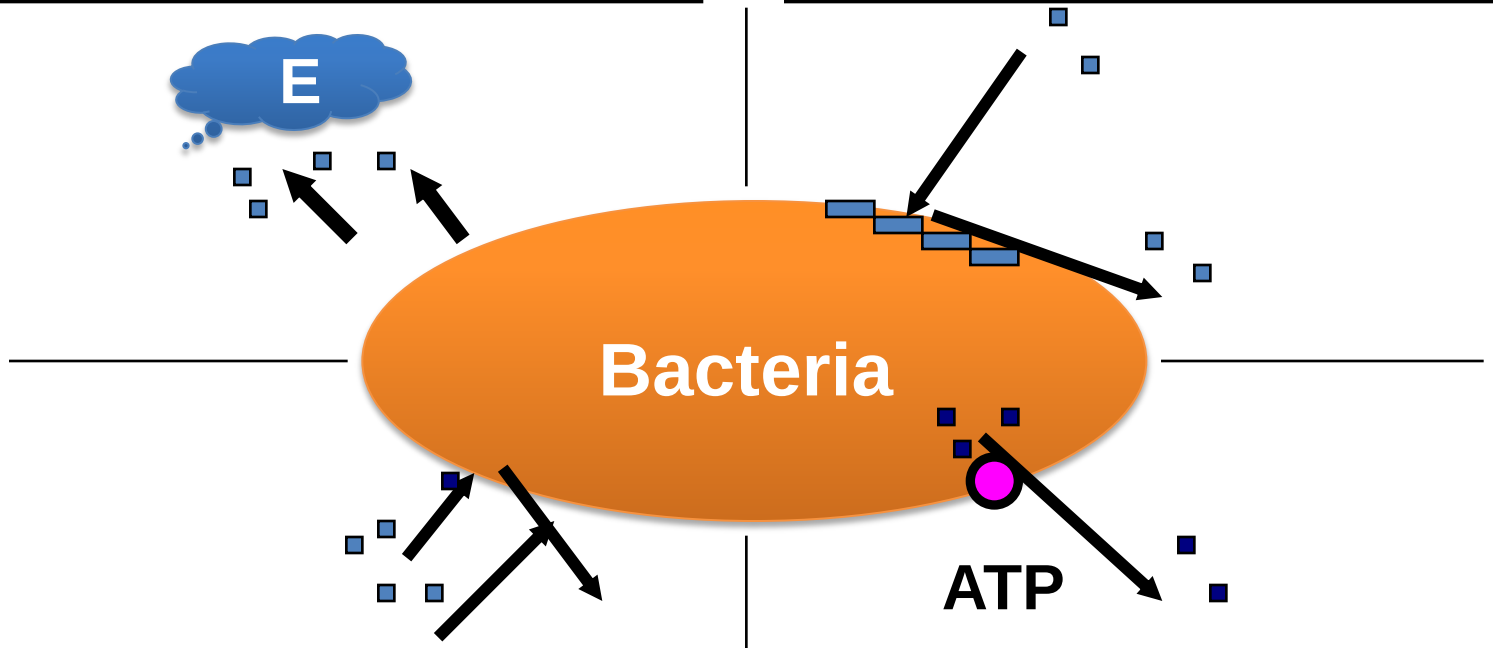
# Mechanisms of Antibiotic Resistance

- Enzymatic alteration
- Decreased permeability
- Efflux
- Alteration/protection of target site
- Overproduction of target
- Bypass of inhibited process
- Bind-up antibiotic

# 抗藥性細菌的抗藥機轉

Produce enzyme to inactivate drugs

Modify binding targets




Drug penetration barrier (porins)

Drug efflux pumping

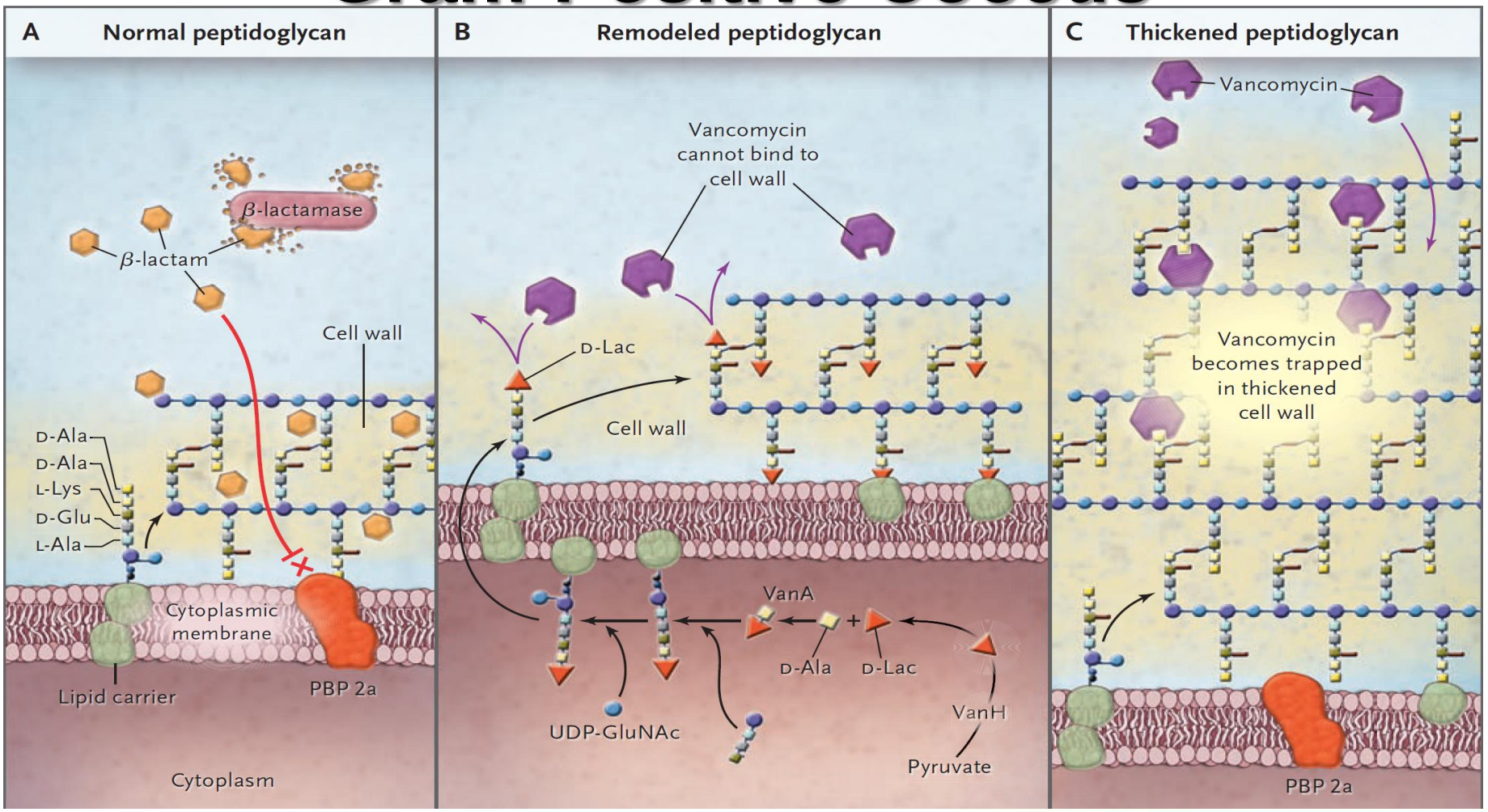
# Resistant Mechanism of Common Pathogens

| Antibiotic Class | Mechanism of Resistance |
|---|---|
| Cephalosporins | Extended-spectrum β-lactamases, chromosomal cephalosporinases |
| β-Lactamase inhibitors | Hyperproducers of β-lactamases, new β-lactamases resistant to inhibitors, chromosomal cephalosporinases |
| Carbapenems | Zinc metalloenzymes and other β-lactamases |
| Vancomycin, teicoplanin | Modified cell-wall precursors with decreased affinity for vancomycin |
| Quinolones | Alterations in DNA topoisomerase, efflux mechanisms, permeability changes |
| Trimethoprim–sulfamethoxazole | Resistant enzymes in folate-synthesis pathway |
| Erythromycin, new macrolides | Methylation of the bacterial ribosome producing resistance to macrolides, clindamycin, and streptogramin B antibiotics |
| Aminoglycosides | Aminoglycoside-modifying enzymes |

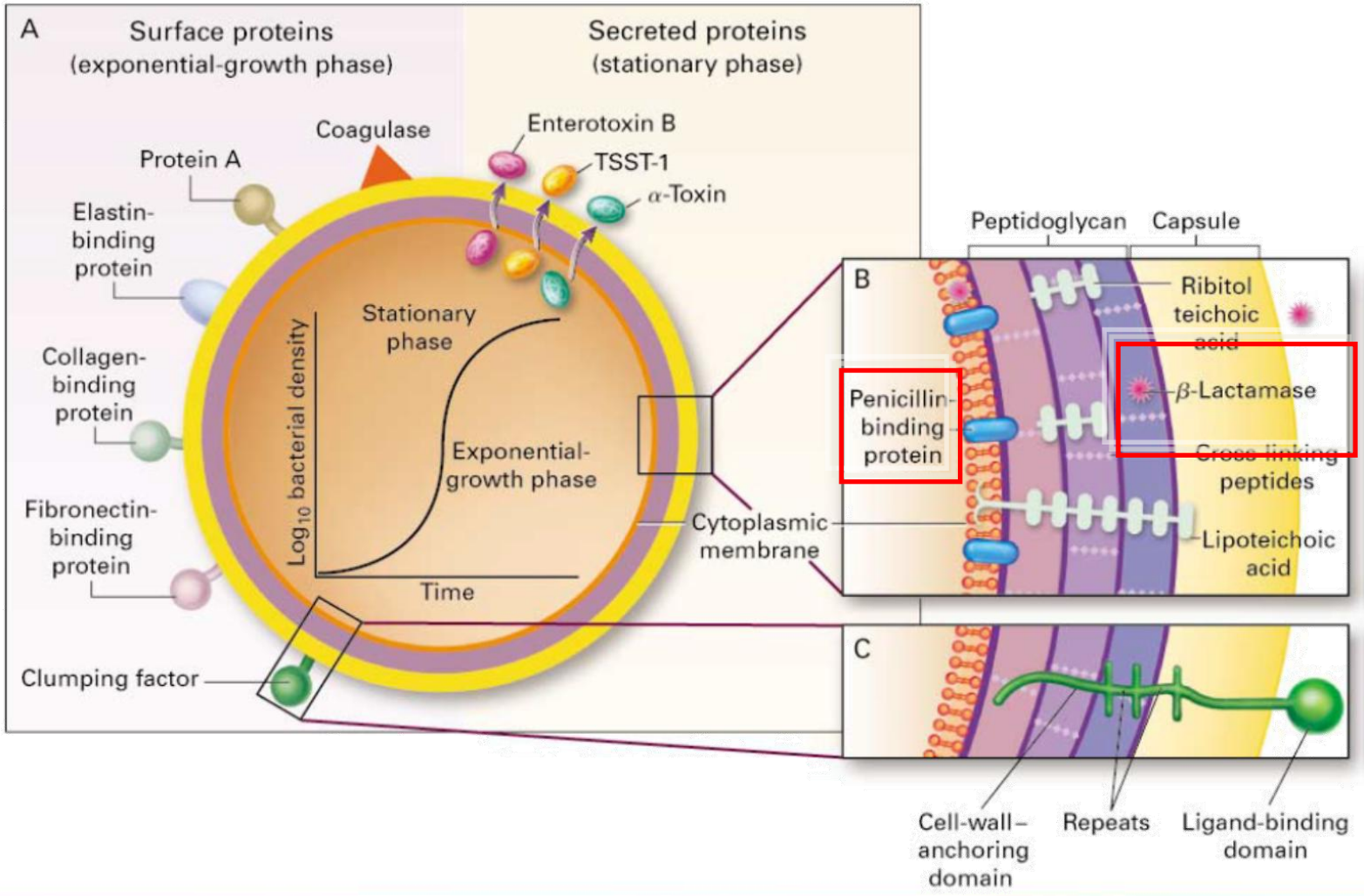
資料來源：Gold HS. N Engl J Med 1996; 335:1445:53

