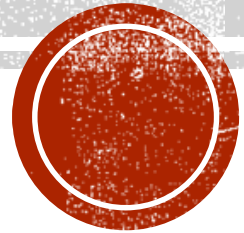
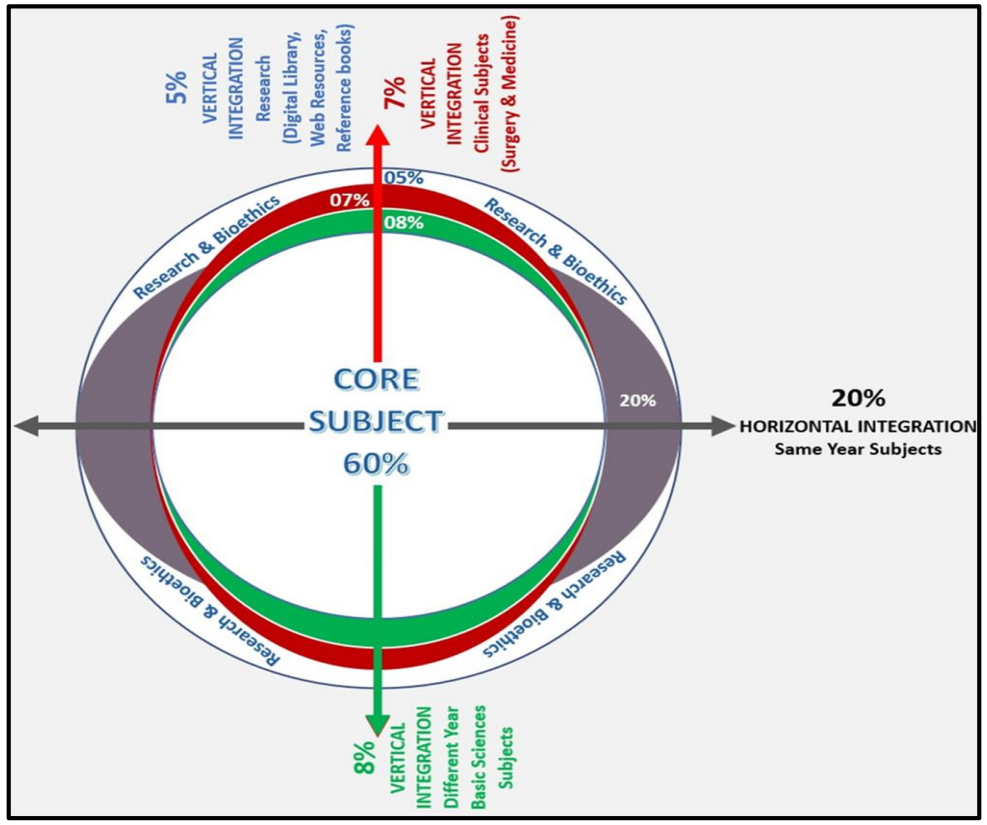
GENERAL PRINCIPLES OF CHEMOTHERAPY AND MECHANISMS OF RESISTANCE



- Katzung's Basic & Clinical Pharmacology, 15th Edition
- Goodman and Gilmans The Pharmacological Basis of Therapeutics, 13th Edition

UMAR'S MODEL OF INETGRATION



3rd Year Pharmacology LGIS	
Core Subject – 60%	
Pharmacology	
Horizontal Integration – 10%	
Same Year Subjects	• Pathology (10%)
Vertical Integration – 10%	
Clinical Subjects	• Medicine (10%)
Spiral Integration – 15%	
Different Year Basic Sciences Subjects	• Physiology (10%) • Biochemistry (5%)
Vertical Integration – 05%	
Research & Bioethics	

LEARNING OBJECTIVES

At the end of the session, students of 3rd Year MBBS will be able to;

Define & differentiate between antimicrobials and antibiotics

Classify antimicrobials into general classes

Outline the general principles of selection and use of antimicrobial

Define antimicrobial resistance and discuss different mechanisms of resistance

He coined the word “chemotherapy” in 1906 and produced the first successful synthetic agent “SALVARSAN” to cure a human infection (syphilis) in 1910.

PAUL EHRLICH (1854-1915)

CHEMOTHERAPY

- Treatment of disease by means of a chemical or biological agent that have a specific toxic effect upon the disease producing organism or **that selectively destroy cancerous tissues**
- Treatment of systemic infections with specific drugs that selectively suppress or kill the infecting microorganism without significantly affecting the host

CHEMOTHERAPY

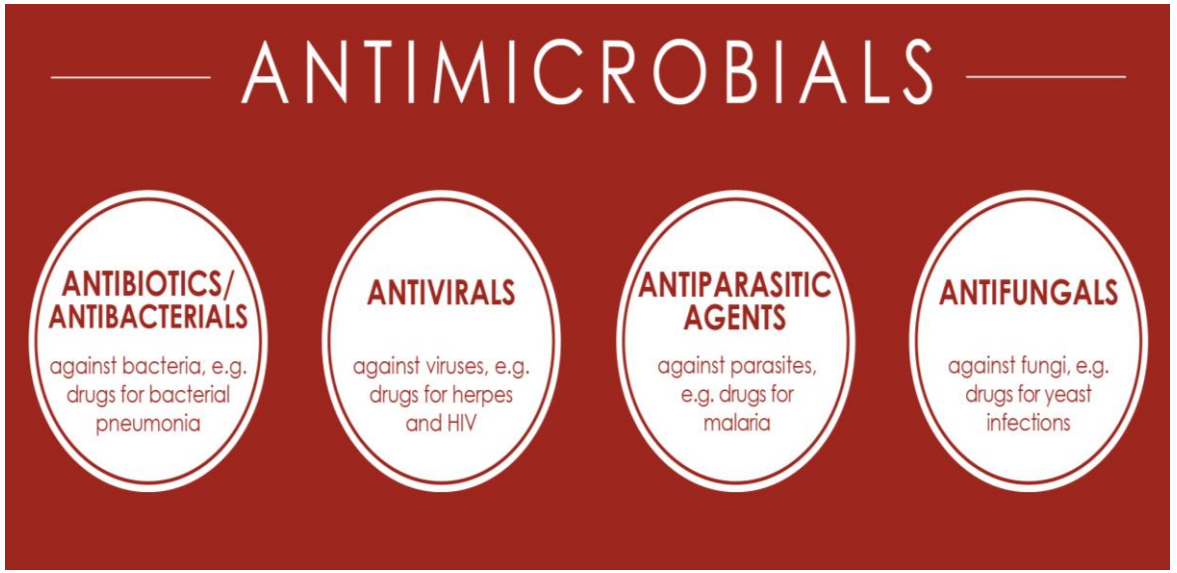
- **Chemotherapeutic agent:** A chemical that binds to and specifically kills microbes or tumour cells
- **Anti microbial molecules:** Ligands
- **Pharmacophore:** Active chemical moiety that binds to the microbial receptors

ANTIBIOTICS & ANTI MICROBIALS

- **ANTIBIOTICS:** These are the substances produced by micro organisms, which selectively suppress the growth of or kill other micro organisms at very low concentration
- **ANTI MICROBIAL AGENT**: These are synthetic as well as naturally obtained drugs that attenuate micro organisms

CLASSIFICATION OF ANTIMICROBIAL AGENTS

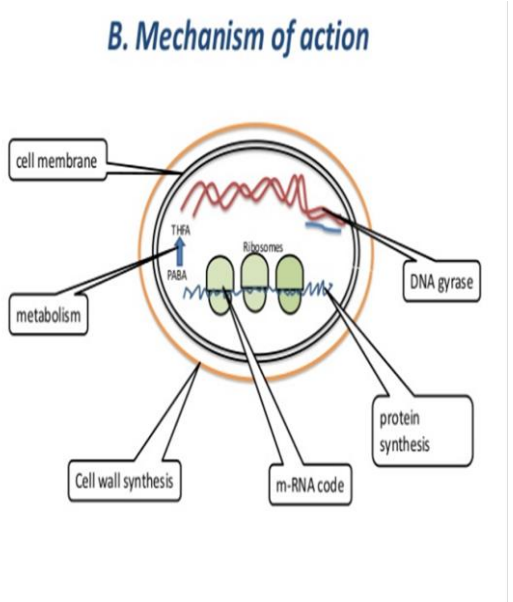
1. **Class & spectrum of micro organism it kills**
   - Antibacterial
   - Antifungal
   - Antiviral
   - Antiparasitic

