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Antimicrobials

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This session covers:

- A classification of antimicrobials
- Mechanisms of action
- Mechanisms of resistance
- Genetics of resistance
- Susceptibility testing
- Brief information on key antibacterials
- An introduction to antifungal, antiviral & antiprotozoal agents

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A very brief history

- 1910 Paul Ehrlich discovered 1st agent
  - A systematic survey of synthesised arsenicals to exploit 'selective toxicity' '606' (Salvarsan) for syphilis
- 1928 Fleming discovers penicillin – the first antibiotic
- 1935 Domagk developed Prontosil
  - 1st sulphonamide red dye binding to bacteria & parasites
- 1941 Florey et al use penicillin for the first time
- 1940s/50s streptomycin, chloramphenicol, tetracycline, cephalosporins, erythromycin, vancomycin
- 1960s gentamicin
- Very few new classes in last few decades

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Antimicrobials – classification

- Antibacterial, antifungal, antiviral & antiprotozoal agents
- Antibacterial agents can be classified:
  - Bactericidal or bacteriostatic
  - Spectrum – 'broad' v. 'narrow'
  - Target site (mechanism of action)
  - Chemical structure (antibacterial class)

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Ideal features of antimicrobial agents

- Selectively toxic
- Few adverse effects
- Reach site of infection
- Oral/IV formulation
- Long half-life (infrequent dosing)
- No interference with other drugs

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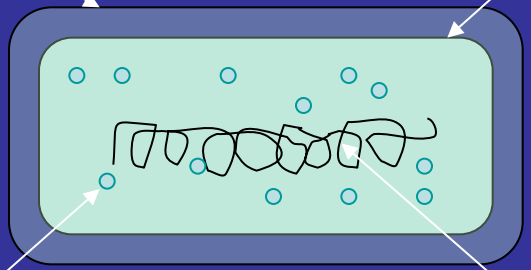
Classes of antibacterials and their mechanism of action

Cell wall synthesis

Beta-lactams

glycopeptides



Cell membrane function

Polymixins (e.g. colistin)

