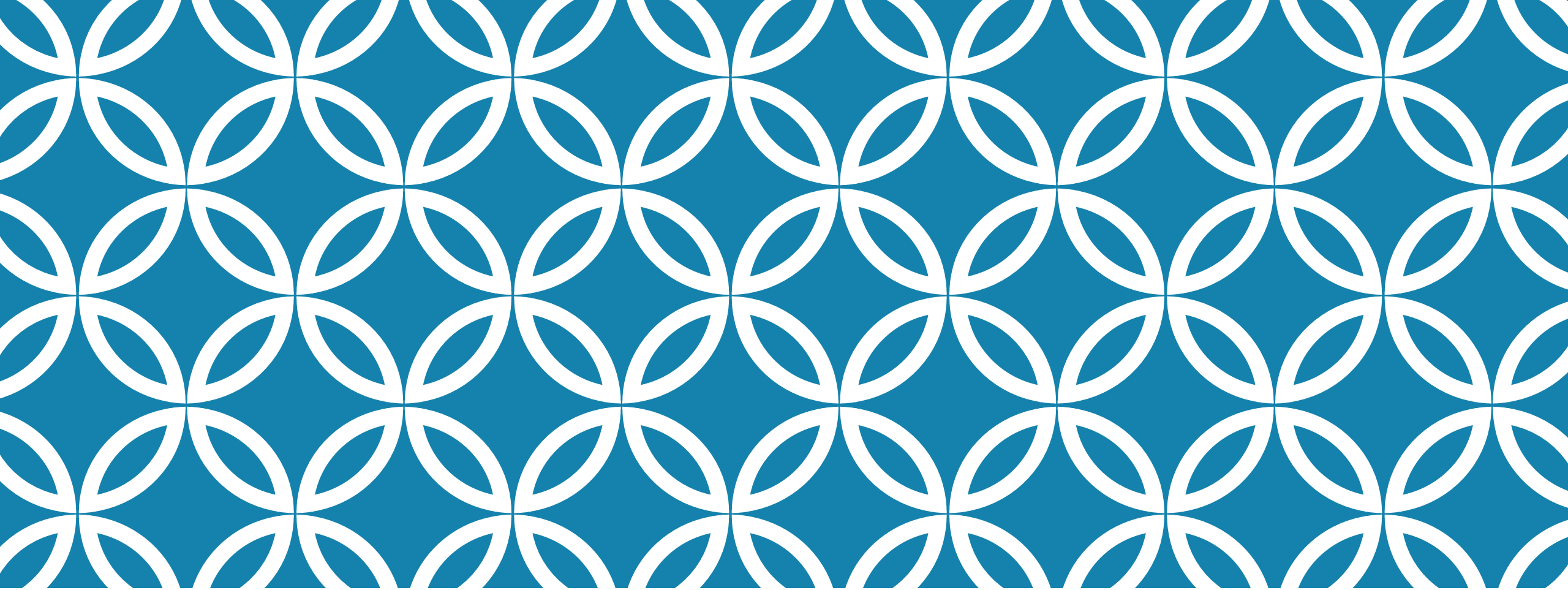

PHARMACOLOGY – II

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DRUG RESISTANCE

- Discuss , what is resistance ?
- Reduction in effectiveness of a **drug** such as an antimicrobial, anthelmintic or an antineoplastic in curing a disease or condition.
- SHORT generation time leads to adaptation to drug

DRUG RESISTANCE, HOW BIG IS THIS PROBLEM

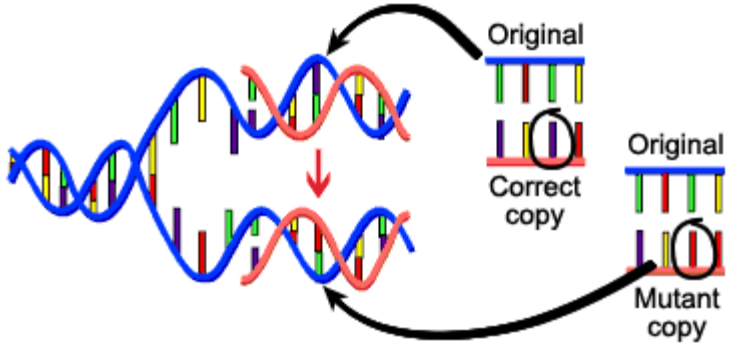
CDC

Salmonella typhi, which causes typhoid fever, is one type of bacteria that has developed resistance to several antibiotics.