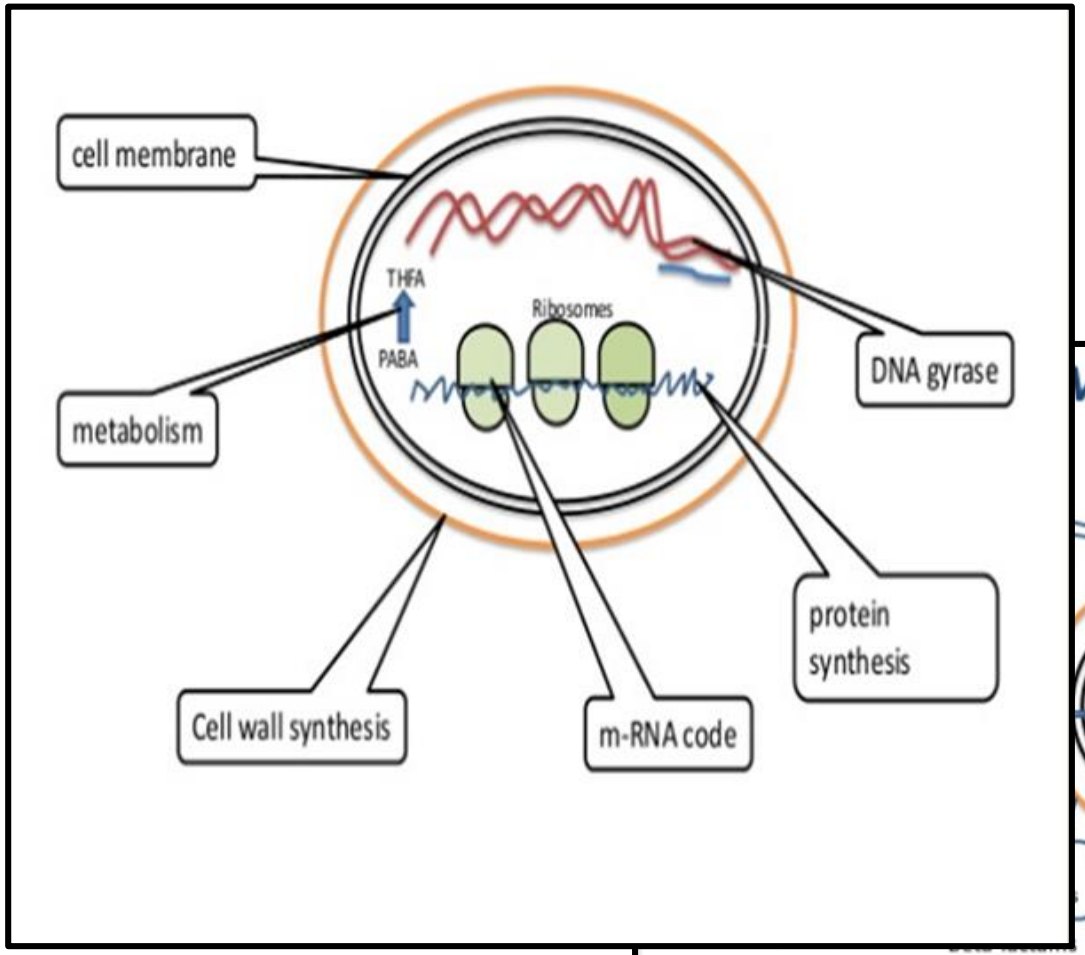


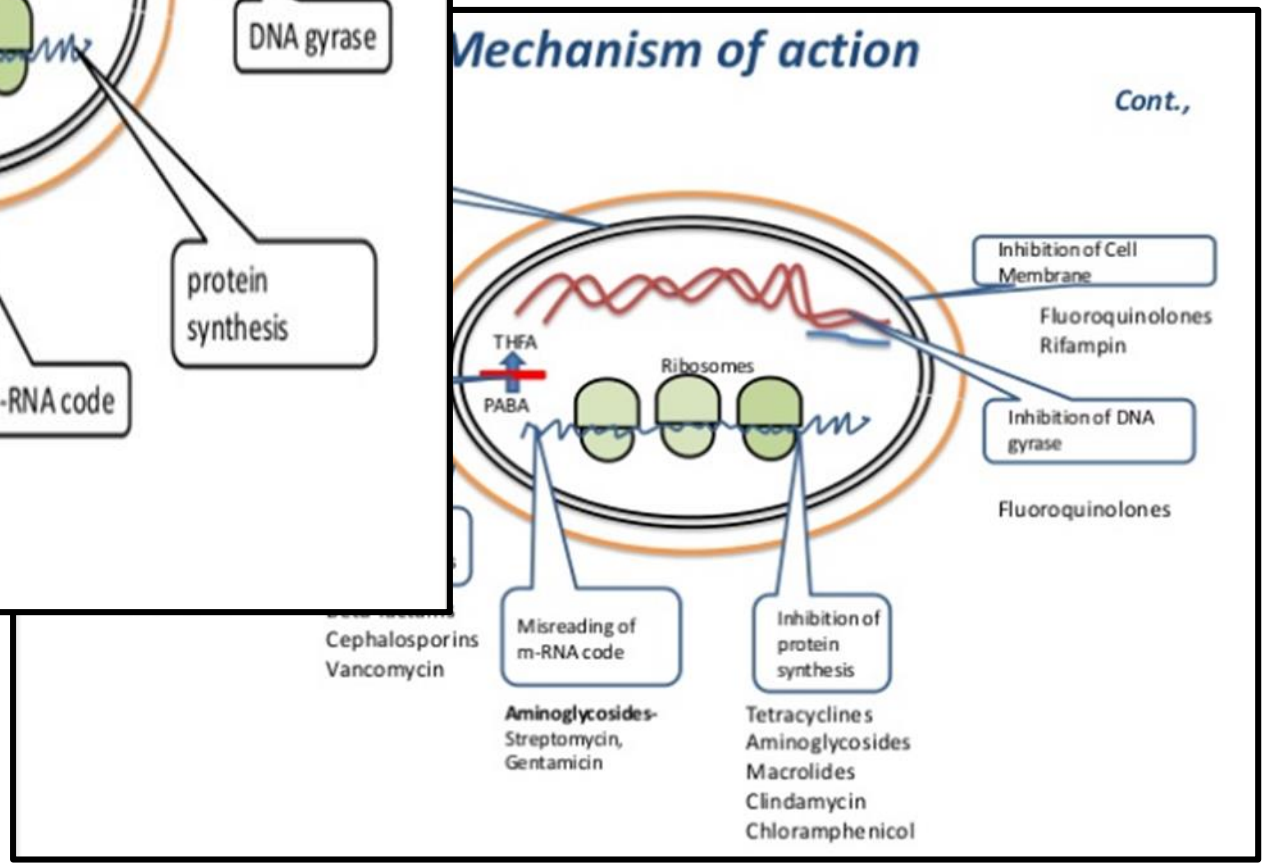
CLASSIFICATION OF ANTIMICROBIAL AGENTS

2. The biological pathway it interferes with

- Cell wall synthesis inhibitors
- Protein synthesis inhibitors
- Cause leakage from cell membranes
- Inhibit DNA Gyrase
- Interfere with DNA synthesis or function
- Interfere with intermediary metabolism




cell membrane
THFA
PABA
Ribosomes
DNA gyrase
metabolism
protein synthesis
Cell wall synthesis
m-RNA code


Mechanism of action
Cont.,
THFA
PABA
Ribosomes
Inhibition of Cell Membrane
Fluoroquinolones
Rifampin
Inhibition of DNA gyrase
Fluoroquinolones
Cephalosporins
Vancomycin
Misreading of m-RNA code
Aminoglycosides-
Streptomycin,
Gentamicin
Inhibition of protein synthesis
Tetracyclines
Aminoglycosides
Macrolides
Clindamycin
Chloramphenicol

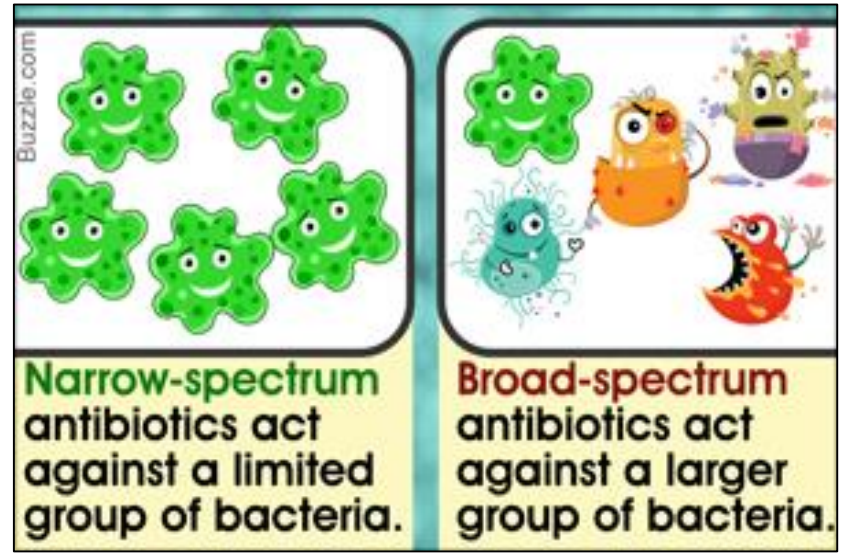
CLASSIFICATION OF ANTIMICROBIAL AGENTS

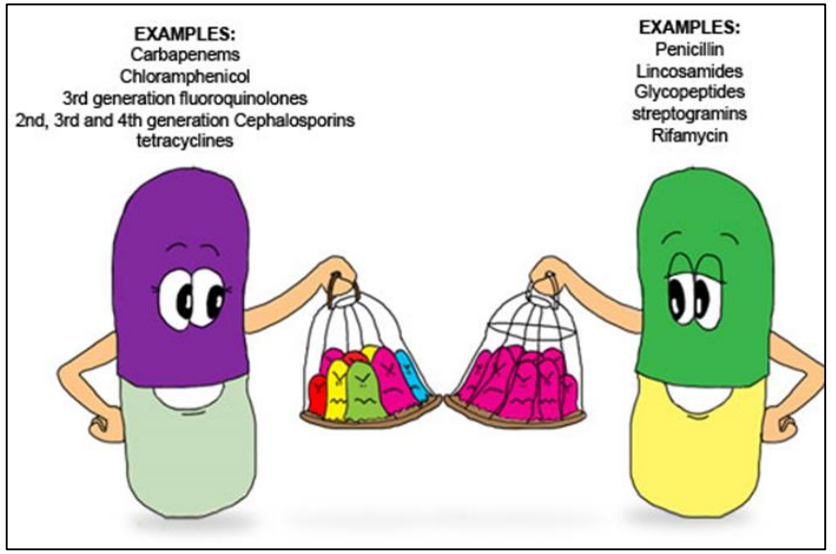
3. **The chemical structure of its microphore**
   - Sulfonamide and related drugs
   - Quinolones
   - Diaminopyrimidines
   - B-lactum antibiotics
   - Tetracycline
   - Aminoglycosides
   - Macrolides
   - Lincosamide antibiotics
   - Azole derivatives