# 3.抗藥性革蘭氏陽性菌之抗藥機轉

# Resistant Mechanism in Gram-Positive Coccus



# Structure of *Staphylococcus aureus*




資料來源：Lowy FD, et al. N Engl J Med 1998; 330:520-32

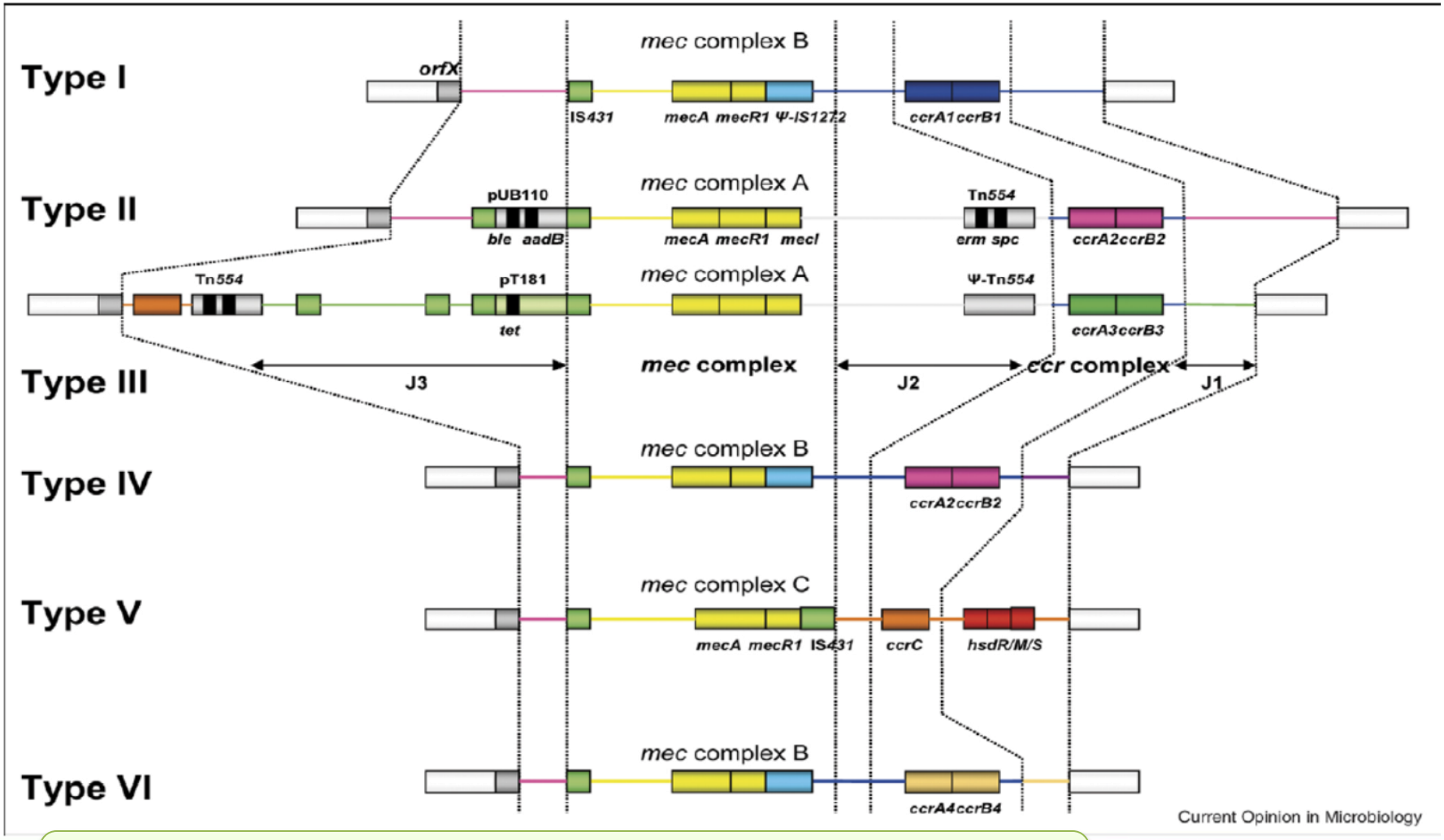
# Methicillin-resistant *Staphylococcus aureus* (MRSA)(1/2)

- Resistant to methicillin also resistant to most penicillins and cephalosporins
- High level methicillin resistance by *mec* gene that encodes penicillin-binding protein 2a
- Horizontal transfer of *mec* DNA
- The expression of resistance to methicillin is often heterogeneous

# Methicillin-resistant *Staphylococcus aureus* (MRSA)(2/2)

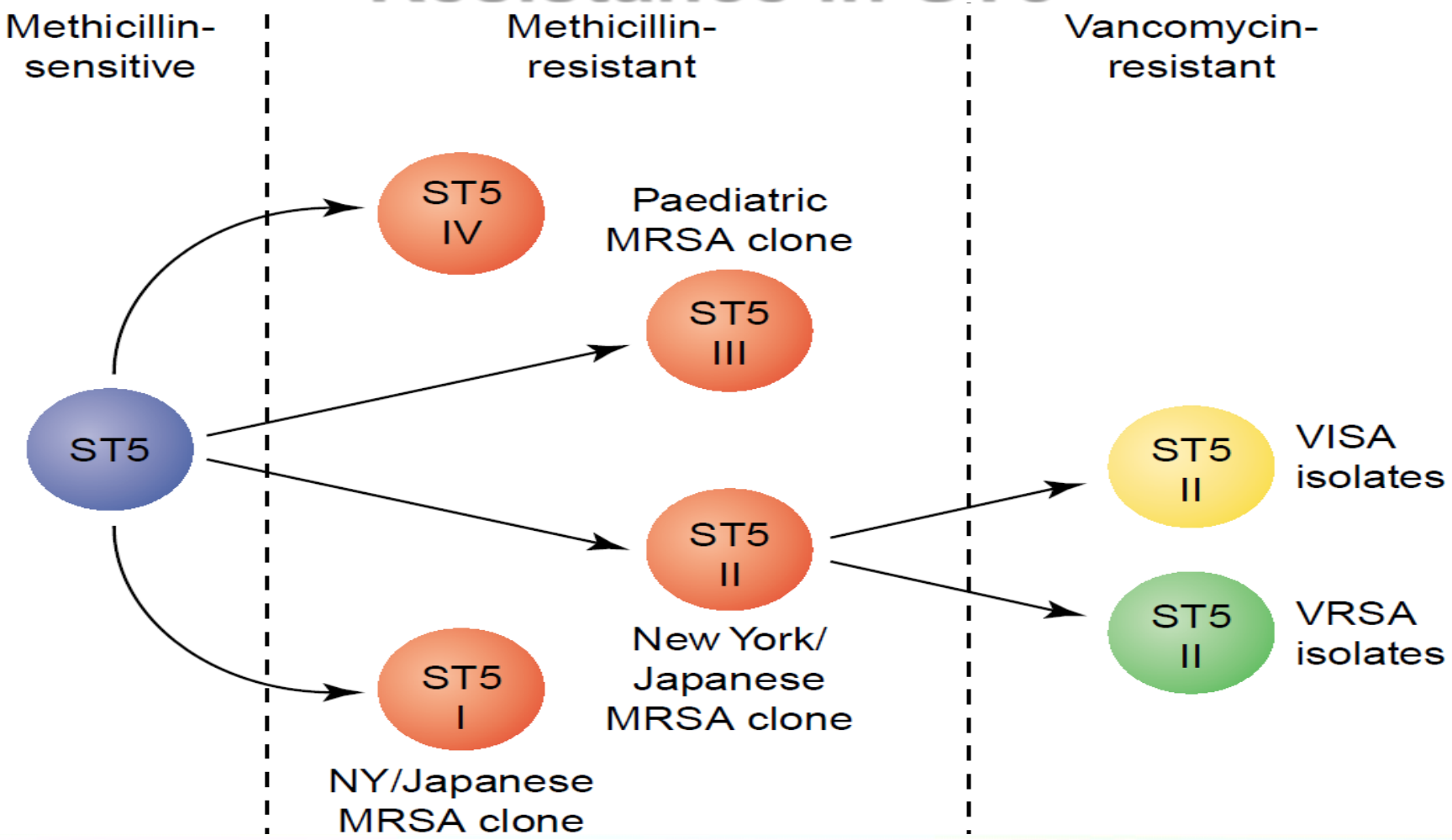
- Reduced-affinity penicillin-binding protein (PBP2a or PBP2').
- Resistant to semi-synthetic penicillin and other β-lactams.
- PBP2a encoded by *mecA* gene, resides within a genomic island, staphylococcal cassette chromosome *mec* (SCC*mec*).
- At least 6 SCC types (I-VI) identified.