Protein synthesis

Tetracyclines

Aminoglycosides

Macrolides

Nucleic acid synthesis

Quinolones

trimethoprim

rifampicin

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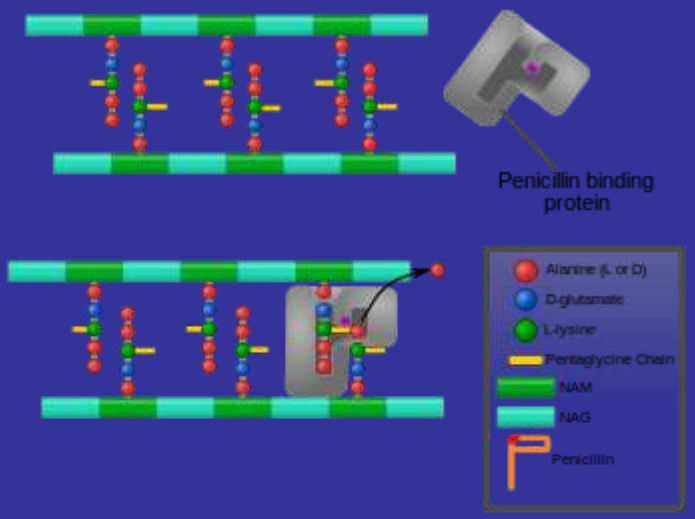
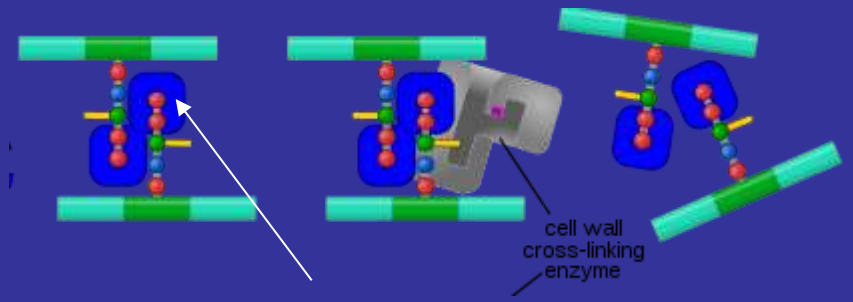
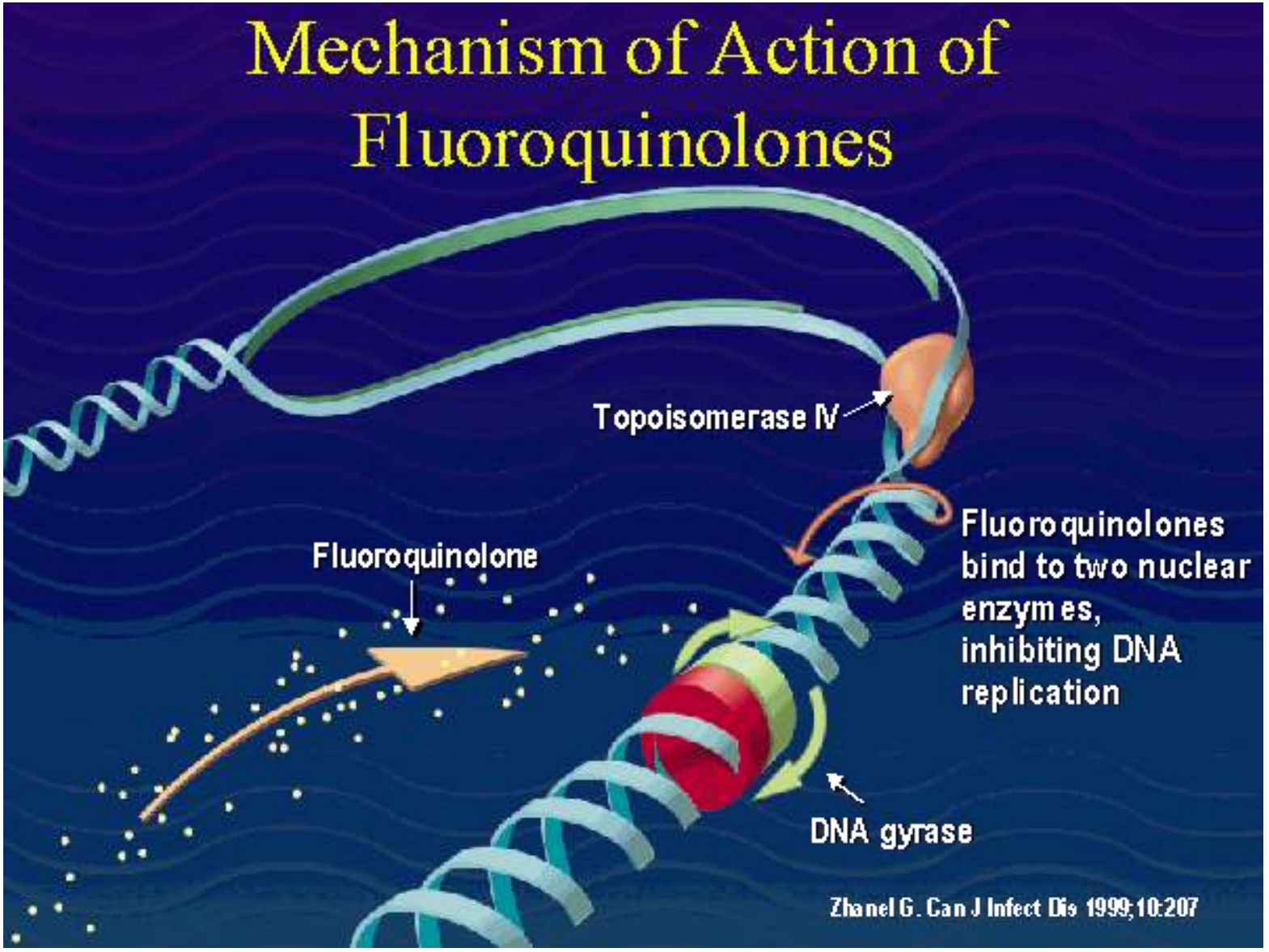




vancomycin

penicillin


Mechanism of Action of Fluoroquinolones
Topoisomerase IV
Fluoroquinolone
Fluoroquinolones bind to two nuclear enzymes, inhibiting DNA replication
DNA gyrase
Zhanel G. Can J Infect Dis 1999;10:207

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Mechanisms of resistance

- Drug inactivating enzymes
  - e.g. B-lactamases, aminoglycoside enzymes
- Altered target
  - Target enzyme has lowered affinity for antibacterial e.g. resistance to meticillin, macrolides & trimethoprim
- Altered uptake
  - ↓permeability (e.g. B-lactams)
  - or ↑efflux (e.g. tetracyclines)