CLASSIFICATION OF ANTIMICROBIAL AGENTS

4. Spectrum of activity

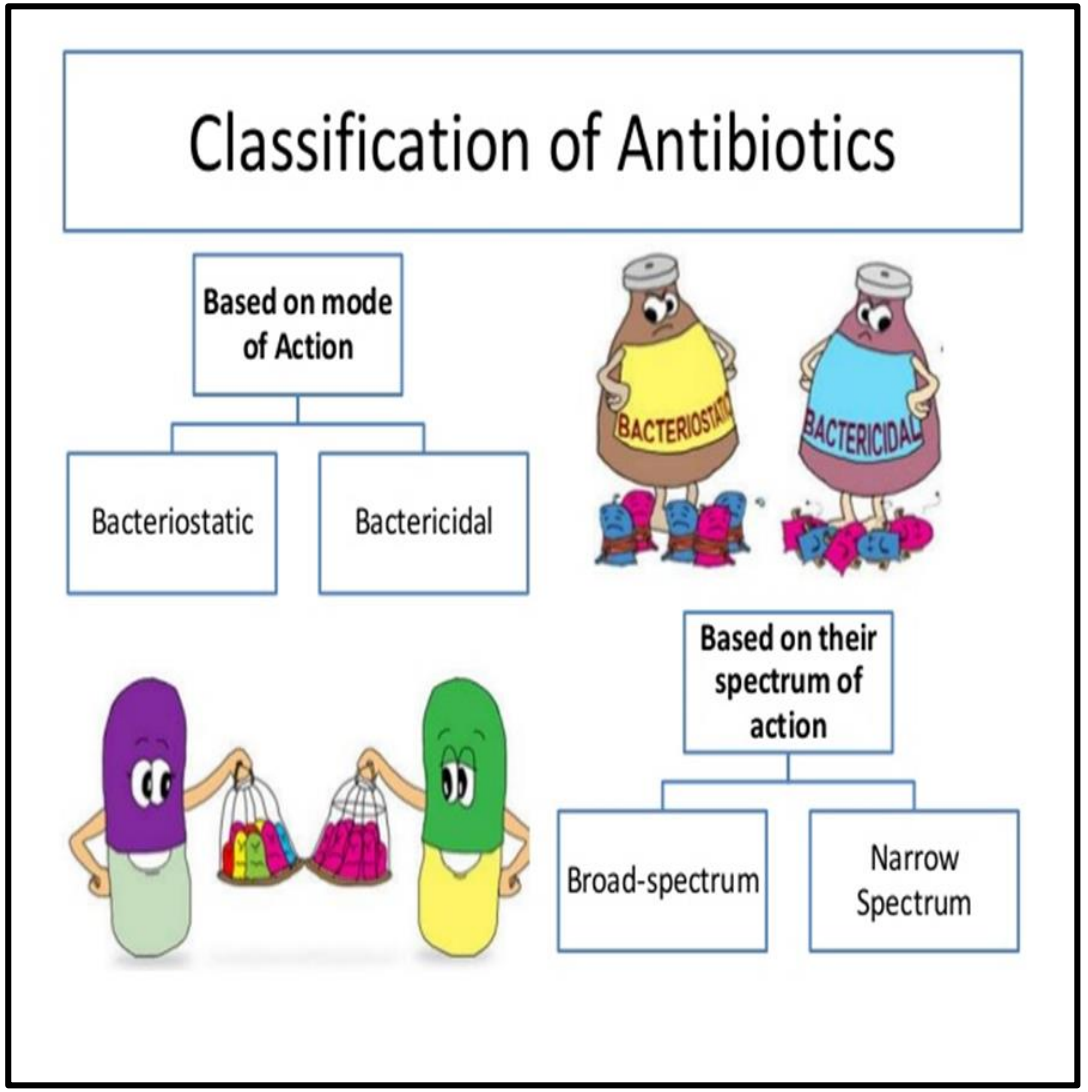
- **Narrow spectrum**
  - Penicillin G
  - Streptomycin
  - Erythromycin
- **Broad spectrum**
  - Tetracycline
  - Quinolones
  - Chloramphenicol





Spectrum of activity of anti microbial agents

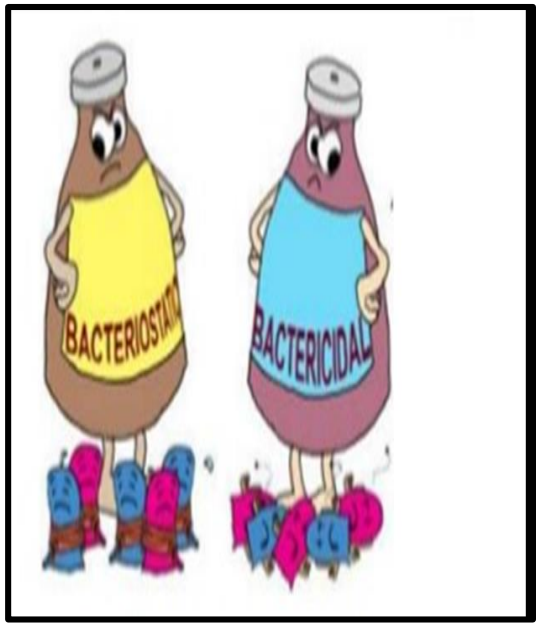
- Gram staining
- Cocci
- Rods
- Aerobic & Anaerobic
- Mycobacteria
- Mycoplasma pneumoniae
- Chlamydia
- Spirochetes
- Fungi



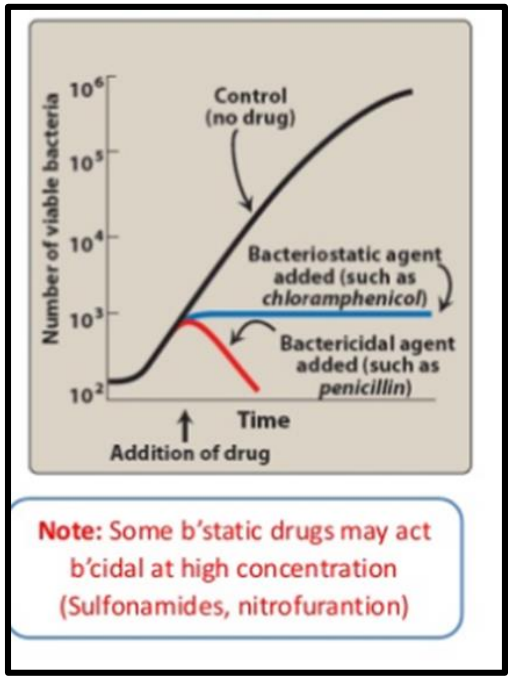
CLASSIFICATION OF ANTIMICROBIAL AGENTS

5. Type of action

- **Bacteriostatic** stops microorganism from reproducing
  - Sulfonamide
  - Erythromycin
  - Tetracycline
  - Clindamycin
  - Linezolid



- **Bacteriostatic** kills microorganism
  - Penicillin
  - Cephalosporin
  - Quinolones
  - Rifampicin
  - Isoniazid