Antibiotic resistant "superbugs" have become one of the world's most pressing public health concerns. An estimated two million people become infected with drug-resistant bacteria in the US each year. Of those, at least 23,000 die.

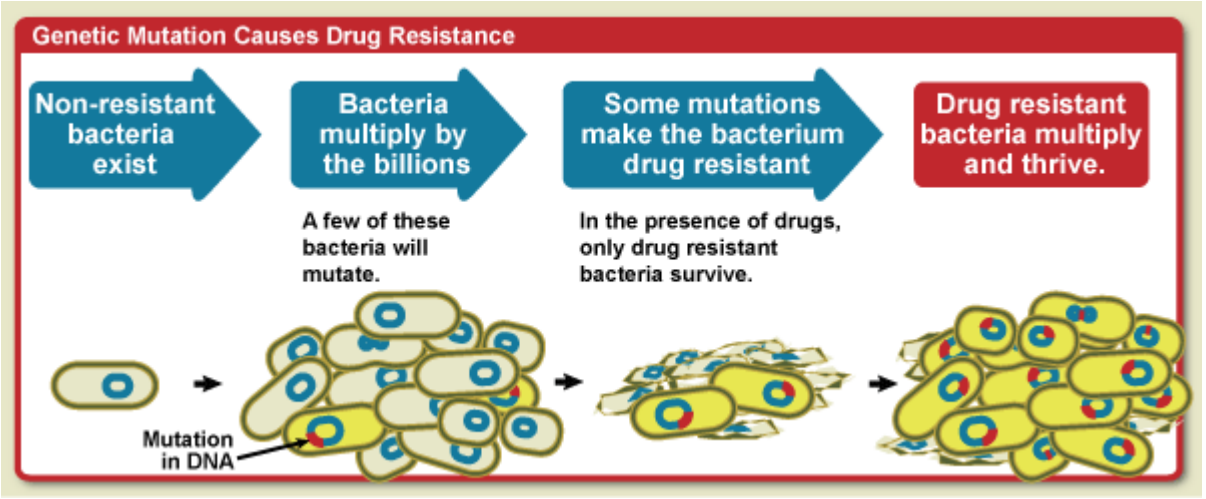
GENETIC BASIS OF RESISTANCE

- Change in DNA that results in resistance
- How can that happen, In several ways !



1. MUTATION

1. Mutation rate in bacterial cell is low 1: 10 million
2. Mutated form resistant, can eventually grow & acquire resistance
3. Not important if the primary infection not caused by Non-mutant form
4. MRSA (Methicillin resistant S.Aureus, TB



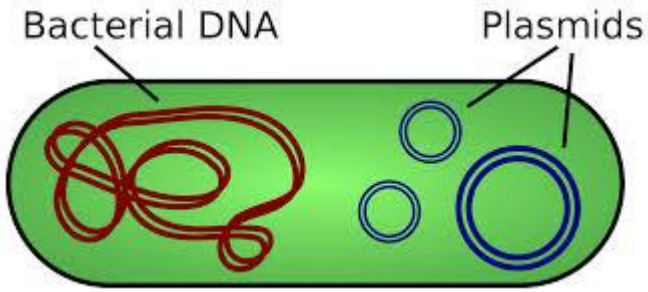
GENETIC BASIS OF RESISTANCE

- GENE AMPLIFICATION

1. Normal DNA replication process is WRONG.
2. Instead of making a single copy of a region of a chromosome, many copies are produced. This leads to the production of many copies of the **genes** that are located on that region of the chromosome
3. Antibiotics can induce Gene amplification of drug resistance genes

GENETIC BASIS OF RESISTANCE

1. EXTRA-CHROMOSOMAL DETERMINANTS: PLASMIDS



1. Extra-chromosomal materials (Plasmids)
2. Many types of plasmids in single cell
3. Plasmids carrying resistant DNA called R-Plasmids
4. Much of Drug Resistance seen in CLINIC is PLASMID mediated !!!!
5. *S Aureus* developed resistance via R-Plasmids mediated mech