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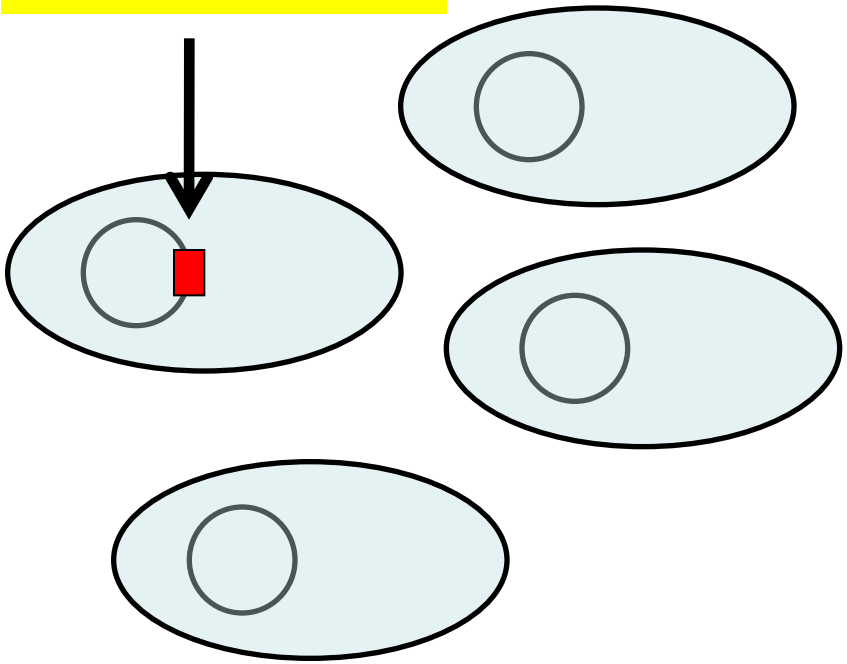
Genetic basis of antibiotic resistance

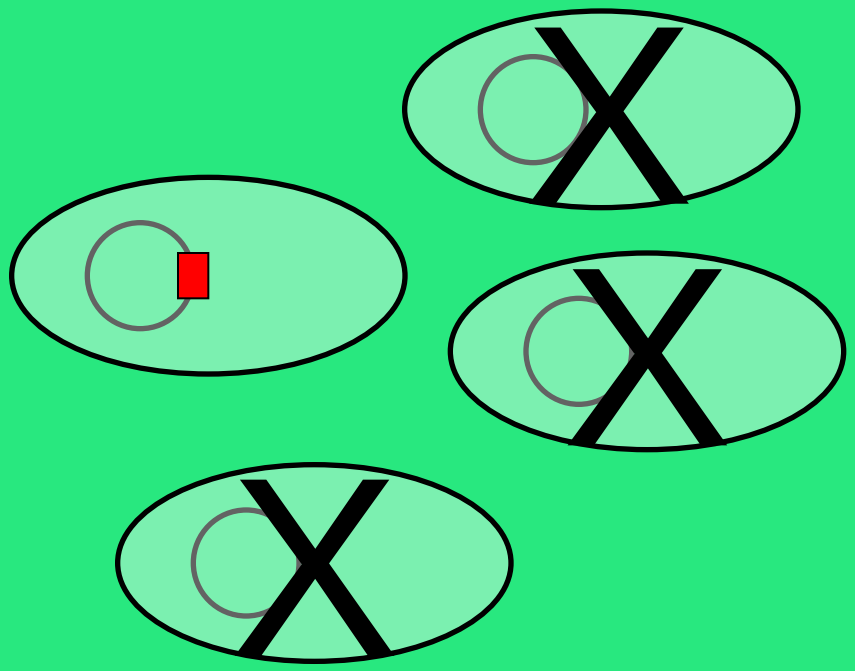
- Chromosomal gene mutation
- Horizontal gene transfer