# MRSA, SCC*mec* Types I–VI




資料來源：De Lencastre H, et al. Current Opinion in Microbiology 2007; 10:428–435

# Evolution of Increasing Resistance in ST5




資料來源：Enright MC. Current Opinion in Pharmacology 2003; 3:474–479

# Vancomycin-resistant *Enterococcus* (VRE)

- Van A strains
  - Teicoplanin (MICs 16-512 mg/l)
  - Vancomycin (MICs 64-1000 mg/l)
- Van B strains
  - Teicoplanin (MICs 0.25-2 mg/l)
  - Vancomycin (MICs 4-1000 mg/l)
- Van C strains
  - Teicoplanin (MICs 0.12-2 mg/l)
  - Vancomycin (MICs 2-32 mg/l)

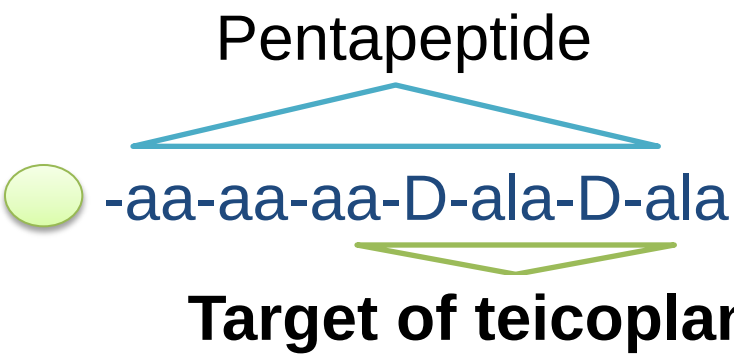
資料來源：NEJM 1988; 319:157-61

# Glycopeptide-resistant *Enterococcus*

| Characteristic | Phenotype | | |
|---|---|---|---|
| | VanA | VanB | VanC |
| Vancomycin MIC (μg/ml) | 64 to >1000 | 4 to 1024 | 2 to 32 |
| Teicoplanin MIC (μg/ml) | 16 to 512 | ≤0.5 | ≤0.5 |
| Most frequent enterococcal species | *Ent. faecium*<br>*Ent. faecalis* | *Ent. faecalis*<br>*Ent. faecium* | *Ent. gallinarum*<br>*Ent. casseliflavus* |
| Genetic determinant | Acquired | Acquired | Intrinsic |
| Transferable | Yes | Yes | No |

資料來源：Gold HS. N Engl J Med 1996; 335:1445:53

# Site of Action of Glycopeptides



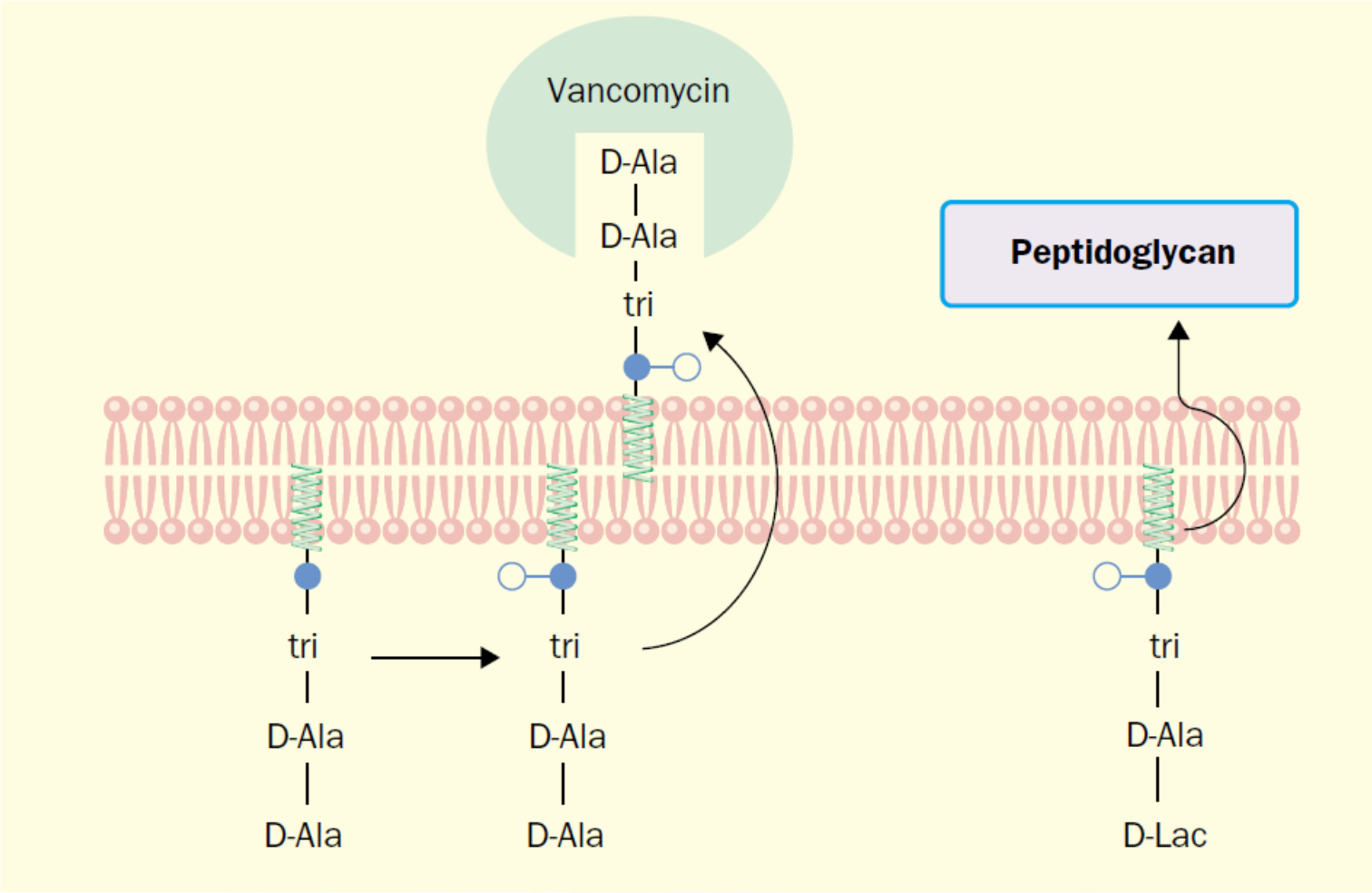

**Cell wall peptidoglycan repeating unit**

= N-Acetyl glucosamine-N-Acetyl muramic acid

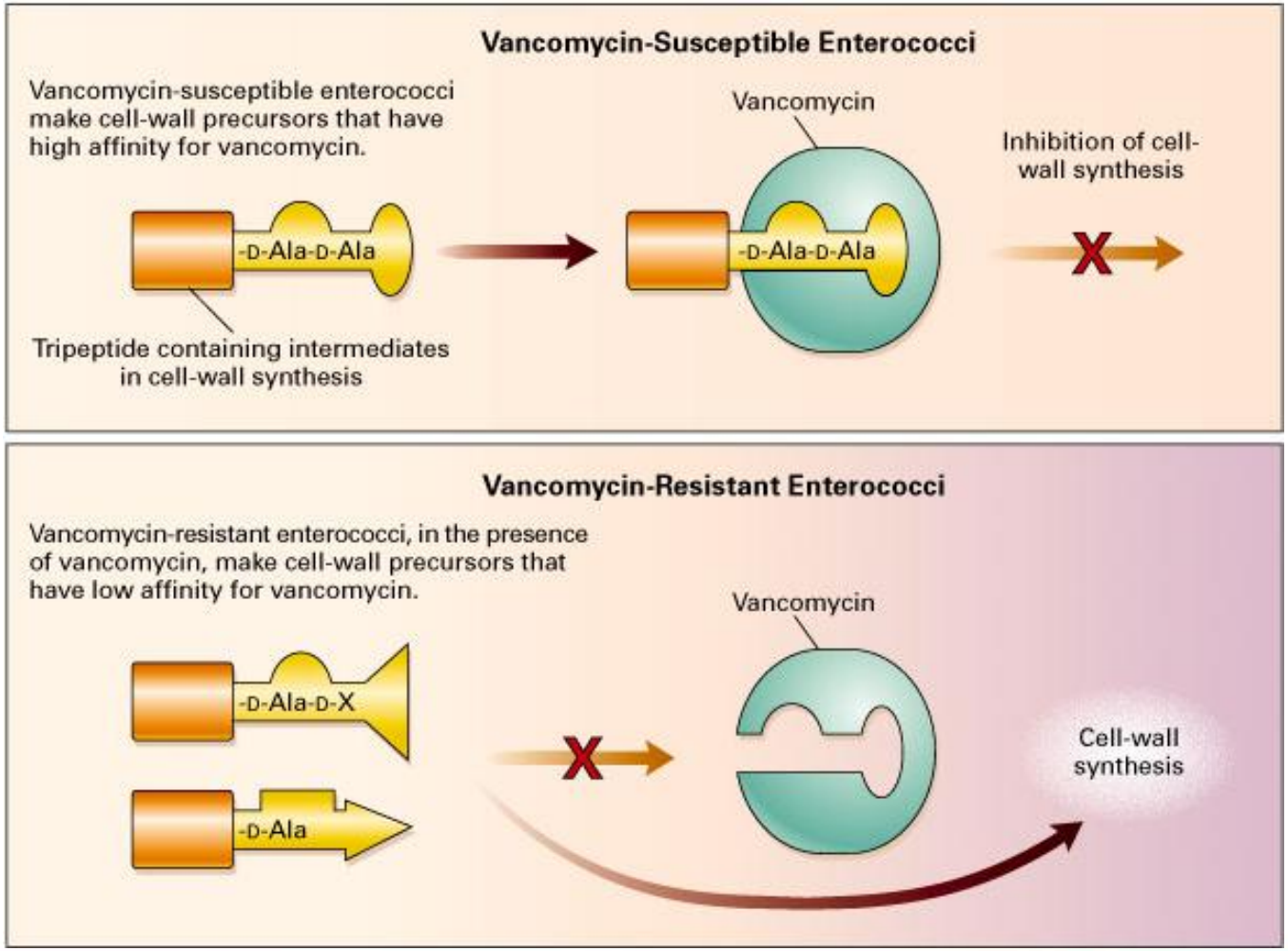
aa = amino acid , D-ala = D-alanine

★**Binds to terminal D-ala-D-ala dipeptide prevent pentapeptide being used for** cell wall synthesis

# VanA-Type Resistance in *Enterococcus*



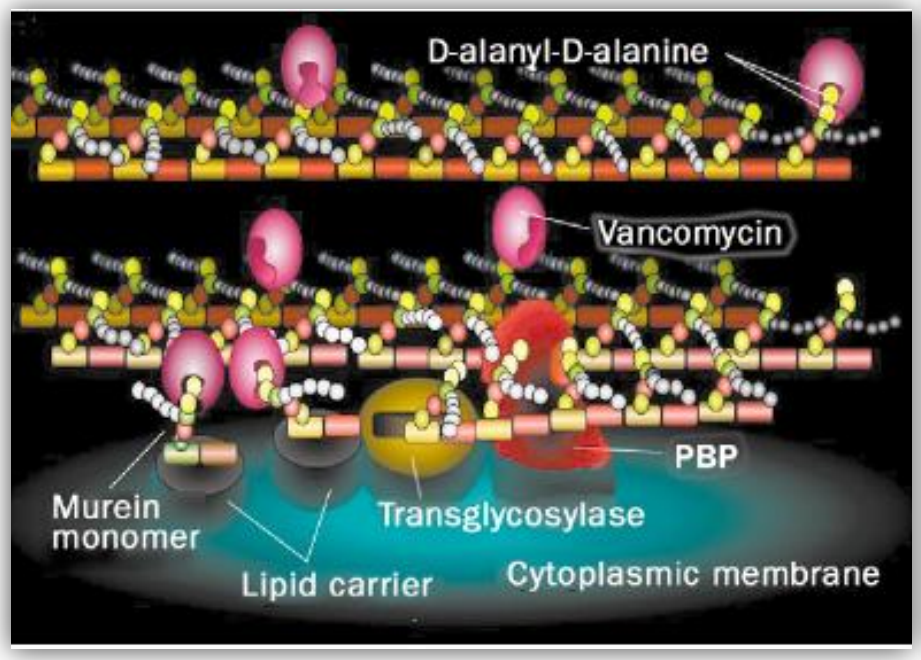
# Mechanism of Vancomycin Resistance in *Enterococcus*