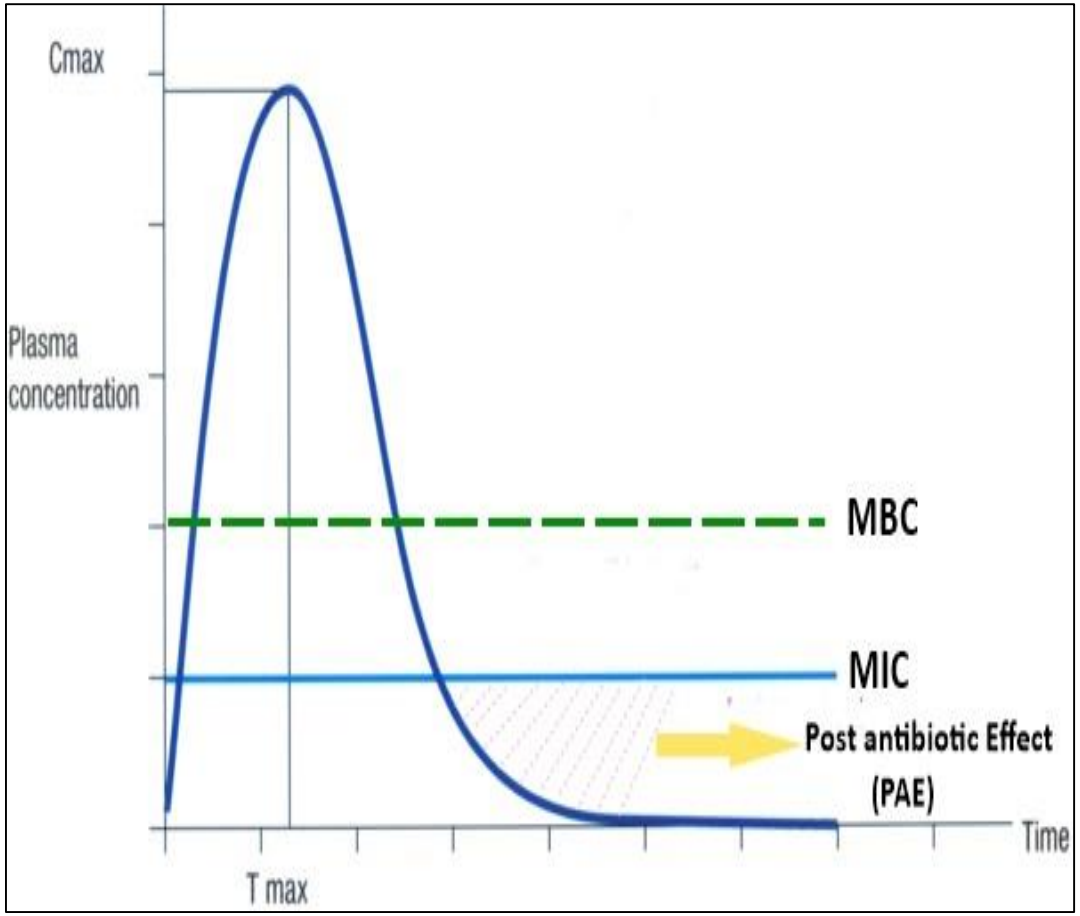
ACTION ON TAREGT PATHOGEN

- **MINIMUM INHIBITORY CONCENTRATION (MIC)**

  Lowest drug concentration that inhibits the visible growth of a bacterial culture after an overnight (18-24hr) incubation

- **MINIMUM BACTERICIDAL CONCENTRATION (MBC)**

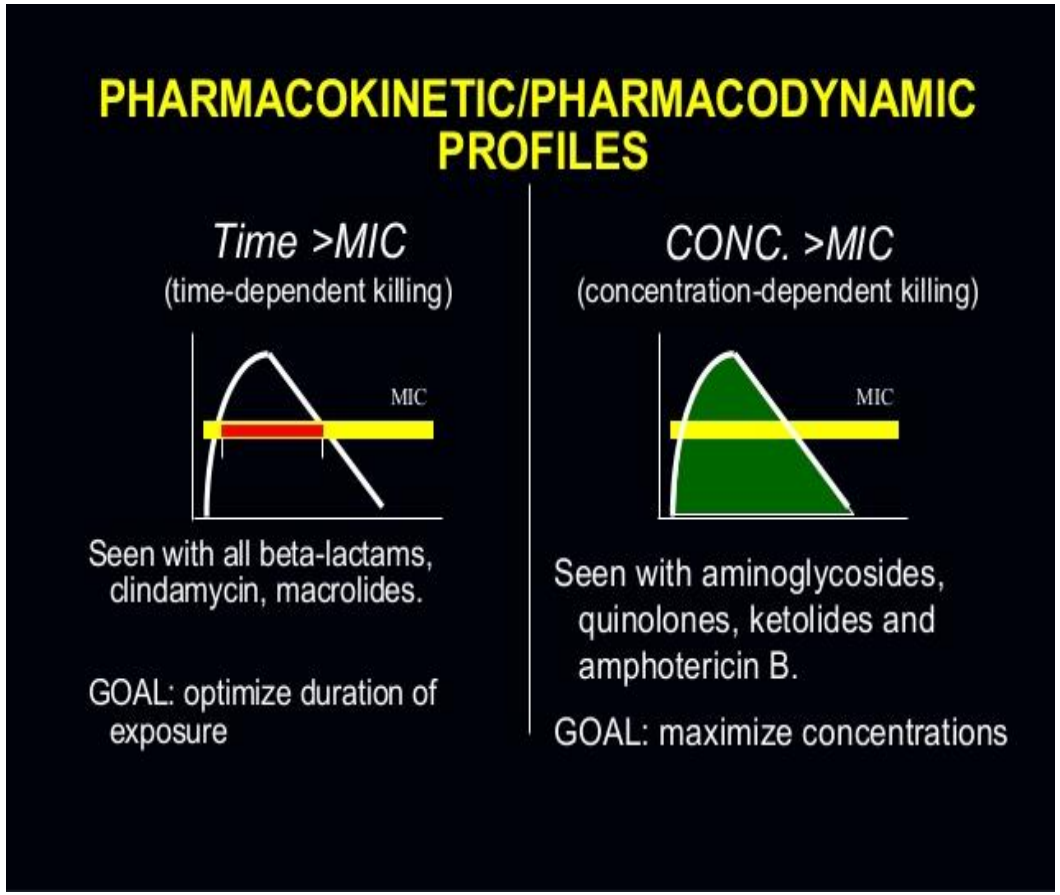
  Lowest drug concentration needed to kill > 99% of bacterial inoculum