Chromosomal gene mutation

Mutated gene conferring resistance



Chromosomal gene mutation



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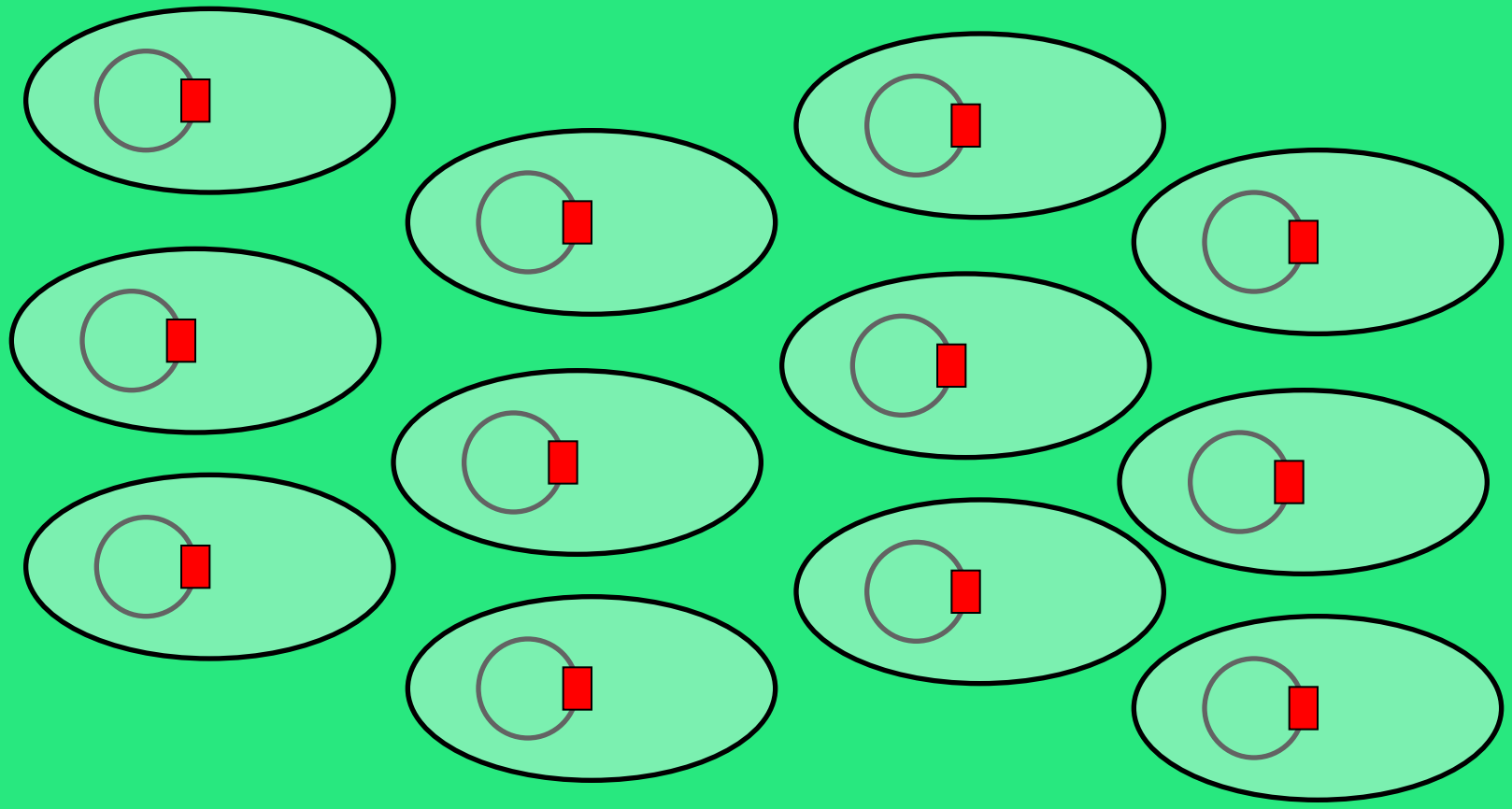
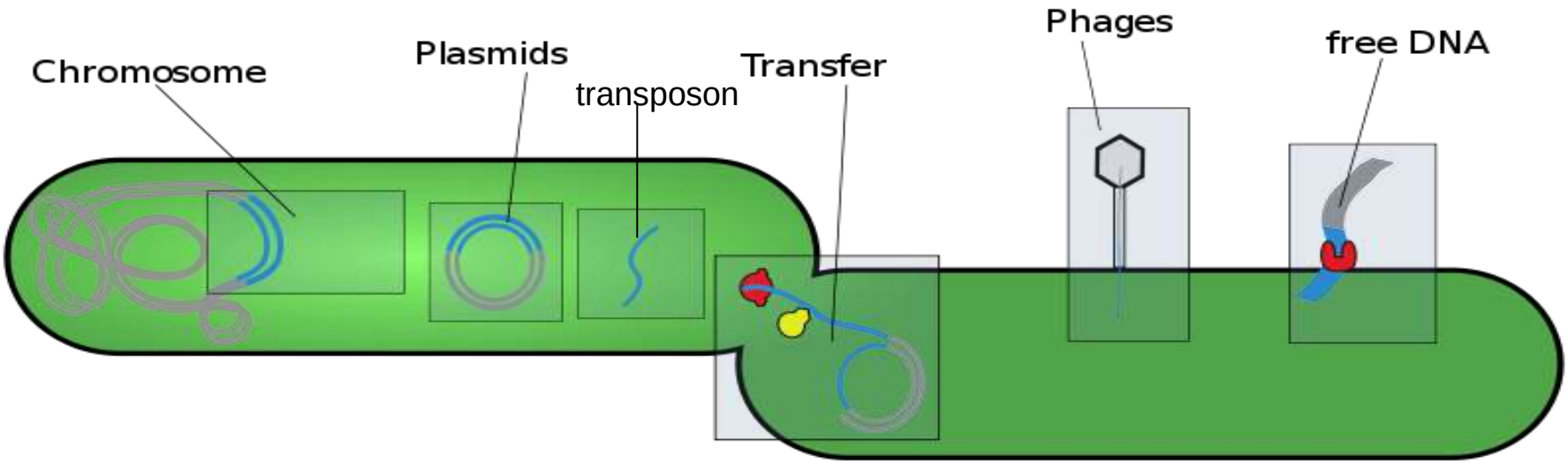
Chromosomal gene mutation