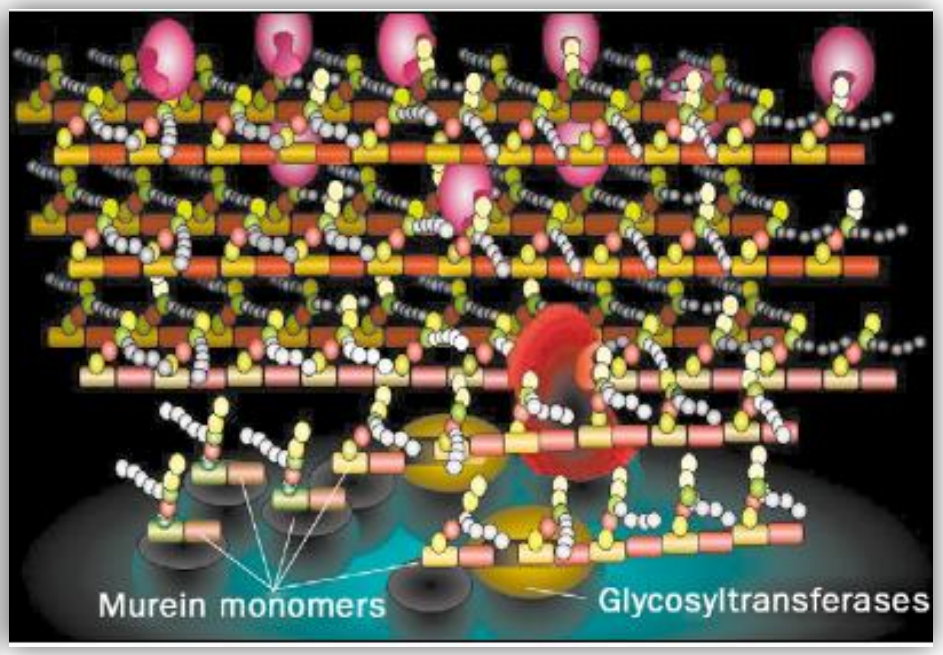



資料來源：Gold HS. N Engl J Med 1996; 335:1445:53

# Resistant Mechanism for VRSA

- Vancomycin resistance is acquired by mutation and thickening of cell wall due to accumulation of excess amounts of peptidoglycan.

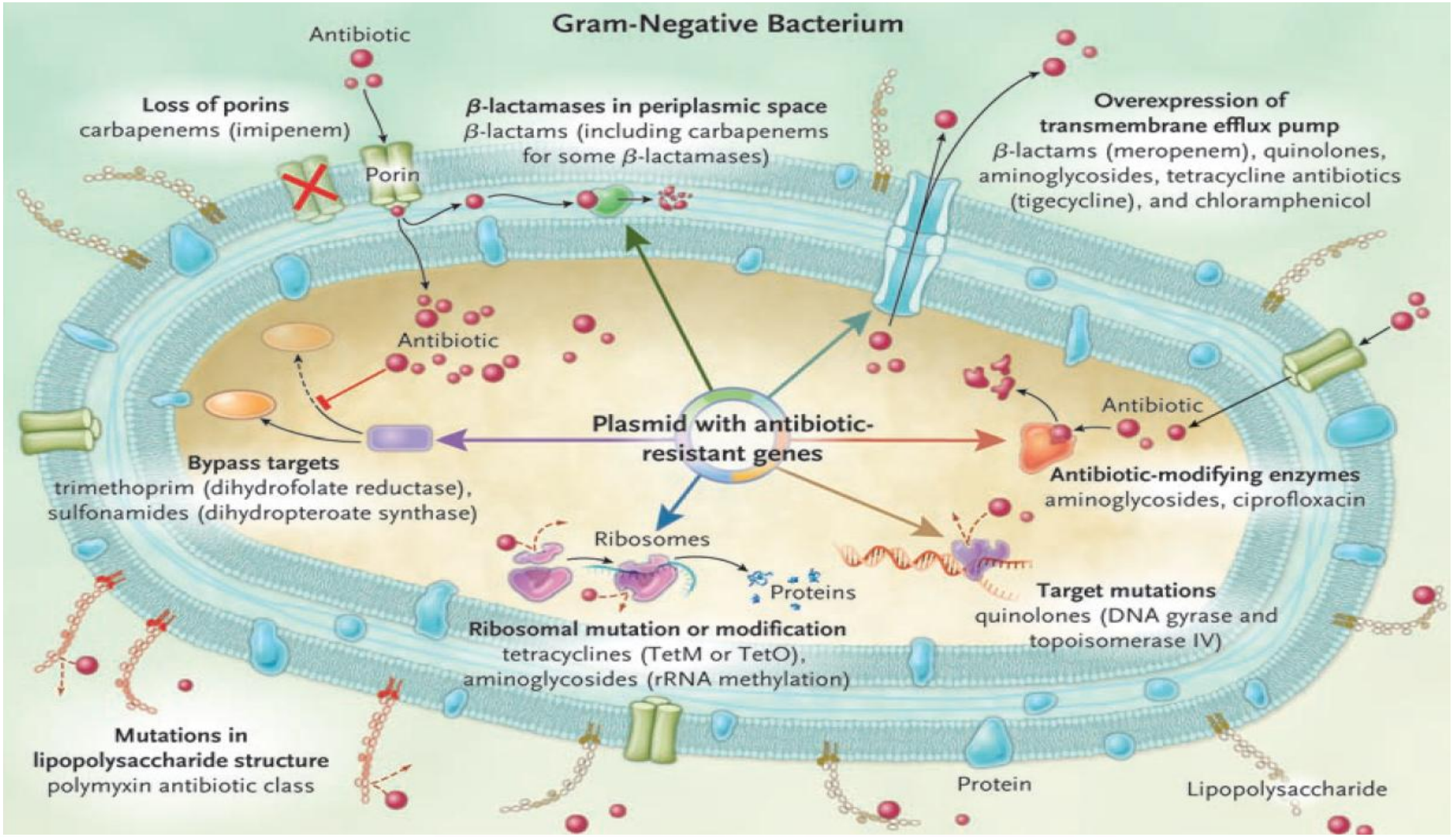



資料來源：Hiramastu K, et al. Lancet Infectious Diseases 2001; 1:147–155

# 4.抗藥性革蘭氏陰性菌之抗藥機轉

# Resistant Mechanisms of Gram-Negative Bacterium




資料來源：Peleg AY, et al. N Engl J Med 2010; 362:1804-13

# Major Resistant Gram-Negative Bacteria: β-Lactamase

## Drug-Resistant Pathogen

Extended-spectrum β-lactamase–producing Enterobacteriaceae

Carbapenemase-producing Enterobacteriaceae

Carbapenem-resistant *Pseudomonas aeruginosa* and *Acinetobacter baumannii*

# Resistance in Enterobacteriaceae

| β-Lactamase | Examples | Substrates | Molecular class |
|---|---|---|---|
| Broad-spectrum | TEM-1, TEM-2, SHV-1 | Penicillin G, aminopenicillins, carboxypenicillins, piperacillin, narrow-spectrum cephalosporins | A |
| | OXA family | Substrates of the broad-spectrum group plus cloxacillin, methicillin, and oxacillin | D |
| Extended-spectrum | TEM family, SHV family | Substrates of the broad-spectrum group plus oxyimino-cephalosporins, and monobactam (aztreonam) | A |
| | CTX-M family | Substrates of the expanded-spectrum group plus, for some enzymes, cefepime | A |
| | OXA family | Same as for CTX-M family | D |
| | Others (PER-1, PER-2, BES-1, GES/IBC family, SFO-1, TLA-1, VEB-1, VEB-2) | Same as for TEM family and SHV family | A |
| AmpC | ACC-1, ACT-1, CFE-1, CMY family, DHA-2, FOX family, LAT family, MIR-1, MOX-1, MOX-2 | Substrates of expanded-spectrum group plus cephamycins | C |
| Carbapenemase | IMP family, VIM family, GIM-1, SPM-1 (metallo-β-enzymes) | Substrates of the expanded-spectrum group plus cephamycins and carbapenems | B |
| | KPC-1, KPC-2, KPC-3 | Same as for IMP family, VIM family, GIM-1, and SPM-1 | A |
| | OXA-23, OXA-24, OXA-25, OXA-26, OXA-27, OXA-40, OXA-48 | Same as for IMP family, VIM family, GIM-1, and SPM-1 | D |

資料來源：Paterson DL. Am J Infect Control 2006; 34:S20-8

# Ambler Molecular Classification of β-Lactamases(1/2)

| β-lactamase-class | | β-lactamases | Important examples | Preferential occurrence | Important phenotypical resistance traits[a] |
|---|---|---|---|---|---|
| A | Serine | Broad-spectrum β-lactamases | TEM-1, TEM-2 SHV-1, SHV-11 | Enterobacteriaceae and nonfermenters[b] | ampicillin, cephalotin |
| | | ESBL TEM-type | TEM-3, TEM-52 | | penicillins, 3rd gen. cephalosporins |
| | | ESBL SHV-type | SHV-5, SHV-12 | | |
| | | ESBL CTX-M-type | CTX-M-1, CTX-M-15 | | |
| | | Carbapenemases | KPC, GES, SME | | all β-Lactams[c] |
| C | Serine | AmpC cephamycinases (chromosomal-encoded) | AmpC | Enterobacter spp. Citrobacter spp. | cephamycins (cefoxitin), 3rd gen. cephalosporins |

資料來源：Pfiefer Y, et al. Int J Med Microbiol 2010; 300:371-9

# Ambler Molecular Classification of β-Lactamases(2/2)

| β-lactamase-class | | β-lactamases | Important examples | Preferential occurrence | Important phenotypical resistance traits[a] |
|---|---|---|---|---|---|
| D | Serine | AmpC cephamycinases (plasmid-encoded) | CMY, DHA, MOX FOX, ACC, | Enterobacteriaceae | cephamycins (cefoxitin), 3rd gen. cephalosporins |
| | | Broad-spectrum β-lactamases | OXA-1, OXA-9 | Enterobacteriaceae; A. baumannii | oxacillin, ampicillin cephalotin |
| | | ESBL OXA-type | OXA-2, OXA-10 | | penicillins, 3rd gen. cephalosporins |
| | | Carbapenemases; Carbapenemases | OXA-48; OXA-23,-24,-58 | | ampicillin, imipenem; all β-lactams[c] |
| B | MBL-Zn | Metallo-β-lactamases (Carbapenemases) | VIM IMP | Enterobacteriaceae and nonfermenters | all β-lactams[c] |