GENETIC BASIS OF RESISTANCE

❖ TRANSFER OF RESISTANT GENES WITHIN BACTERIA

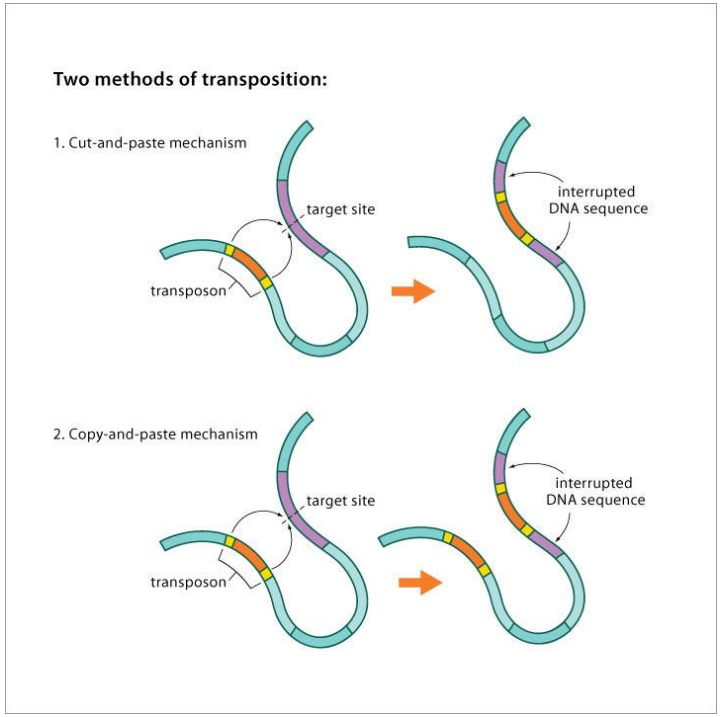
TRANSPOSONS:

Transfer of short stretch of DNA from Plasmid – Plasmid or Plasmid - Chromosome

Short stretch of DNA called *"Transposons"*

Transposons Integrate in to host chromosome

Or Form new indigenous plasmid



GENETIC BASIS OF RESISTANCE

- **TRANSFER OF RESISTANT GENES WITHIN BACTERIA**

GENE CASETTE OR INTEGRONS:

Resistant gene + recognition site = Gene Cassette

Multi –cassette integrated by larger mobile DNA (Integron)

Mechanism provides rapid transfer of genetic elements within bacteria

GENETIC BASIS OF RESISTANCE

- **TRANSFER OF RESISTANT GENES ACROSS BACTERIA**
- Transfer of resistant genes across bacteria is crucial to spread of drug resistance
- 3 MAIN mechanism of transfer