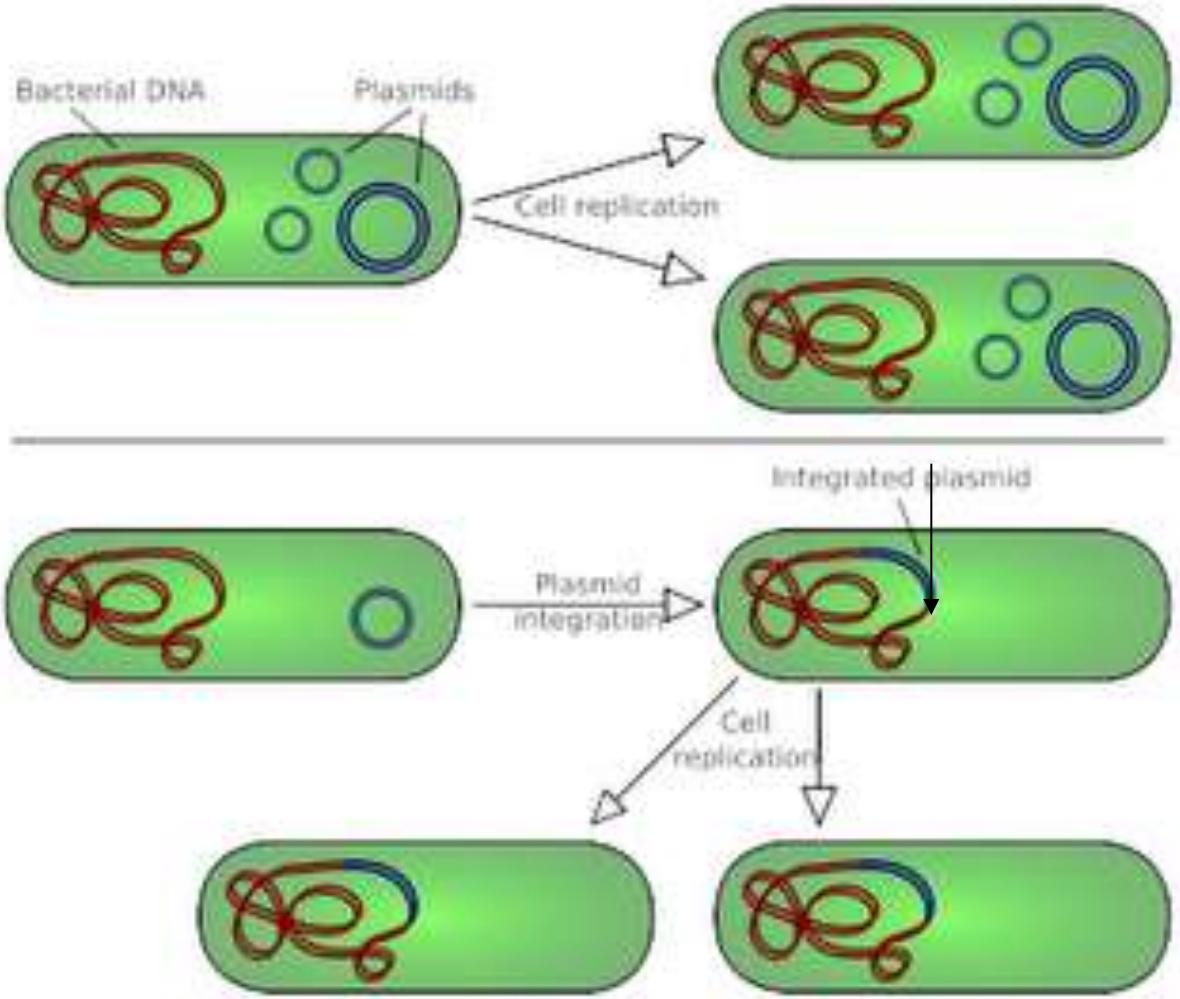


Horizontal gene transfer



conjugation **transduction** **transformation**

Horizontal gene transfer

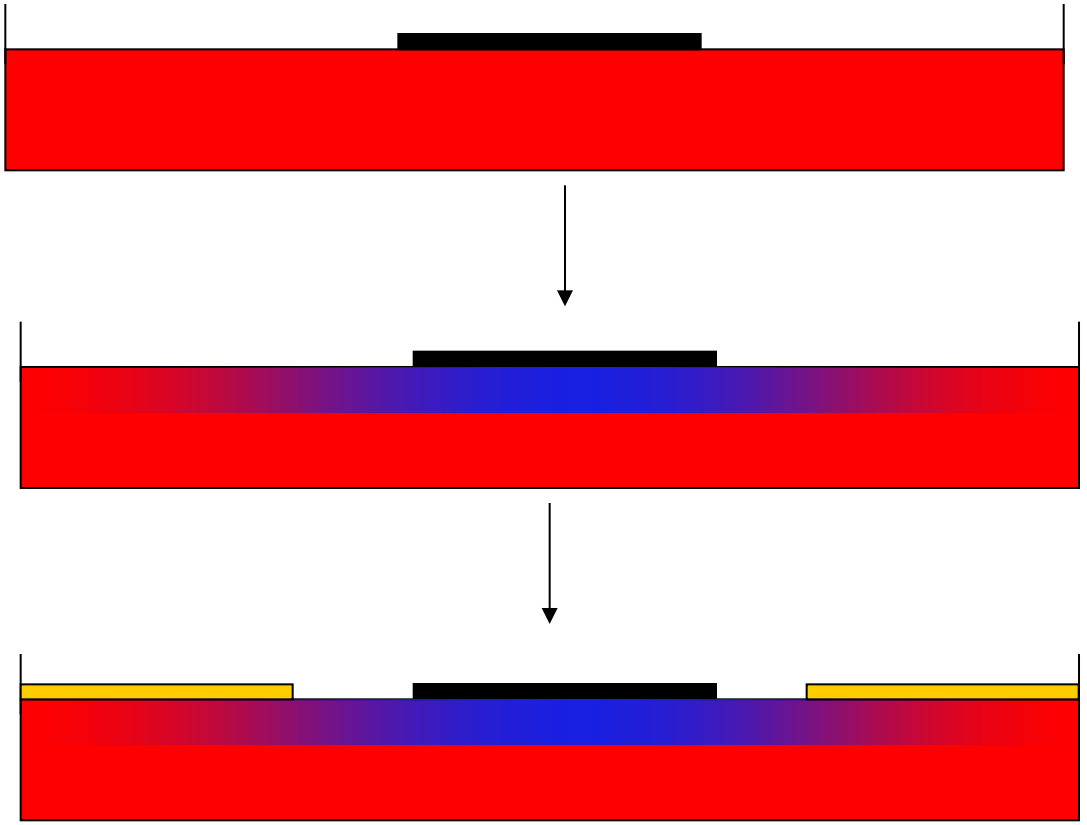


Measuring antibiotic activity

Disc sensitivity testing

Measuring antibiotic activity