資料來源：Pfiefer Y, et al. Int J Med Microbiol 2010; 300:371-9

# Bush-Jacoby Functional Classification of β-Lactamases(1/2)

| Bush-Jacoby group (2009) | Bush-Jacoby-Medeiros group (1995) | Molecular class (subclass) | Distinctive substrate(s) | Inhibited by | | Defining characteristic(s) | Representative enzyme(s) |
|---|---|---|---|---|---|---|---|
| | | | | CA or TZB[a] | EDTA | | |
| 1 | 1 | C | Cephalosporins | No | No | Greater hydrolysis of cephalosporins than benzylpenicillin; hydrolyzes cephamycins | *E. coli* AmpC, P99, ACT-1, CMY-2, FOX-1, MIR-1 |
| 1e | NI[b] | C | Cephalosporins | No | No | Increased hydrolysis of ceftazidime and often other oxyimino-β-lactams | GC1, CMY-37 |
| 2a | 2a | A | Penicillins | Yes | No | Greater hydrolysis of benzylpenicillin than cephalosporins | PC1 |
| 2b | 2b | A | Penicillins, early cephalosporins | Yes | No | Similar hydrolysis of benzylpenicillin and cephalosporins | TEM-1, TEM-2, SHV-1 |
| 2be | 2be | A | Extended-spectrum cephalosporins, monobactams | Yes | No | Increased hydrolysis of oxyimino-β-lactams (cefotaxime, ceftazidime, ceftriaxone, cefepime, aztreonam) | TEM-3, SHV-2, CTX-M-15, PER-1, VEB-1 |
| 2br | 2br | A | Penicillins | No | No | Resistance to clavulanic acid, sulbactam, and tazobactam | TEM-30, SHV-10 |
| 2ber | NI | A | Extended-spectrum cephalosporins, monobactams | No | No | Increased hydrolysis of oxyimino-β-lactams combined with resistance to clavulanic acid, sulbactam, and tazobactam | TEM-50 |
| 2c | 2c | A | Carbenicillin | Yes | No | Increased hydrolysis of carbenicillin | PSE-1, CARB-3 |
| 2ce | NI | A | Carbenicillin, cefepime | Yes | No | Increased hydrolysis of carbenicillin, cefepime, and cefpirome | RTG-4 |
| 2d | 2d | D | Cloxacillin | Variable | No | Increased hydrolysis of cloxacillin or oxacillin | OXA-1, OXA-10 |

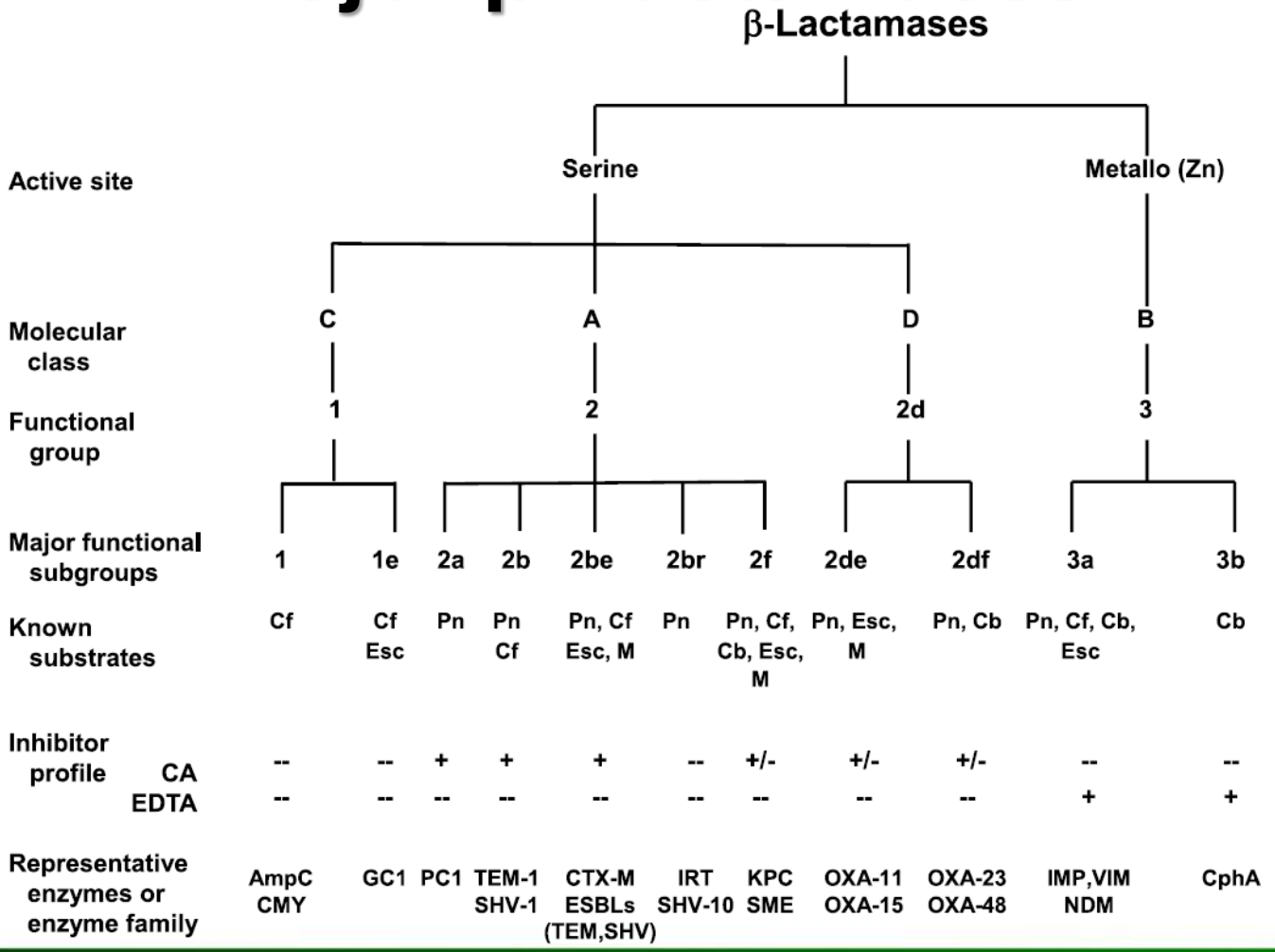
資料來源：Bush K, et al. Antimicrob. Agents Chemother. 2010; 54(3):969-72

# Bush-Jacoby Functional Classification of β-Lactamases(2/2)

| Bush-Jacoby group (2009) | Bush-Jacoby-Medeiros group (1995) | Molecular class (subclass) | Distinctive substrate(s) | Inhibited by | | Defining characteristic(s) | Representative enzyme(s) |
|---|---|---|---|---|---|---|---|
| | | | | CA or TZB[a] | EDTA | | |
| 2de | NI | D | Extended-spectrum cephalosporins | Variable | No | Hydrolyzes cloxacillin or oxacillin and oxyimino-β-lactams | OXA-11, OXA-15 |
| 2df | NI | D | Carbapenems | Variable | No | Hydrolyzes cloxacillin or oxacillin and carbapenems | OXA-23, OXA-48 |
| 2e | 2e | A | Extended-spectrum cephalosporins | Yes | No | Hydrolyzes cephalosporins. Inhibited by clavulanic acid but not aztreonam | CepA |
| 2f | 2f | A | Carbapenems | Variable | No | Increased hydrolysis of carbapenems, oxyimino-β-lactams, cephamycins | KPC-2, IMI-1, SME-1 |
| 3a | 3 | B (B1) | Carbapenems | No | Yes | Broad-spectrum hydrolysis including carbapenems but not monobactams | IMP-1, VIM-1, CcrA, IND-1 |

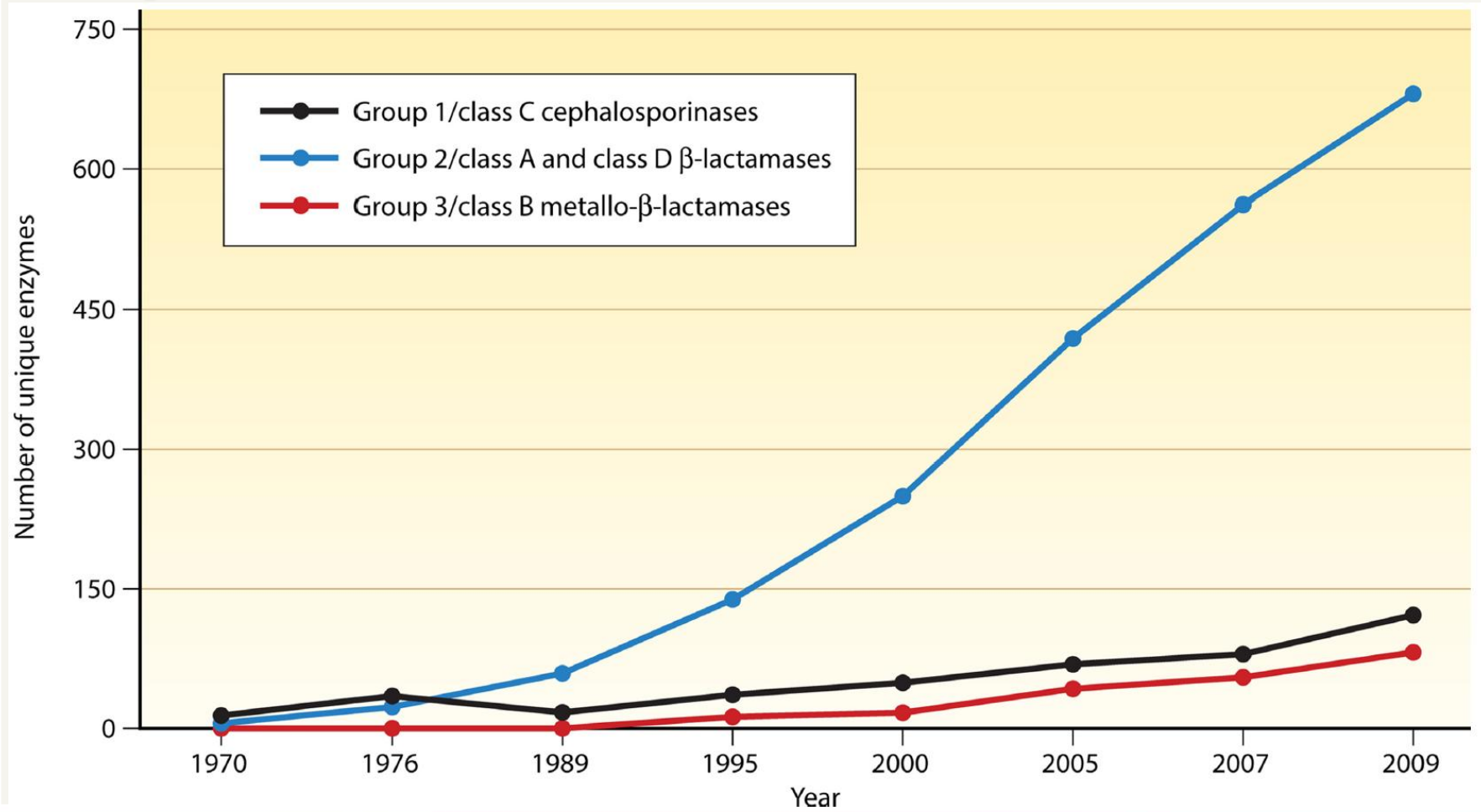
資料來源：Bush K, et al. Antimicrob. Agents Chemother. 2010; 54(3):969-72