CONJUGATION

TRANSDUCTION

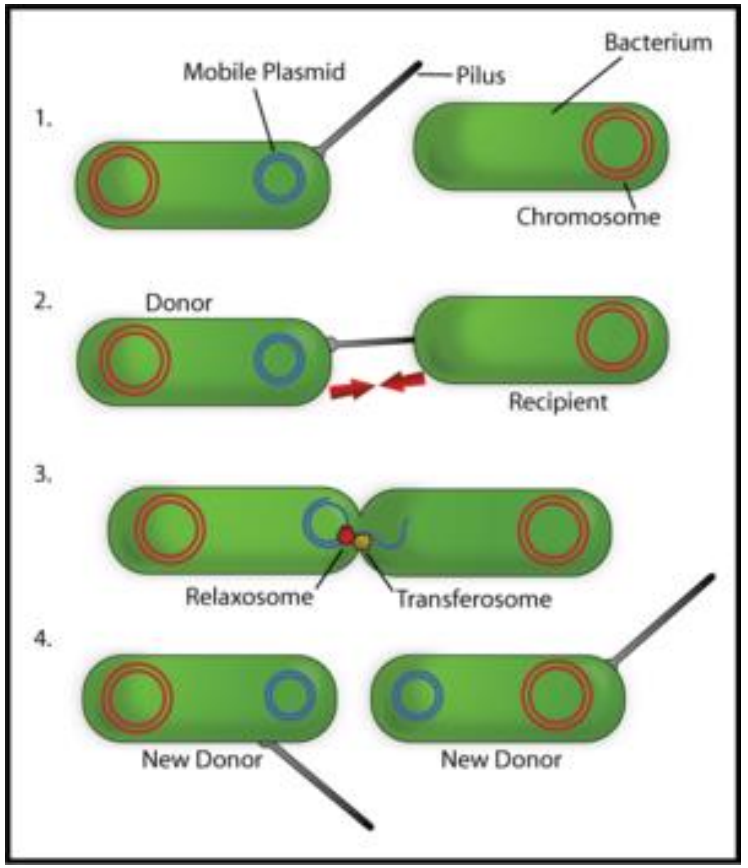
TRANSFORMATION

GENETIC BASIS OF RESISTANCE

❖ TRANSFER OF RESISTANT GENES ACROSS BACTERIA

CONJUGATION

1. Cell to Cell contact, transfer of DNA across
2. Ability to conjugate by "Conjugative Plasmids"
3. Secrete special proteins that can bind to other cell (Pilli)
4. Transfer generally across same species
5. But in some case another species as well