- Disc testing



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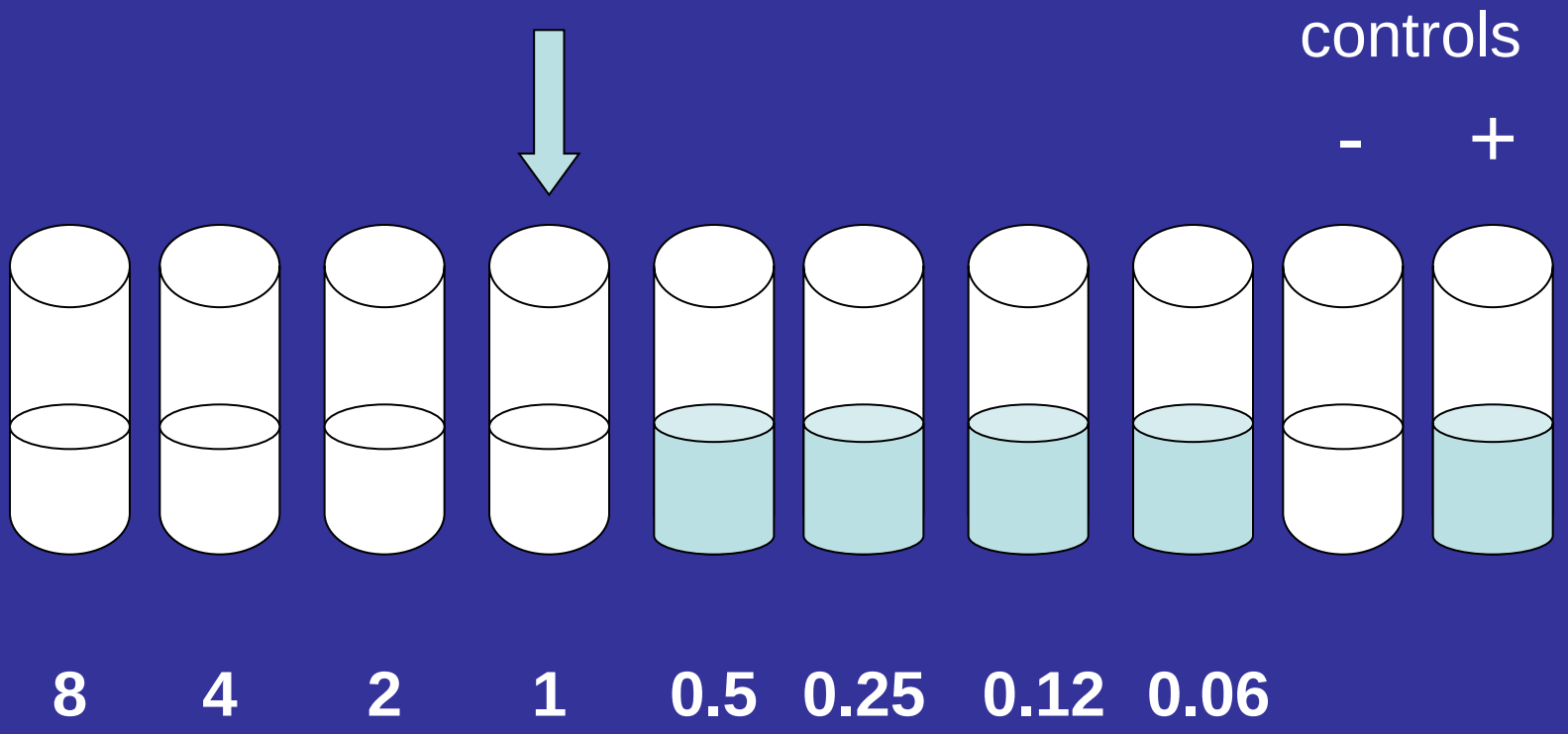
Minimum inhibitory concentration



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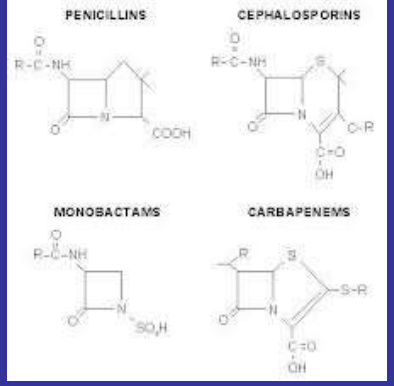
Beta-lactams



Penicillins	cephalosporins		carbapenems	monobactams
benzylpenicillin	Cefalexin	1st	meropenem	aztreonam
penicillin V	Cefuroxime	2nd	imipenem	
amoxicillin	cefotaxime	3rd		
flucloxacillin	Ceftriaxone	3rd		
Co-amoxiclav (amox+clavulanate)	Ceftazidime	3rd		
Tazocin© (piperacillin+ tazobactam				