# Molecular/Functional Features of Major β-Lactamases




資料來源：Bush K. Ann. N.Y. Acad. Sci. 2013; 1277:84–90

# Increasing No. of Group 1, 2, and 3 β-Lactamases from 1970 to 2009

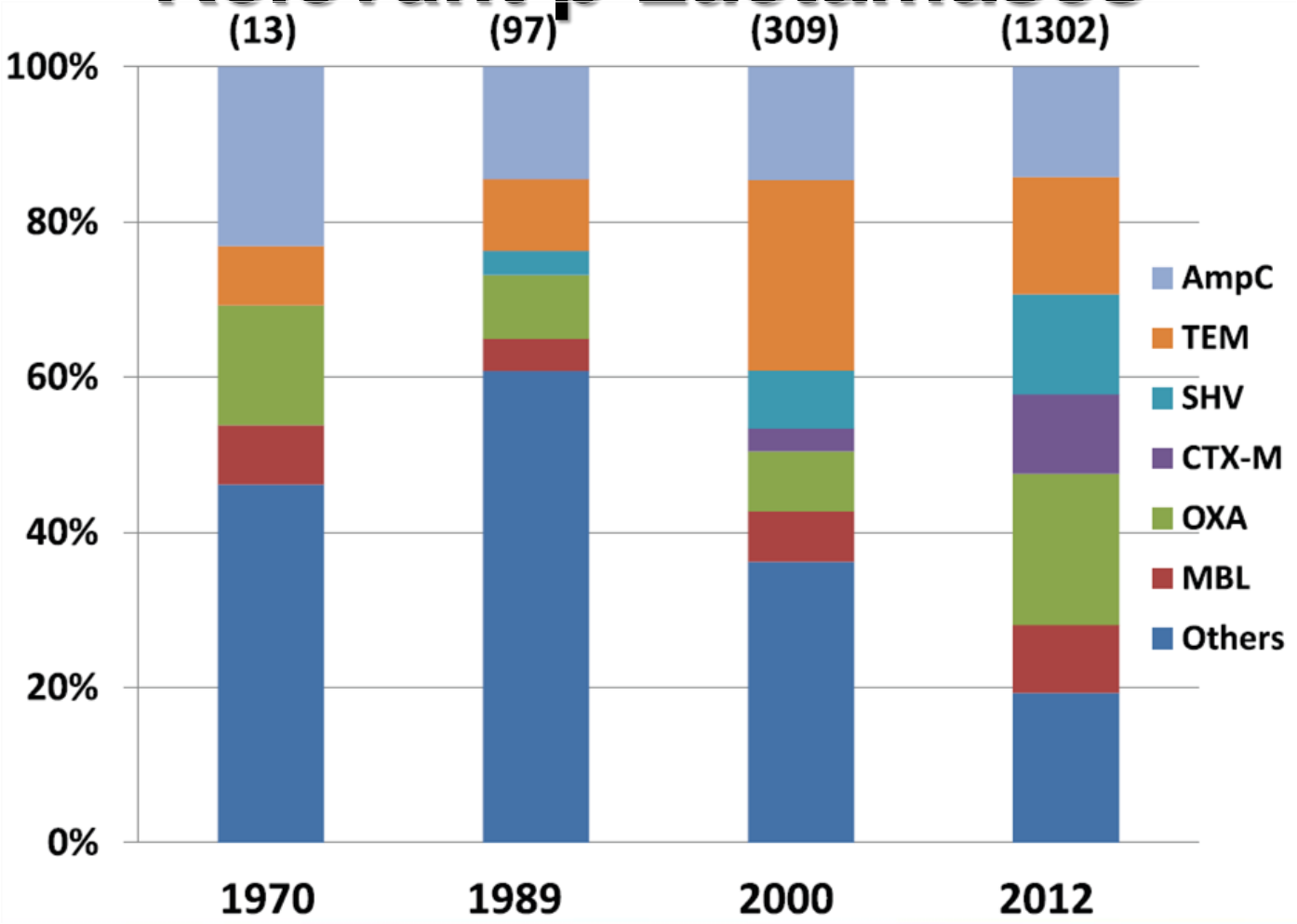


# Extended-Spectrum β-Lactamase-Producing Enterobacteriaceae

| | Country |
|---|---|
| CTX-M1 | Italy |
| CTX-M2 | Israel, Argentina |
| CTX-M3 | Poland |
| CTX-M9 | Spain |
| CTX-M14 | Spain, Canada, China |
| CTX-M15 | Worldwide |

Most common CTX-M enzymes

# Significance of Clinically Relevant β-Lactamases




資料來源：Bush K. Ann. N.Y. Acad. Sci. 2013; 1277:84–90

# Selected β-Lactamases of Gram-Negative Bacteria (1/3)

| β-Lactamase | Examples | Substrates | Inhibition by Clavulanic Acid* | Molecular Class |
|---|---|---|---|---|
| Broad-spectrum | TEM-1, TEM-2, SHV-1 | Benzylpenicillin (penicillin G), aminopenicillins (amoxicillin and ampicillin), carboxypenicillins (carbenicillin and ticarcillin), ureidopenicillin (piperacillin), narrow-spectrum cephalosporins (cefazolin, cephalothin, cefamandole, cefuroxime, and others) | +++ | A |
| | OXA family | Substrates of the broad-spectrum group plus cloxacillin, methicillin, and oxacillin | + | D |

資料來源：Jacoby GA, et al. N Engl J Med 2005; 352:380-91

# Selected β-Lactamases of Gram-Negative Bacteria (2/3)

| β-Lactamase | Examples | Substrates | Inhibition by Clavulanic Acid* | Molecular Class |
|---|---|---|---|---|
| Expanded-spectrum | TEM family and SHV family | Substrates of the broad-spectrum group plus oxyimino-cephalosporins (cefotaxime, cefpodoxime, ceftazidime, and ceftriaxone) and monobactam (aztreonam) | ++++ | A |
| | Others (BES-1, GES/IBC family, PER-1, PER-2, SFO-1, TLA-1, VEB-1, and VEB-2) | Same as for TEM family and SHV family | ++++ | A |
| | CTX-M family | Substrates of the expanded-spectrum group plus, for some enzymes, cefepime | ++++ | A |

資料來源：Jacoby GA, et al. N Engl J Med 2005; 352:380-91

# Selected β-Lactamases of Gram-Negative Bacteria (3/3)

| β-Lactamase | Examples | Substrates | Inhibition by Clavulanic Acid* | Molecular Class |
|---|---|---|---|---|
| AmpC | ACC-1, ACT-1, CFE-1, CMY family, DHA-1, DHA-2, FOX family, LAT family, MIR-1, MOX-1, and MOX-2 | Substrates of expanded-spectrum group plus cephamycins (cefotetan, cefoxitin, and others) | 0 | C |
| Carbapenemase | IMP family, VIM family, GIM-1, and SPM-1 | Substrates of the expanded-spectrum group plus cephamycins and carbapenems (ertapenem, imipenem, and meropenem) | 0 | B |
| | KPC-1, KPC-2, and KPC-3 | Same as for IMP family, VIM family, GIM-1, and SPM-1 | +++ | A |
| | OXA-23, OXA-24, OXA-25, OXA-26, OXA-27, OXA-40, and OXA-48 | Same as for IMP family, VIM family, GIM-1, and SPM-1 | + | D |

資料來源：Jacoby GA, et al. N Engl J Med 2005; 352:380-91

# Metallo-β-Lactamases

| IMP-1 | |
|---|---|
| Japan | *Pseudomonas aeruginosa*[7] |
| Japan | Enterobacteriaceae[8] |
| Japan | *Acinetobacter baumannii*[9] |
| Japan | *Acinetobacter xylosoxidans*[10] |

| IMP-2 | |
|---|---|
| Italy | *A baumannii*[11] |
| Japan | *P aeruginosa*[10] |

| IMP-8 | |
|---|---|
| Taiwan | Enterobacteriaceae[18] |
| China | *A baumannii*[19] |
| Portugal | *Pseudomonas mendocina*[20] |

| VIM-2 | |
|---|---|
| France | *P aeruginosa*[35] |
| Korea | *A baumannii*[36] |
| Taiwan | Enterobacteriaceae[37] |
| Greece | *A xylosoxidans*[38] |

| VIM-3 | |
|---|---|
| Taiwan | *P aeruginosa*[39] |
| Taiwan | *A baumannii*[30] |
| Taiwan | Enterobacteriaceae[30] |

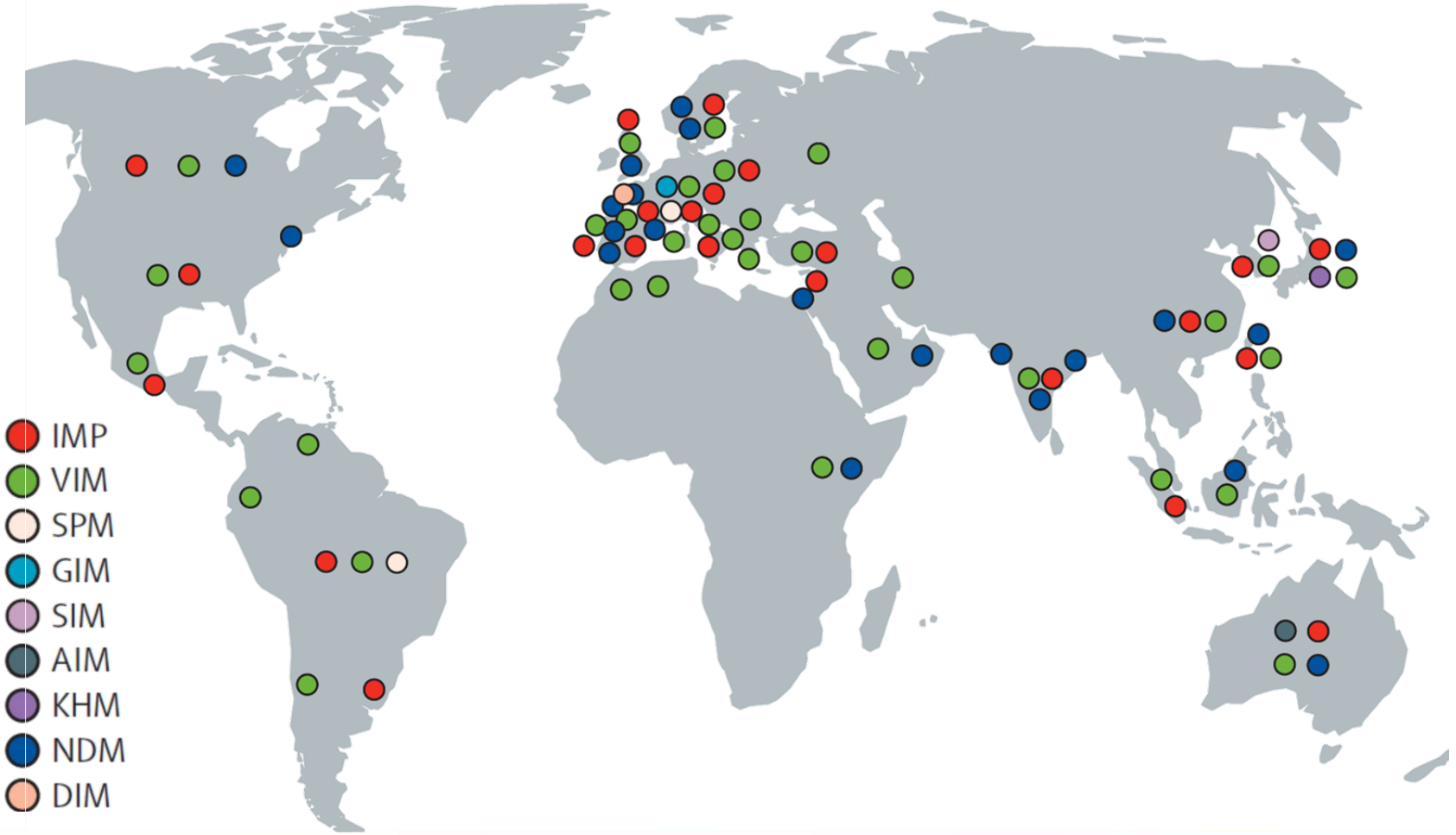
| VIM-11 | |
|---|---|
| Argentina | *P aeruginosa*[50] |
| Taiwan | *A baumannii*[51] |
| Taiwan | Enterobacteriaceae[51] |