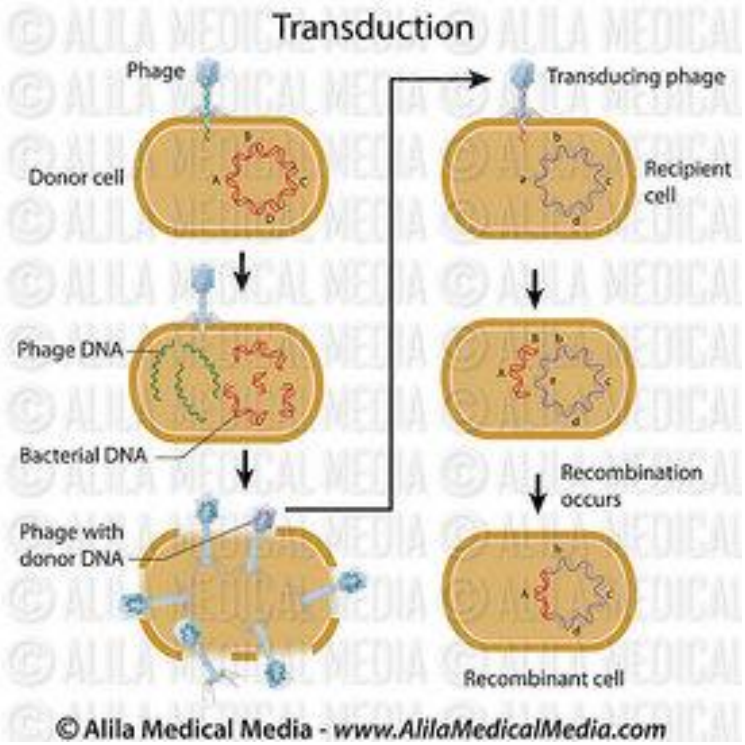


GENETIC BASIS OF RESISTANCE

❖ TRANSFER OF RESISTANT GENES ACROSS BACTERIA

TRANSDUCTION

1. Plasmid DNA enclosed by bacterial virus
2. Transferred to another bacterium
3. Less Important mechanism

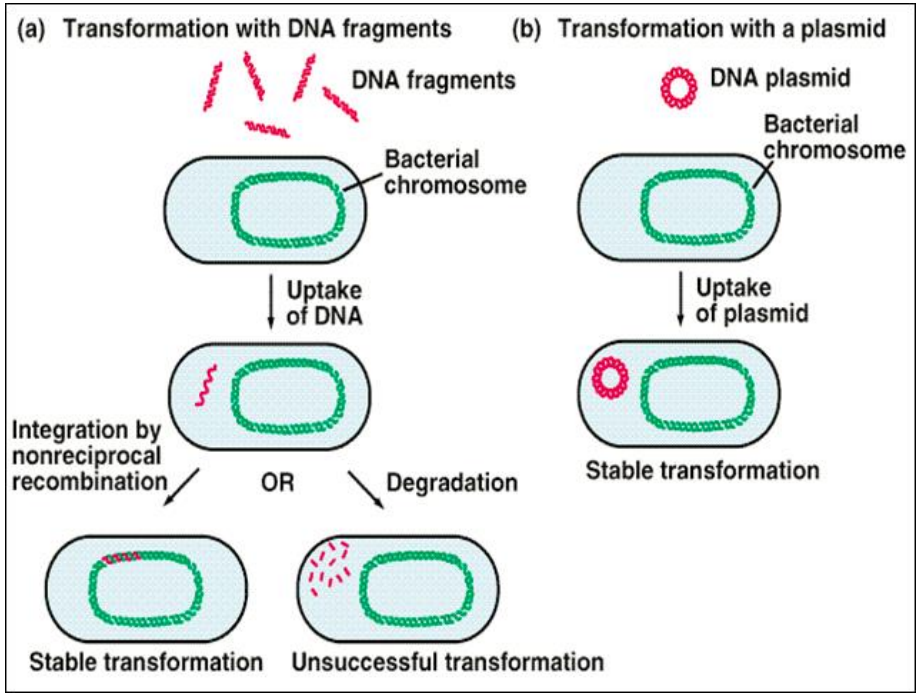


GENETIC BASIS OF RESISTANCE

❖ TRANSFER OF RESISTANT GENES ACROSS BACTERIA

TRANSFORMATION

1. Few Bacterial species can take up DNA from environment
2. Take this new DNA & add this to it's own Genome
3. Not very important mechanism clinically



BIOCHEMICAL MECHANISM OF RESISTANCE

Major Biochemical mechanism of Drug Resistance

Production of Enzyme that inactivates Drug

Change of Drug Binding Site

Decrease in drug inside bacteria

Development of pathway that bypasses reaction

PRODUCTION OF ENZYME THAT INACTIVATES DRUG

Inactivation of beta-Lactam Antibiotics

- Bacteria secreted enzyme that target b-lactam ring of penicillins & cephalosporins
- Enzyme secreted is b-lactamases
- Staphylococci is principal bacterial species secreting enzyme
- Genes on Plasmids, can be transferred

Inactivation of Chloramphenicol

- Enzyme: Chloramphenicol acetyl-transferase inactivates Chloramphenicol
- Both G+/G-ve produce these enzymes
- Resistant Gene is Plasmid Borne

Inactivation of AminoGlycosides

- Drugs inactivated by Phosphorylation, Acetylation, Adenylation
- Both G+/G-ve produce these enzymes
- Resistant Gene is Plasmid Borne

ALTERATION OF DRUG-SENSITIVE OR DRUG-BINDING SITE

1. Chromosomal mutation or plasmid mediated alteration leads to change in binding site
2. Aminoglycosides bind to Bacterial 30S ribosomes
3. Mutation change the ribosomal binding site, Leading to ineffective Drug

DECREASED DRUG ACCUMULATION IN BACTERIUM

1. Resistant genes in plasmid encode of proteins that act as efflux pumps, throwing out drug from cell
2. Tetracyclines, erythromycin, fluoroquinolines are effluxed by similar pumps
3. These pumps are INDUCIBLE proteins, energy dependent pumps
4. Pump inhibitors can be used along Drugs to improve efficacy

BACTERIA DEVELOPS PATHWAY THAT BY-PASS DRUG REACTION

1. Resistant genes in plasmid encode enzymes with low/zero affinity towards antibiotics
2. Trimethoprim: Target= ***Dihydrofolate reductase enzyme***
3. Low affinity enzyme produced making bacteria resistant to Trimethoprim
4. Sulphonamides: Target= ***Dihydropteroate synthetase enzyme***
5. Low affinity enzyme produced making bacteria resistant to Sulphonamides but NO change in affinity to PABA

CURRENT STATE OF ANTIBIOTIC RESISTANCE

- **Staphylococci,** Most common source of Hospital Infections (nosocomial)
- Staphylococci has acquired resistance to almost all antibiotics by various mechanisms
- MRSA (Methicillin Resistant SA): Major issue in hospitals
- Rapid spread amongst elderly, seriously ill, burns/wounds
- Vancomycon was last resort but that too has shown resistant

CURRENT STATE OF ANTIBIOTIC RESISTANCE

- Enterococci, second most common Nosocomial pathogen
- Non-pathogenic enterococci are common in GI tract, resistant to antibiotics
- Can transfer this resistance to invading pathogenic Enterococci
- Resistance in developed countries like USA: 0.8 to 18 % in less than 10 yrs

WHO IS TO BLAME ?