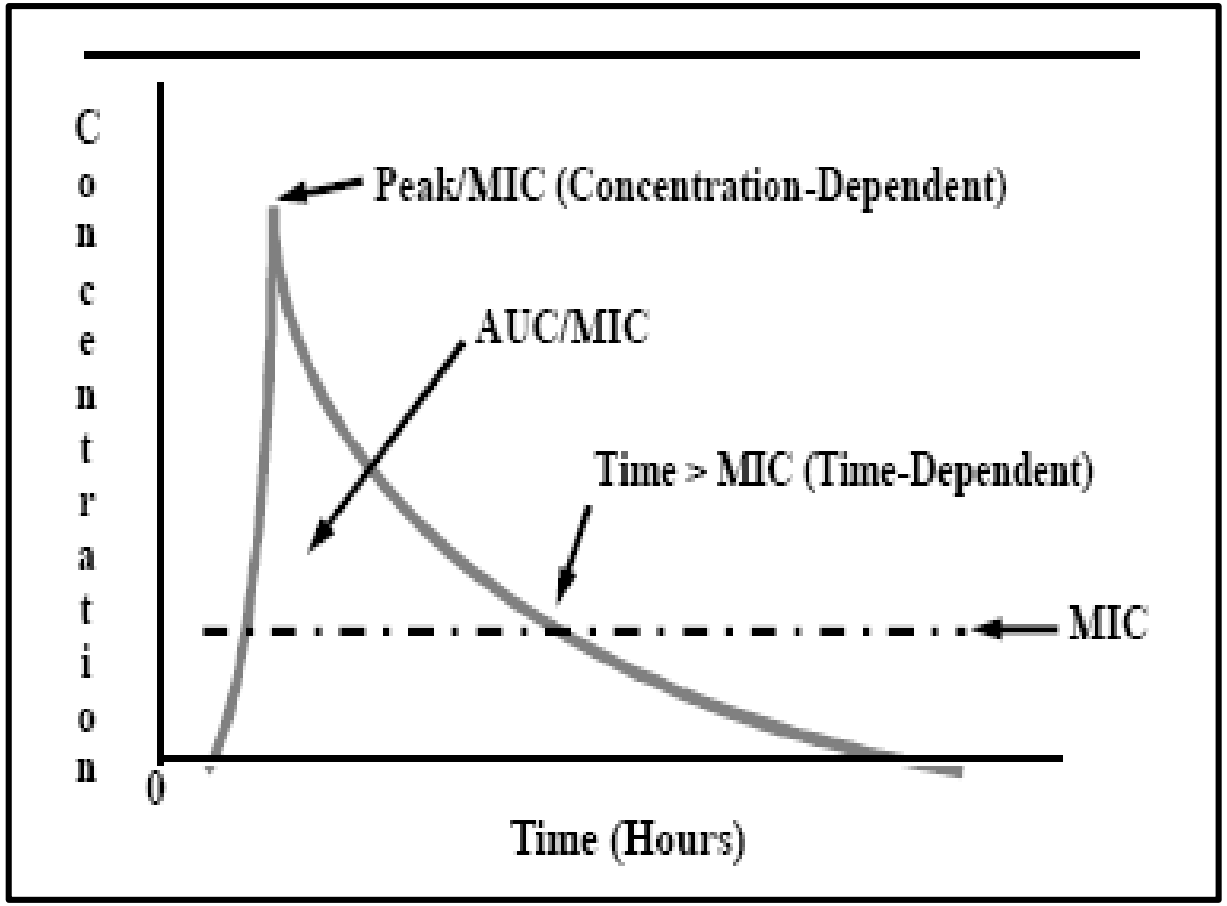


BACTERICIDAL AGENTS

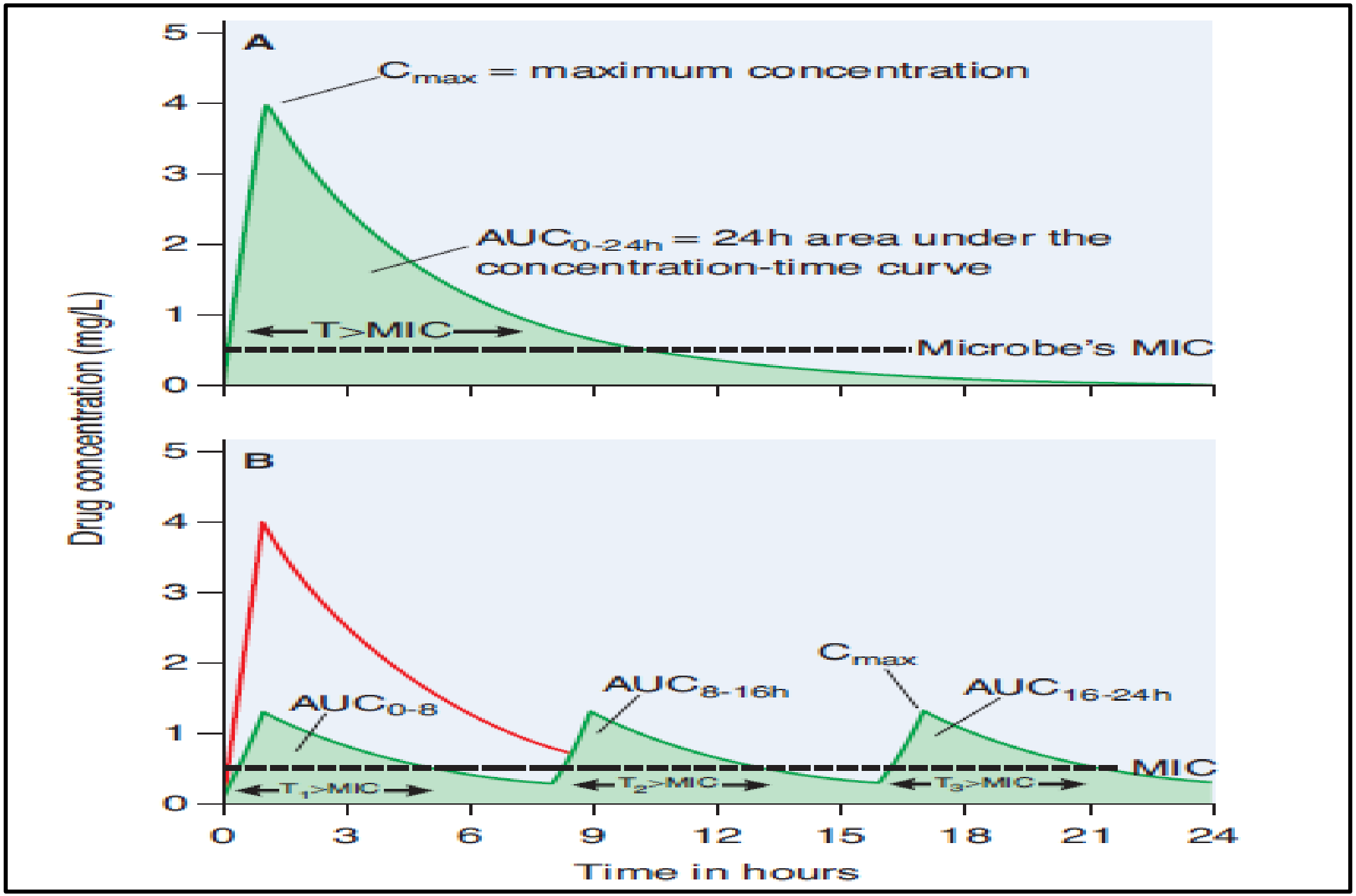
- **Concentration dependent killing:**
  - Rate & extent of killing increases with increased concentration (MIC__Minimal inhibitory concentration___the concentration of the drug required to inhibit the growth of organism)
- **Time dependent killing:**
  - Bactericidal activity continues as long as serum concentration are greater than MBC(Minimal bactericidal concentration_____The concentration of drug required to kill the organism)

CONCENTRATION DEPENDENT/ TIME DEPENDENT KILLING





Core- Pharmacology


A
C_{max} = maximum concentration
AUC_{0-24h} = 24h area under the concentration-time curve
T>MIC
Microbe's MIC
B
AUC_{0-8}
AUC_{8-16h}
C_{max}
AUC_{16-24h}
MIC
T_1>MIC
T_2>MIC
T_3>MIC
Drug concentration (mg/L)
Time in hours
0
1
2
3
4
5
0
3
6
9
12
15
18
21
24

PHARMACOKINETIC BASIS OF ANTI MICROBIAL THERAPY

- **Route of administration**
  - Usually oral
  - I/V route
    - Critically ill patients(endocarditis, meningitis etc.)
    - Patients with nausea, vomiting & diarrhoea or with disease that impair oral absorption
    - Drug is poorly absorbed through oral route(Aminoglycosides)
- **Conditions that alter antimicrobial pharmacokinetics**

  Reduced dose (Renal, hepatic insufficiency)

  Increased dose(Cystic fibrosis, burns)

PHARMACOKINETIC BASIS OF ANTI MICROBIAL THERAPY

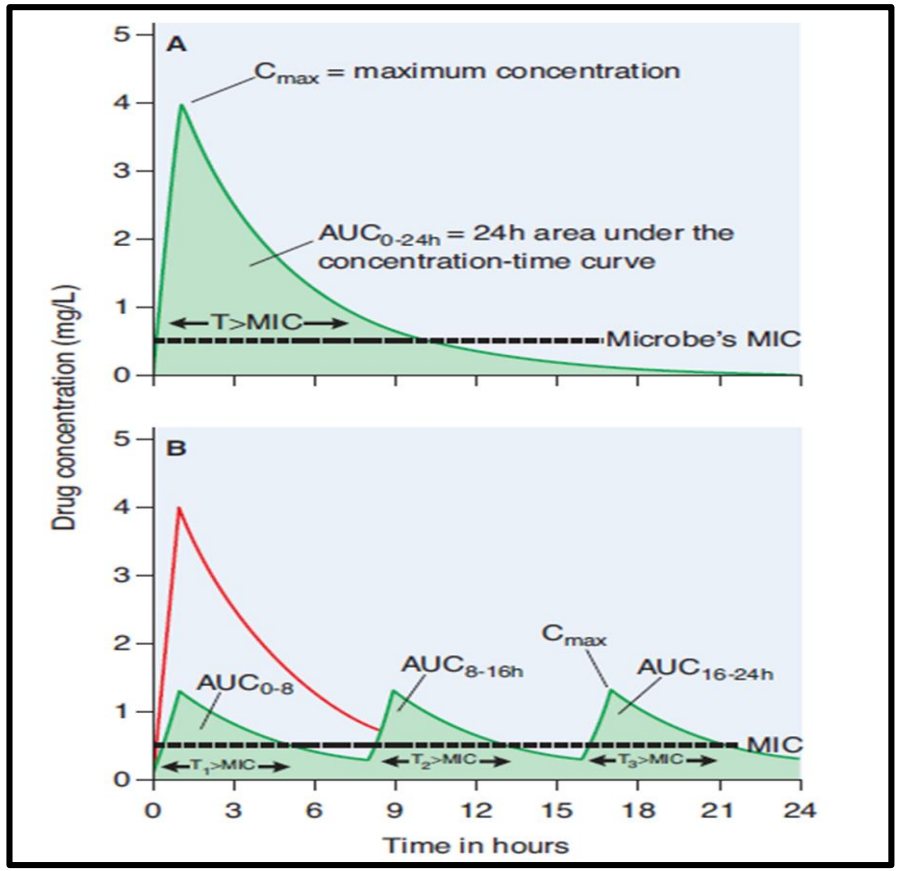
- **Drug concentration in body fluids**
  - Penetration of drugs
    - Physical barriers
    - Chemical properties
    - Transporters

Meningitis leads to increase penetration of different AMA

- **Population pharmacokinetics and variability in drug response**
  (Between patient variability/ within patient variability)
- Dose adjustment in elderly, neonates,& Pregnancy

BASIS FOR SELECTION OF DOSE AND DOSING SCHEDULE

- Drug concentration achieved at site of infection
- Optimal microbial kill by the antibiotic may be best achieved by maximizing certain shapes of concentration time curve