資料來源：Cornaglia, G, et al. Lancet Infect Dis 2011; 11:381–93

# Carbapenem-resistant Enterobacteriaceae

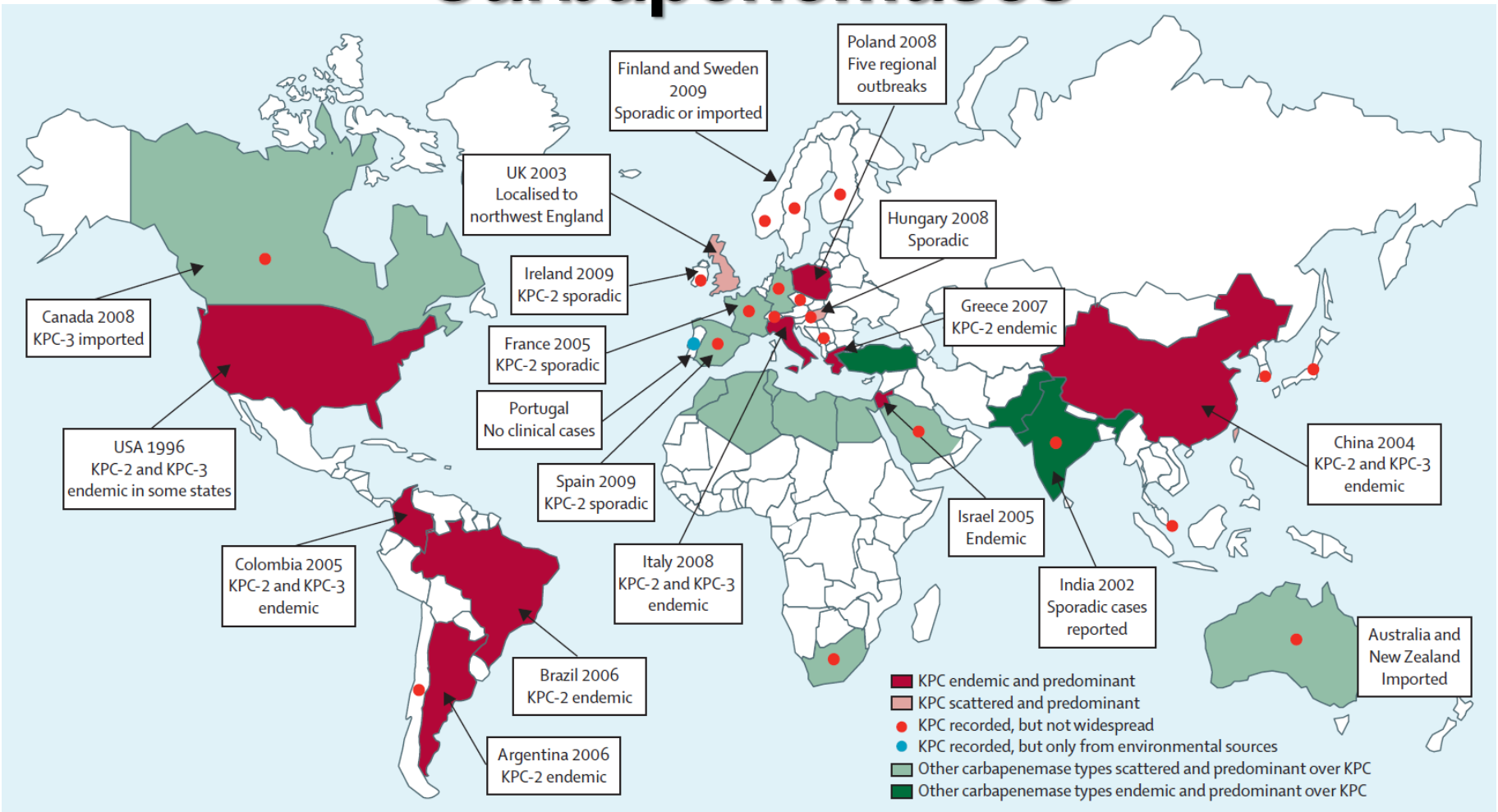
- 同時為ESBL-producing (CTX-M)，並帶有outer membrane change。
- 同時為ESBL-producing (CTX-M)，並帶有up-regulation of efflux pump。
- 同時為AmpC β-lactamase-producing，並帶有outer membrane change。
- 同時為AmpC β-lactamase-producing，並帶有up-regulation of efflux pump。
- Secretion of carbapenemases in the plasmid.

# Worldwide Types of Metallo-β-Lactamases




資料來源：Cornaglia, G, et al. Lancet Infect Dis 2011; 11:381–93

# Global Expansion of KPC Carbapenemases



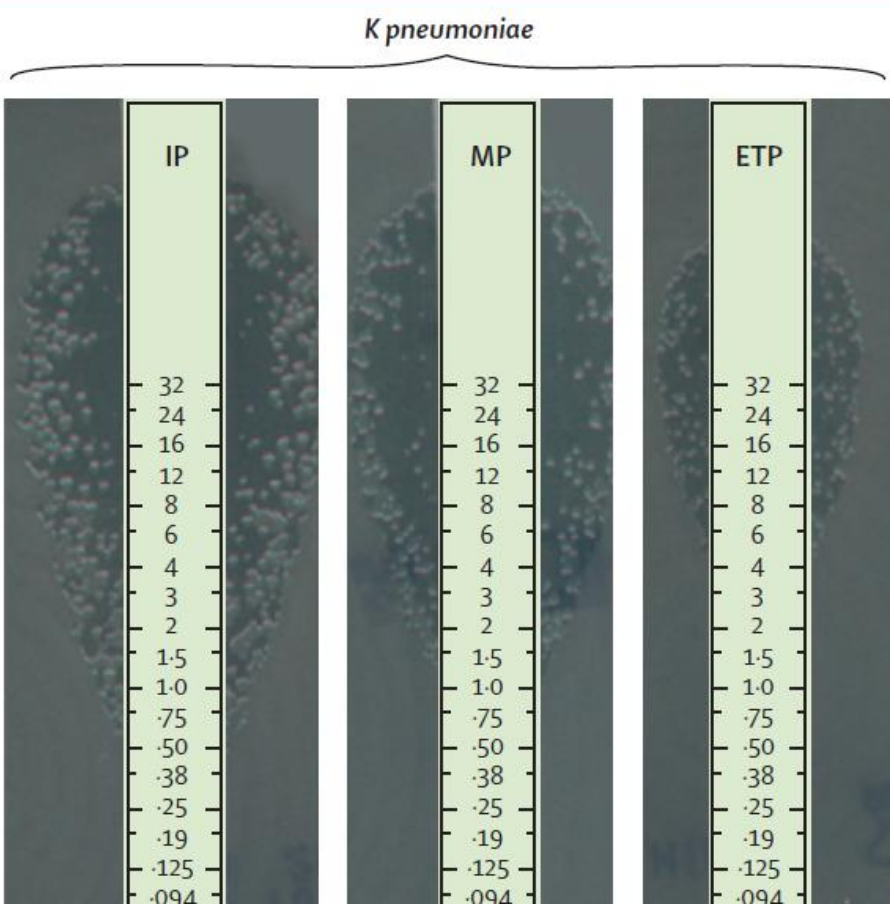

資料來源：Munoz-Price LS, et al. Lancet Infect Dis 2013; 13:785–96

# Mechanisms Involving Carbapenem Resistance of AB

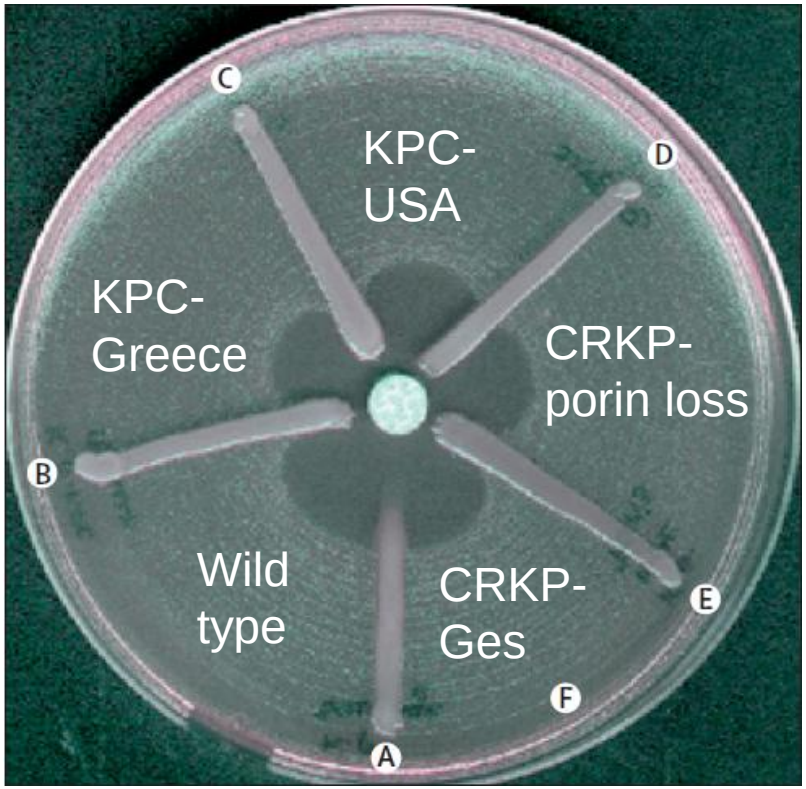
- Metallo-β-lactamases (MBLs)
  - IMP-, VIM- group
- Carbapenem-hydrolysing oxacillinases (CHDLs)
  - OXA- group
- Loss of outer membrane proteins (OMPs [porin])
  - Decreased permeability
- Over expression of efflux pump

資料來源：Poirel L, et al. Clin Microbiol Infect 2006; 12:826–36
Giamarellou H, et al. Int J Antimicrob Agents 2008; 32:106–19