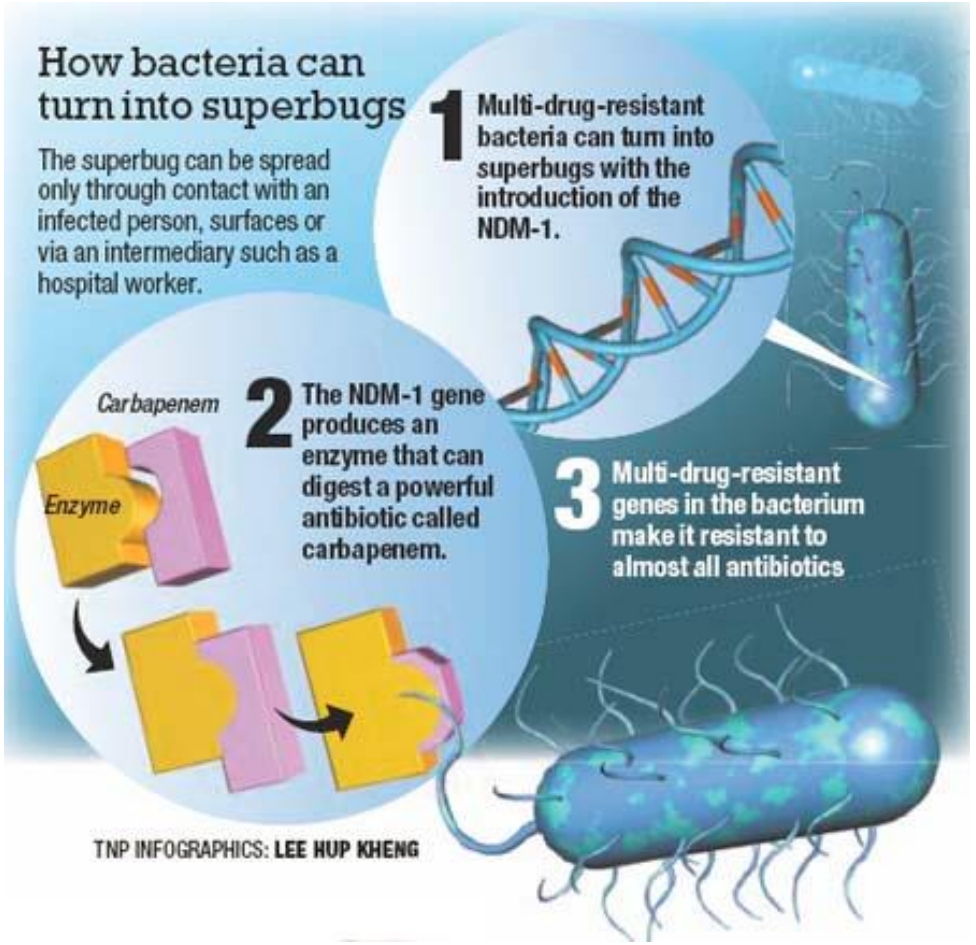
- Indiscriminate use of antibiotics in Humans/Vetr
- Use in animal food stuff
- Very less interest in Pharma to develop antibiotics
- At one point in 1960's, war on infectious diseases was declared over
- Pharma moved to Chronic/life style diseases

WHAT ARE WE DOING TO SOLVE THIS

- <u>WHO at recent meeting (May, 2015) agreed on 5 Objectives</u>

1. Improve awareness and understanding of antimicrobial resistance;
2. Strengthen surveillance and research;
3. Reduce the incidence of infection;
4. Optimize the use of antimicrobial medicines;
5. Ensure sustainable investment in countering antimicrobial resistance.

WE ARE IN SPOTLIGHT !



New Delhi metallo-beta-lactamase 1 India's Famous Superbug

- New Delhi Metallo-beta-lactamase (NDM-1) is a gene that makes bacteria resistant to antibiotics of the Carbapenems family. It encodes a type of beta-lactamase enzyme called a carbapenemases

SPREAD OF NDM-1 SUPERBUG

- x