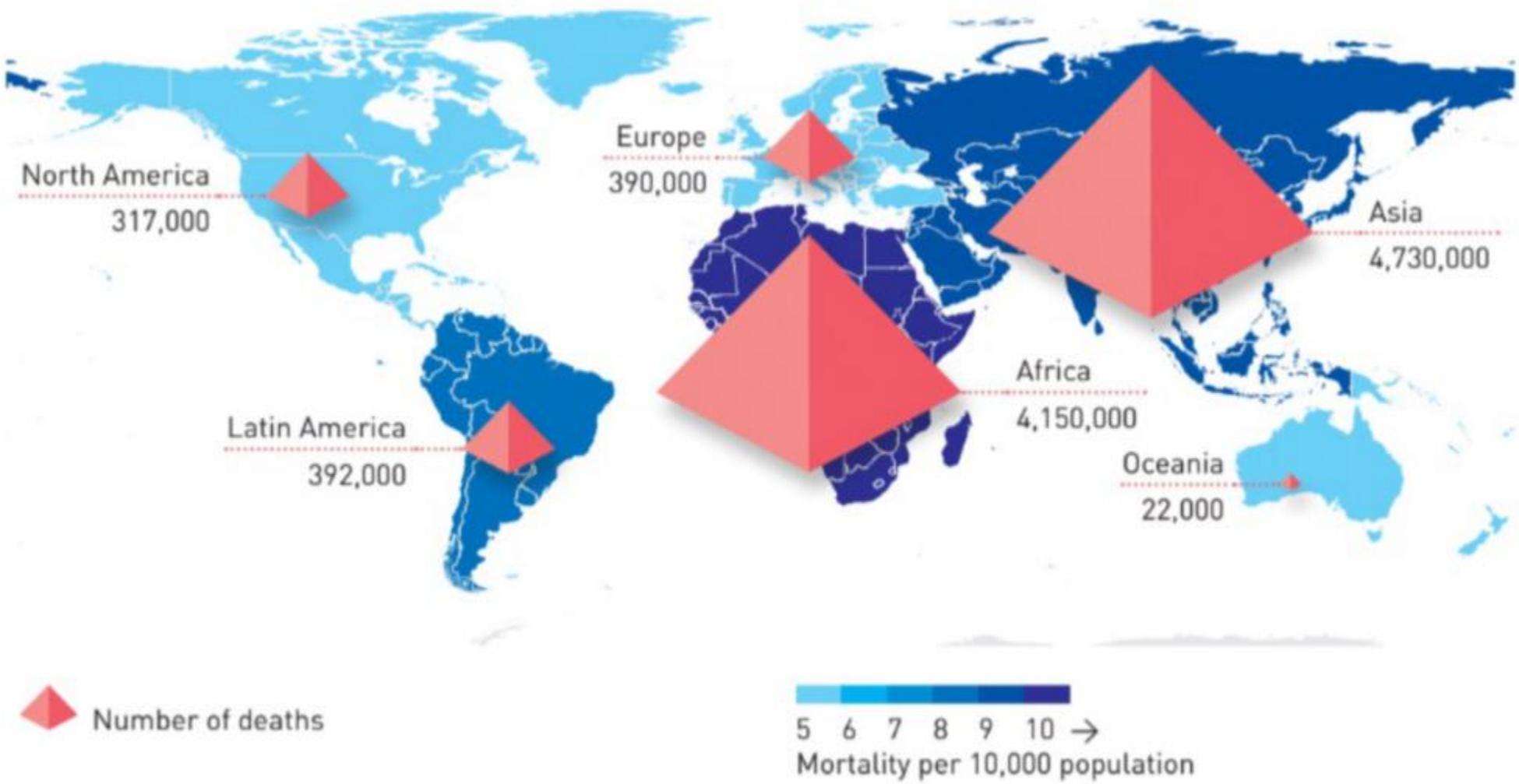
ANTI MICROBIAL PHARMACODYNAMICS

- Bacteriostatic vs Bactericidal activity
- **Post antibiotic effect(PAE)** : Persistent suppression of bacterial growth after limited exposure to an anti microbial agent(Aminoglycosides, Quinolones)
  - Slow recovery after reversible lethal damage to cell structure
  - Persistence of the drug at the binding site /within the periplasmic space
  - Need t synthesize new enzymes before growth can resume
- **Post antibiotic leukocyte enhancement(PALE)**

PROBLEMS: WITH THE USE OF ANTI MICROBIAL AGENTS

- **Toxicity**
  - Local irritancy(gastric irritation, thrombophlebitis, abscess formation)
  - Systemic toxicity(Dose related & organ specific.. AMG, Tetracycline, Vancomycin)
- **Hypersensitivity reactions**(Rash, anaphylaxis)
- **Drug resistance**
- **Super infection**

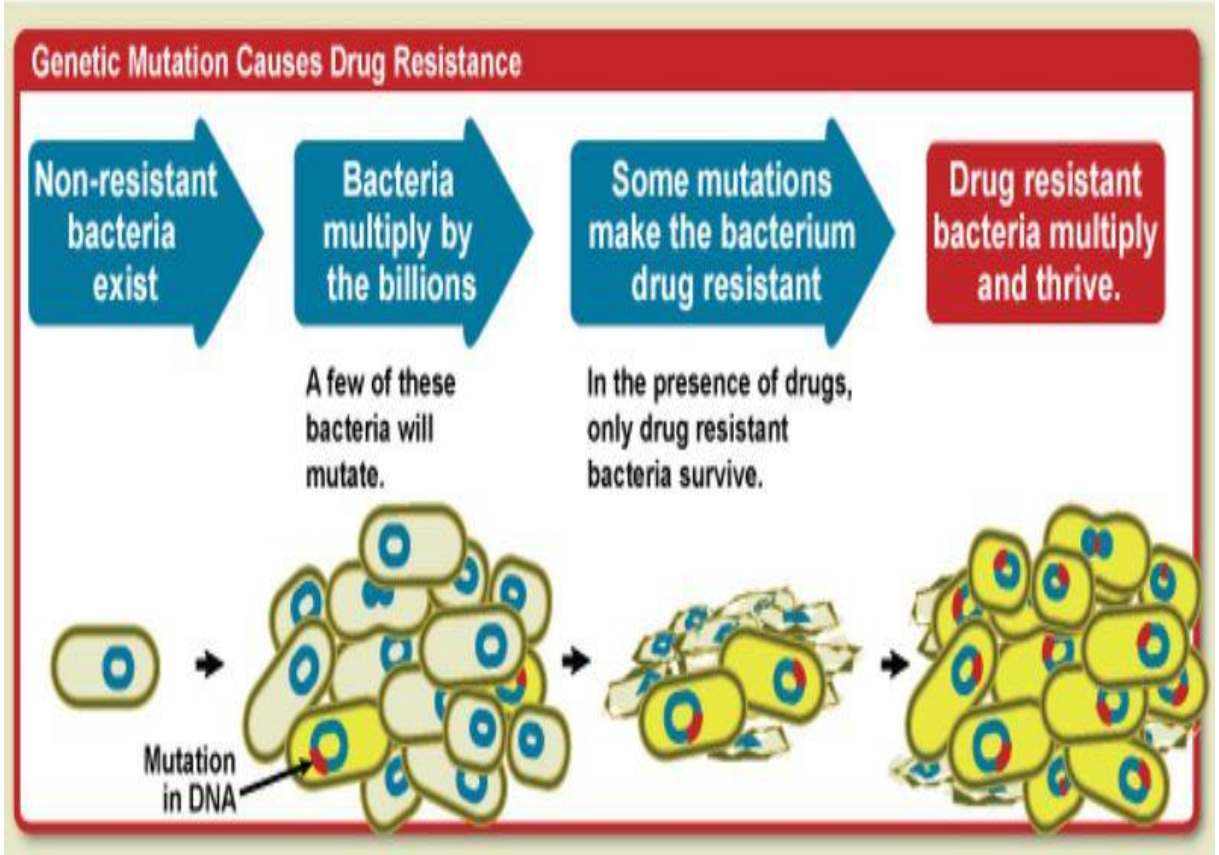
ANTIMICROBIAL RESISTANCE



VERTICAL INTEGRATION WITH COMMUNITY MEDICINE

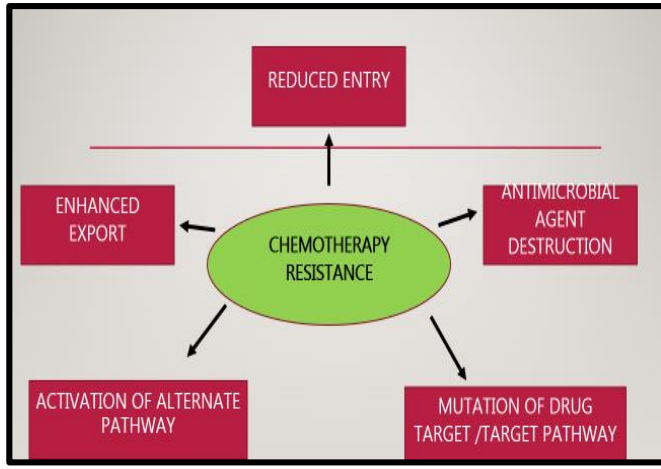
DRUG RESISTANCE

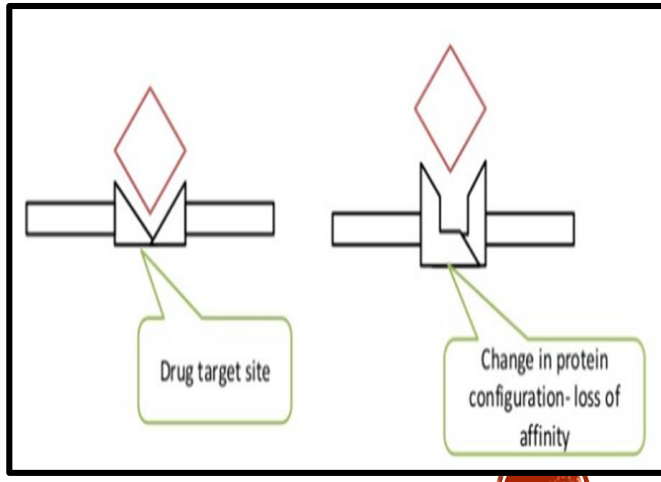
- Natural resistance
- Acquired resistance
  - Spontaneous mutation
  - Transmission of genes from other organisms