# KPC-Enterobacteriaceae




Susceptibility- Etest




Modified Hodge test

# Detection Carbapenemase in CRAB

| Name | Nucleotide sequence (5′–3′) | Location |
|---|---|---|
| Ab-GF | ACAAGAAATCTGCTCGT | *gyrA* |
| Ab-GR | CGAAGTTACCCTGACCATC | *gyrA* |
| 5′-CS | GGCATCCAAGCAGCAAG | Integron |
| 3′-CS | AAGCAGACTTGACCTGA | Integron |
| ACI10 | GCTGAACGCGATAAACTTC | IS*Aba1* of $bla_{AmpC}$ |
| ACI2 | TAGTACTGCTATTTACGGCT | $bla_{AmpC}$ |
| IMP-A | GAAGGYGTTTATGTTCATAC | $bla_{IMP}$ |
| IMP-B | GTAMGTTTCAAGAGTGATGC | $bla_{IMP}$ |
| VIM2004A | GTTTGGTCGCATATCGCAAC | $bla_{VIM}$ |
| VIM2004B | AATGCGCAGCACCAGGATAG | $bla_{VIM}$ |
| OXA23-F | GATCGGATTGGAGAACCAGA | $bla_{OXA-23}$ |
| OXA23-R | ATTTCTGACCGCATTTCCAT | $bla_{OXA-23}$ |
| OXA24-F | GGTTAGTTGGCCCCCTTAAA | $bla_{OXA-24-like}$ |
| OXA24-R | AGTTGAGCGAAAAGGGGATT | $bla_{OXA-24-like}$ |
| OXA51-F | TAATGCTTTGATCGGCCTTG | $bla_{OXA-51-like}$ |
| OXA51-R | TGGATTGCACTTCATCTTGG | $bla_{OXA-51-like}$ |
| OXA-58-F | AAGTATTGGGGCTTGTGCTG | $bla_{OXA-58}$ |
| OXA-58-R | CCCCTCTGCGCTCTACATAC | $bla_{OXA-58}$ |
| OXA-58A | CGATCAGAATGTTCAAGCGC | $bla_{OXA-58}$ |
| OXA-58B | ACGATTCTCCCCTCTGCGC | $bla_{OXA-58}$ |
| ISAba3B | CGTTTACCCCAAACATAAGC | *tnpA* of IS*Aba3* (but not in IS*Aba3*-like) |
| ISAba3C | AGCAATATCTCGTATACCGC | *tnpA* of *ISAba3*-like and IS*Aba3* |
| ISAba1-F | GGATCCCTCTGTACACGAYAAATTTC | IS*Aba1* |
| OXA23-R1 | GAATTCTTAAATAATATTCAGCTGTTTTAATG | $bla_{OXA-23}$ |
| OXA51-R1 | GAATTCCTATAAAATACCTAATTGTTCTAAAC | $bla_{OXA-51-like}$ |

資料來源：Lin YC, Sheng WH, et al. Antimicrob Agents Chemother 2010; 54:2078-84

# Main Mechanisms of Antimicrobial Resistance of *A. baumannii*

**Remarkable capacity to show resistance to antibiotics of most classes**

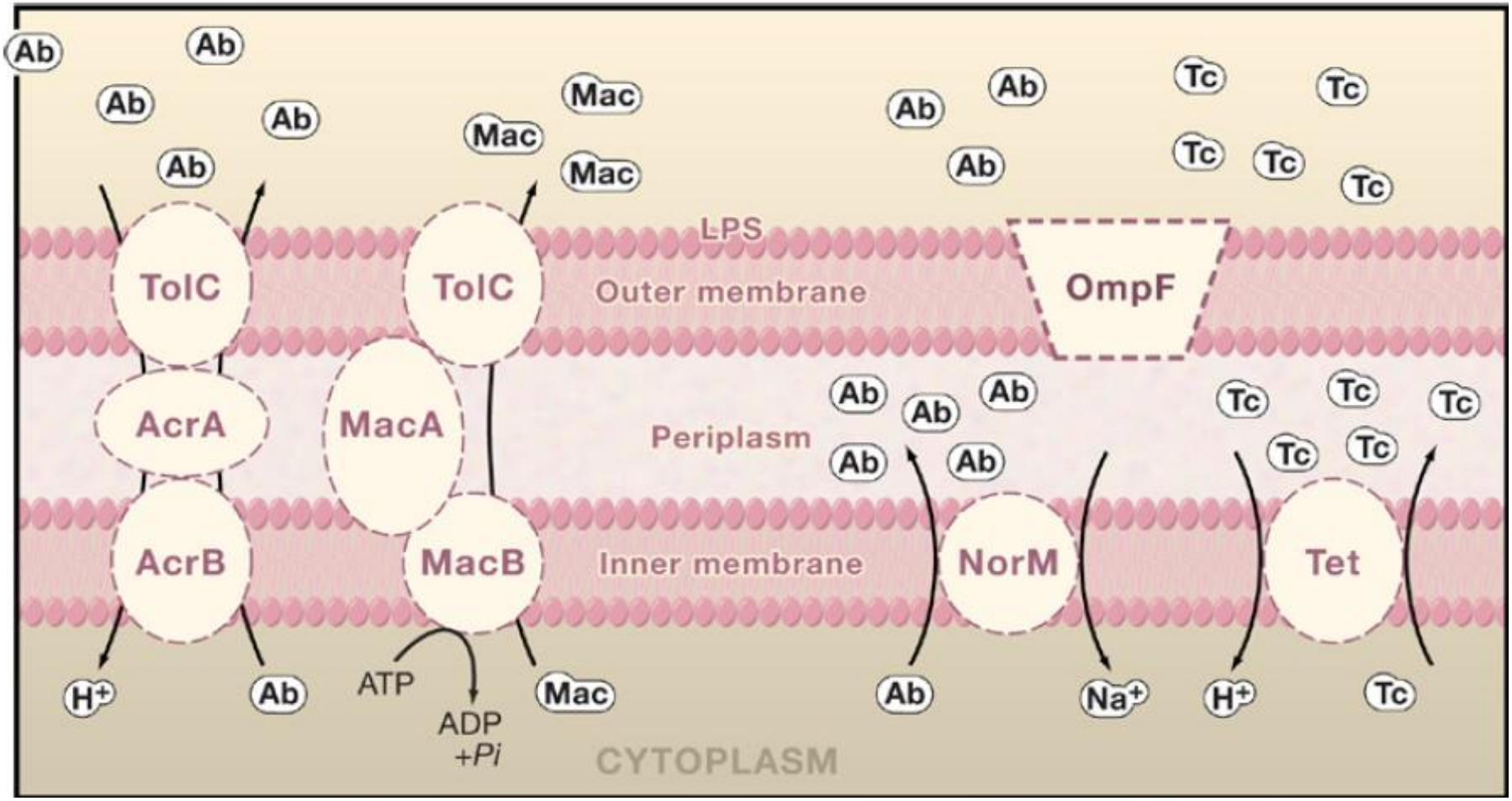
- Intrinsically, or
- Following acquisition of resistance

**Various mechanisms of resistance**

- Production of β lactamases
- Efflux pumps
- Lower permeability of the outer membrane
- Mutations in antibiotic targets (eg, for quinolones)
- Production of enzymes inactivating aminoglycosides

資料來源：Karageorgopoulos D, et al. Lancet Infect Dis 2008; 8:751–62

# Efflux Pump and Outer Membrane Protein

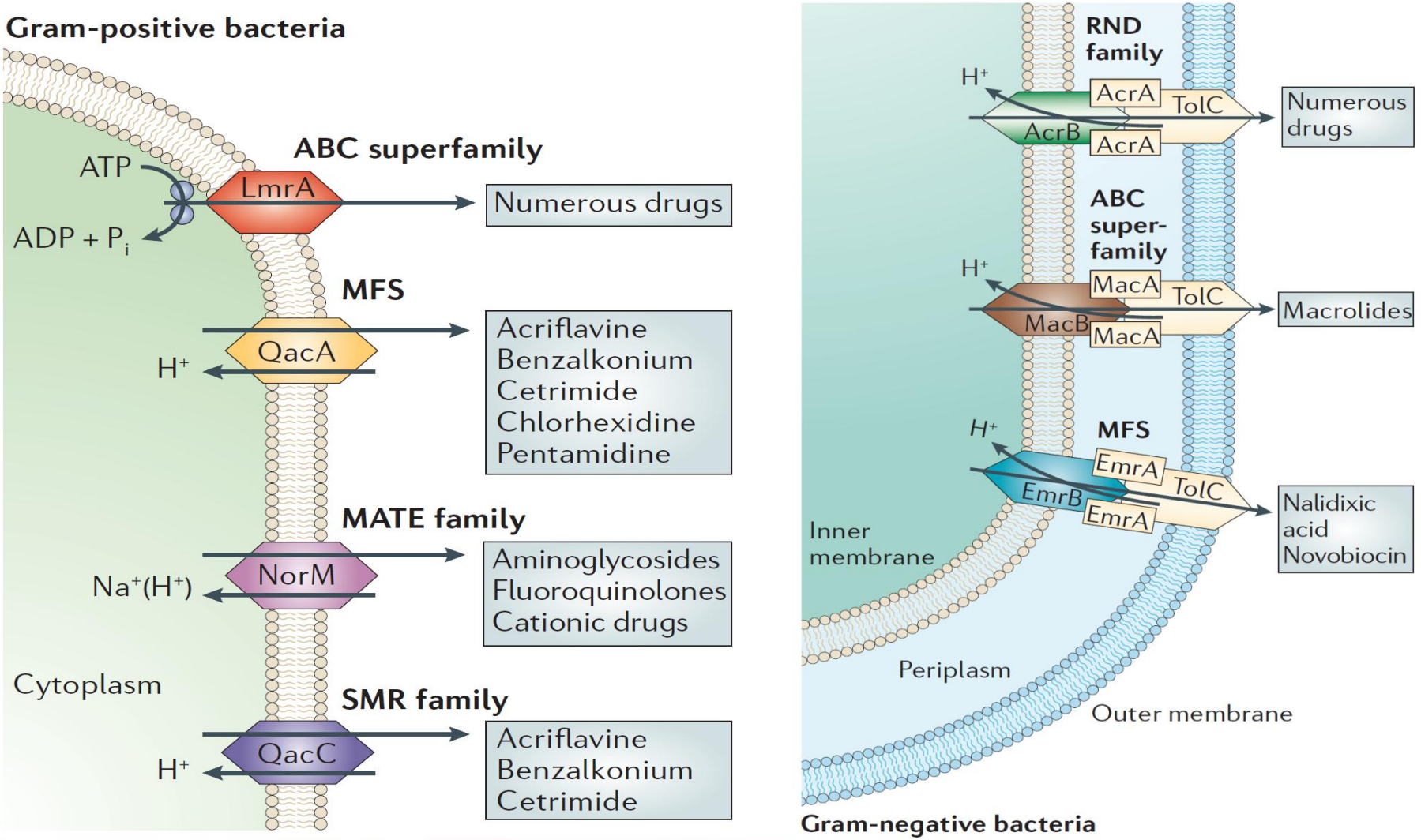



資料來源：Alekshun MN, et al. Cell 2007; 128:1037-50

# Families of Multidrug-resistant Efflux Pumps

- ATP-binding cassette (ABC) superfamily
- Major facilitator superfamily (MFS)
- Multidrug and toxic-compound extrusion (MATE) family
- Small multidrug resistance (SMR) family
- Resistance nodulation division (RND) family

# Multidrug-resistant Efflux Pumps




資料來源：Piddock LJV. Nature Reviews Microbiol 2006; 4:629-36

# 5.結論

# 結論

- 抗藥性細菌增加與抗生素大量使用有關。
- 細菌發展不同抗藥機轉的演進，可導致細菌對不同類抗生素均有抗藥性。
- 抗藥性基因可以利用多種機制（如質體或轉位子）在不同細菌間傳遞。
- 細菌可以同時存在抗藥性基因於染色體或質體上於抗生素環境時使用。

# 課程結束