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Penicillins

- Penicillin
  - Mainly active against streptococci
- Amoxicillin
  - Also some activity against Gram-negatives
- Flucloxacillin
  - Active against staphylococci & streptococci
- B-lactamase inhibitor combinations
  - Co-amoxiclav (all of above +anaerobes + ↑Gneg
  - Piperacillin/tazobactam (as above + ↑↑ Gneg incl pseudomonas)

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Cephalosporins

- 'Generations' with ↑Gneg and ↓Gpos
- ↑broad-spectrum but no anaerobe activity
- Cetriaxone has good activity in the CSF
- Concern over association with *C. difficile*

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Carbapenems

- Carbapenems: Meropenem (& imipenem)
  - Very broad spectrum (incl anaerobes)
  - Active against most (not all) Gram negs
  - Generally safe in penicillin allergy, other than anaphylaxis

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Glycopeptides

- Vancomycin
  - Active against most Gram pos (not Gnegs)
  - Some enterococci resistant (VRE)
  - Resistance in staphs rare
  - Not absorbed (oral for *C. difficile* only)
  - Therapeutic drug monitoring (TDM) required (narrow therapeutic window)
- Teicoplanin
  - Similar activity to vancomycin
  - Easier to administer

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Tetracyclines

- Tetracycline & doxycycline
  - Similar spectrum, both oral only
  - Broad-spectrum but specific use in penicillin allergy, usually for Gram pos
  - Active in atypical pathogens in pneumonia
  - Active against chlamydia & some protozoa
  - Shouldn’t be given to children <12 years

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Aminoglycosides

- Most common agent is gentamicin
- Profound activity against Gram negs
- Good activity in the blood/urine
- Potentially nephrotoxic/ototoxic
- Therapeutic drug monitoring (TDM) required
- Generally reserved for severe Gram neg sepsis

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Macrolides

- e.g. erythromycin (& clarithromycin)
- Well distributed including intracelleluar penetration
- Alternative to penicillin for mild Gram pos infections
- Also active against atypical respiratory pathogens

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Quinolones

- Commonest example ciprofloxacin
- Inhibit DNA gyrase
- Very active against Gram negs
- Also active against atypical pathogens
- Increasing resistance and risk of *C. difficile*

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Trimethoprim & sulphonamides

- Inhibitors of folic acid synthesis
- Trimethoprim used alone in the UK for UTI
- When combined with sulphamethoxazole
  - Co-trimoxazole
  - Used to treat PCP
  - Has activity against MRSA

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Antifungals

- Azoles (active against yeasts +/- molds
  - Inhibit cell-membrane synthesis
  - Fluconazole used to treat Candida
    - Itra/vori/posaconazole also active against Aspergillus
- Polyenes (nystatin and amphotericin)
  - Inhibit cell membrane function
  - Nystatin for topical treatment of candida
  - Amphotericin for IV treatment of systemic fungal infections (e.g. aspergillus)

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Antivirals

- Aciclovir
  - When phosphorylated inhibits viral DNA polymerase
  - Herpes simplex – genital herpes, encephalitis
  - Varicella zoster – chicken pox & shingles
- Oseltamivir ('Tamiflu')
  - Inhibits viral neuraminidase
  - Influenza A & B
- Specialist agents for HIV, HBV, HCV, CMV

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Metronidazole: an antibacterial and Antiprotozoal agent

- Active against anaerobic bacteria
- Also active against protozoa:
  - Amoebae (dysentery & systemic)
  - Giardia (diarrhoea)
  - Trichomonas (vaginitis)

Benzylpenicillin (Penicillin G) BNF SPC

- A penicillin
- Usual adult dose 1.2 g IV QDS increasing to 1.2 g 4-hourly for streptococcal endocarditis or 2.4 g QDS for meningococcal sepsis
- Dosage reduction necessary if renal impairment
- Available IV only.
- Crosses CSF only if meninges inflamed.

Main indications

- Streptococcal endocarditis
- Other serious streptococcal infections, including neonatal sepsis

Active against most strains of:

- Streptococci (Group A, B, C, G, viridans, pneumoniae, milleri)
- *Neisseria meningitidis*
- *Neisseria gonorrhoeae* - although many strains have low level resistance
- *Clostridium difficile*
- *Clostridium perfringens*

Not active against most strains of:

- Staphylococci
- Coliforms
- *Haemophilus influenzae*
- *Pseudomonas* spp.
- *Bacteroides fragilis*

Page last edited: 06/04/2011