DRUG RESISTANCE: MECHANISMS OF RESISTANCE

- **Reduced entry** of antibiotic into pathogen
- **Enhanced export** of antibiotic by efflux pumps
- Release of microbial enzymes that **destroy the antibiotic**
- **Alteration of microbial synthesis** that transform pro drugs to the effective moieties
- **Alteration of target proteins**
- Development of **alternative pathways** to those inhibited by the antibiotic





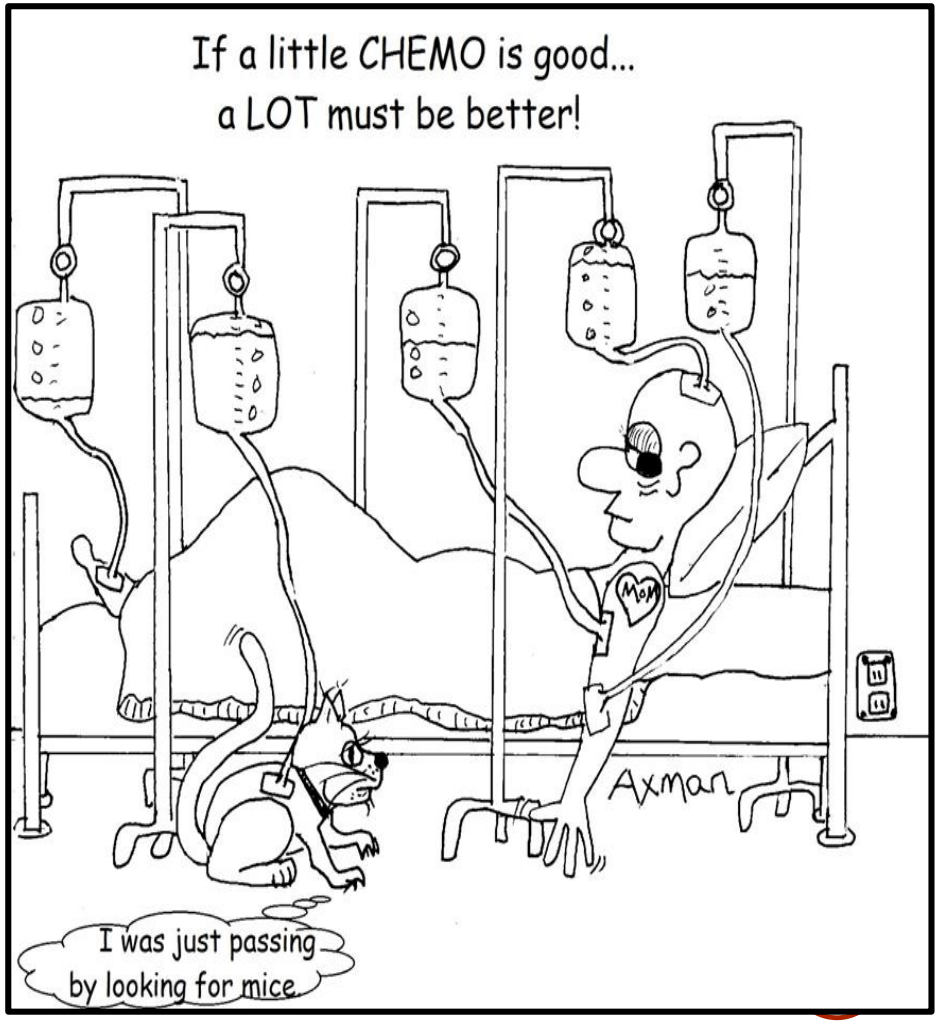
DRUG RESISTANCE: TYPES OF RESISTANCE

- **CROSS RESISTANCE:** Acquisition of resistance to one AMA conferring resistance to another AMA, to which the organism has not been exposed
  - Chemically related (Sulphonamide)
  - Mechanistically related(Tetracycline)
- **CROSS RESISTANCE** may be
  - Two way(Erythromycin& Clindamycin & vice versa)
  - One way(Neomycin resistance to enterobacteriaciae & Streptomycin)

COMPLETE OR INCOMPLETE

DRUG RESISTANCE: PREVENTION OF ANTI MICROBIAL AGENT RESISTANCE

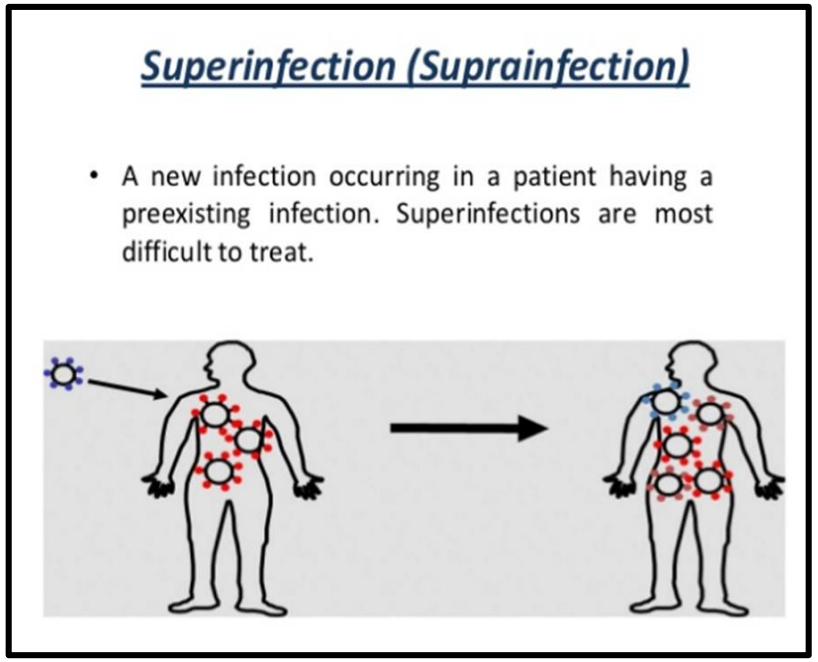
- Avoidance of indiscriminate & inadequate use
- Prefer rapid acting & selective anti microbial agent
- Use combination of AMAs in prolonged therapy(T.B)
- Constant monitoring of resistance
- Restricting use of broad spectrum drug
- Avoiding transmission of resistant bacteria



VERTICAL INTEGRATION WITH MEDICINE

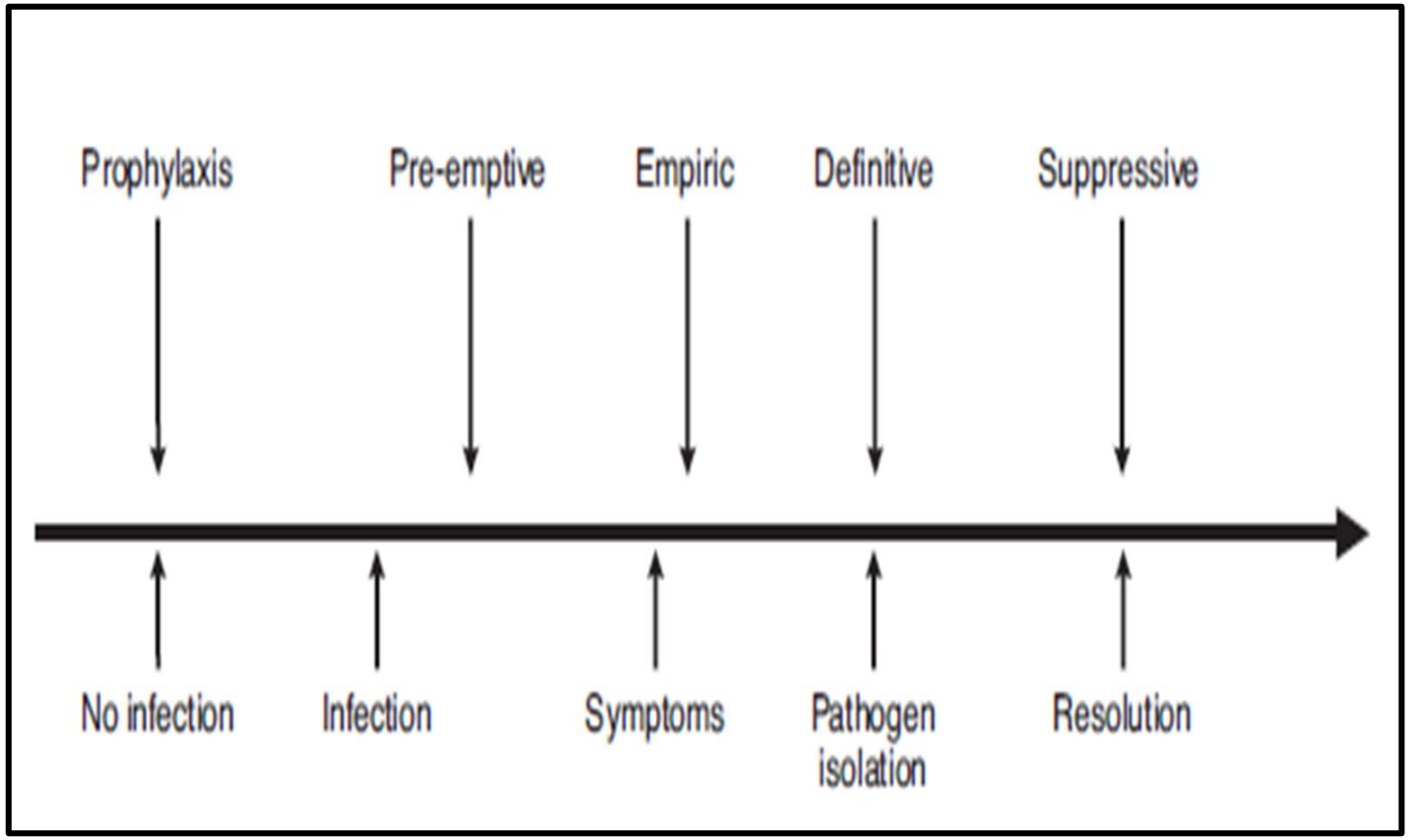
PROBLEMS: ARISE WITH THE USE OF ANTI MICROBIAL AGENTS

- **SUPERINFECTION(SUPRAINFECTION):** Appearance of new infection as a result of anti microbial therapy
- **Mechanism**
- Association with broad spectrum antibiotics
- **Condition predisposing to superinfection**
  - Suppressed immunity
  - Leukaemia and other malignancies
  - Agranulocytosis
  - Diabetes



TYPES AND GOALS OF ANTI-MICROBIAL THERAPY

- Prophylactic therapy
- Pre emptive therapy
- Empirical therapy
- Definitive therapy
- Post treatment suppressive therapy



VERTICAL INTEGRATION WITH MEDICINE

PRINCIPLES OF ANTI-MICROBIAL CHEMOTHERAPY

- Make a diagnosis
- Remove barriers to cure
- Establish need for chemotherapy
- **Choice of an anti microbial agent**

1. Patient related factors
   - Age
   - Renal & hepatic function
   - Removal of barriers (Abscess, necrotic material, foreign body, hematomas)
   - Drug allergy
   - Impaired host factors
   - Pregnancy
   - Genetic factors

2. Drug related factors
   - Spectrum of activity
   - Type of activity
   - Relative toxicity
   - Pharmacokinetic profile

ANTIMICROBIAL CHEMOPROPHYLAXIS

- Should always be directed towards specific pathogen
- No resistance should develop during course of treatment
- Use should be of limited duration
- Conventional therapeutic dose should be used
- Should be used only in situations of documented drug efficacy

ANTIMICROBIAL COMBINATIONS

- To give broad spectrum empiric therapy
- To treat polymicrobial infections
- To decrease emergence of resistant bacteria
- To decrease dose related toxicity
- To obtain enhanced inhibition or killing

ANTIBIOTICS COMBINATIONS

- **Synergism:**
- Marked by four fold or greater reduction in MIC/MBC when used in combination
  - **Mechanisms:**
    - Blockade of sequential steps in a metabolic sequence(Trimethoprim+ Sulfamethoxazole)
    - Inhibition of enzymatic inactivation(Penicillin + Clavulanic acid)
    - Enhancement of anti microbial agent uptake(Penicillin+ Aminoglycosides)
- **Antagonism:**
- Combined inhibitory or killing effects of two or more antimicrobial agents are less as compared to individual use
  - **Mechanisms:**
    - Inhibition of bactercidal activity by static agents
    - Induction of enzymatic inactivation

RESEARCH

- Hudson, M.A. and Lockless, S.W., 2022. Elucidating the mechanisms of action of antimicrobial agents. *Mbio*, *13*(3), pp.e02240-21.

- Miethke, M., Pieroni, M., Weber, T. et al. Towards the sustainable discovery and development of new antibiotics. Nat Rev Chem 5, 726–749 (2021). https://doi.org/10.1038/s41570-021-00313-1

BIOETHICS

‘the greatest possibility of evil…is the use of too-small doses [of penicillin], so that, instead of clearing up the infection, the microbes are educated to resist penicillin and a host of [resistant] organisms is bred out which can be passed on to other individuals and perhaps from there to others until they reach someone who gets a septicemia or a pneumonia which penicillin cannot save. In such a case the thoughtless person playing with penicillin treatment is morally responsible for the death of the man who finally succumbs to infection with the penicillin-resistant organism”

Alexander Fleming, 1945

BIOETHICS

Hays, J.P., Ruiz-Alvarez, M.J., Roson-Calero, N. *et al.* Perspectives on the Ethics of Antibiotic Overuse and on the Implementation of (New) Antibiotics. *Infect Dis Ther* **11**, 1315–1326 (2022). https://doi.org/10.1007/s40121-022-00656-2

Jamrozik E, Heriot GS. Ethics and antibiotic resistance. Br Med Bull. 2022 Mar 21;141(1):4-14. doi: 10.1093/bmb/ldab030. PMID: 35136968; PMCID: PMC8935610.

Adebisi, Y.A. Balancing the risks and benefits of antibiotic use in a globalized world: the ethics of antimicrobial resistance. Global Health 19, 27 (2023). https://doi.org/10.1186/s12992-023-00930-z

ARTIFICIAL INTELLIGENCE

Lv, J., Deng, S. and Zhang, L., 2021. A review of artificial intelligence applications for antimicrobial resistance. *Biosafety and Health*, *3*(01), pp.22-31.

REFERENCES

- Katzung and Betram's Basic and Clinical Pharmacology, 15th Edition
  Chapter 51: Clinical use of Antimicrobial Agents
  Page:941-953

- Goodman & Gilmans, The Pharmacological Basis of Therapeutics, 13th Edition
  Chapter 52: General Principles of Antimicrobial Therapy
  Page:957-968

END OF LECTURE ASSESSMENT

1. Which of the following terms refers to the ability of an antimicrobial drug to harm the target microbe without harming the host?

a. mode of action
b. resistance
c. selective toxicity
d. spectrum of activity
e. therapeutic level

2. The term magic bullet was coined for

a. Ehrlich discovering the drug salvarsan for the treatment of syphilis
b. Fleming discovering the antibacterial effect of penicillium notatum
c. Florey showing the effectiveness of penicillin in patients
d. Wilson discovering the broad spectrum antibiotic streptomycin

3. Post-antibiotic effect is associated with

a. Aminoglycosides
b. Chloramphenicol
c. Penicillin
d. Tetracyclines
e. Vancomycin

4. Choose the best answer for the following. The emergence of microbial antibiotic drug resistance

a. Requires the concurrent administration of more than one antibiotic

b. Is a direct result of the use of antibiotics in livestock

c. Is a problem that was overcome by the development of vancomycin

d. Is due in large part to the indiscriminate use of antibiotics in humans

e. Is due to lack of development of new drugs

5. Anti-microbial drug act on which of the following sites?

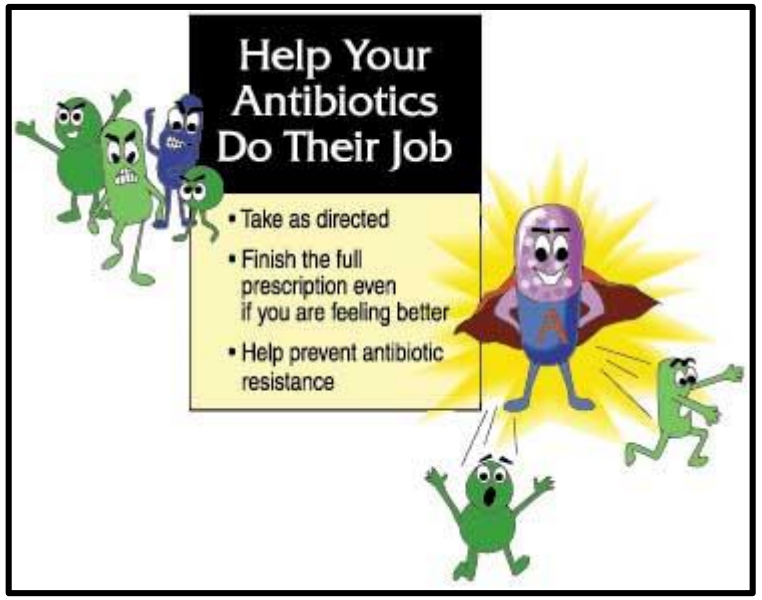
a. Cell wall

b. Golgi complex

c. Mitochondria

d. Nucleic acid

e. Ribosomes


Help Your Antibiotics Do Their Job
• Take as directed
• Finish the full prescription even if you are feeling better
• Help prevent antibiotic resistance

THANK YOU


Think before dispensing