

# Antibiotic resistance

- Antimicrobial resistance is the ability of a microbe to resist the effects of antibiotics that once could successfully treat the microbe.
- The term antibiotic resistance is a subset of AMR, as it applies only to bacteria becoming resistant to antibiotics.
- Antimicrobial Resistance (**AMR**) is resistance of a microorganism to an antimicrobial **medicine** to which it was previously sensitive.
- **Antibiotic resistant bacteria** are **bacteria** that are not controlled or killed by **antibiotics**. They are able to survive and even multiply in the presence of an **antibiotic**.

# Why resistance is a concern?

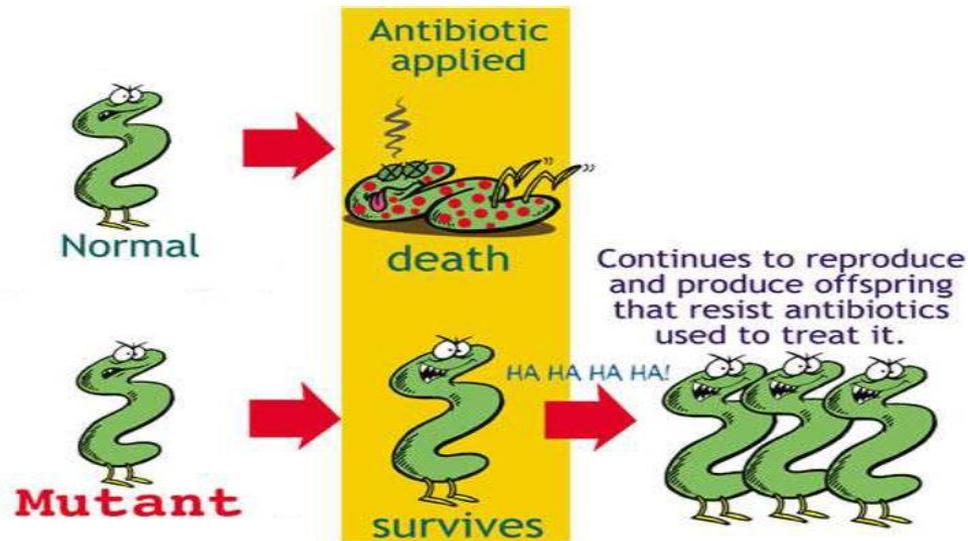
- Resistant organisms lead to treatment failure
- Increased high fish mortality
- Resistant bacteria may spread in other environment.
- Added burden on Fish healthcare costs.
- Threatens to return to pre-antibiotic era.

# Drug Resistance

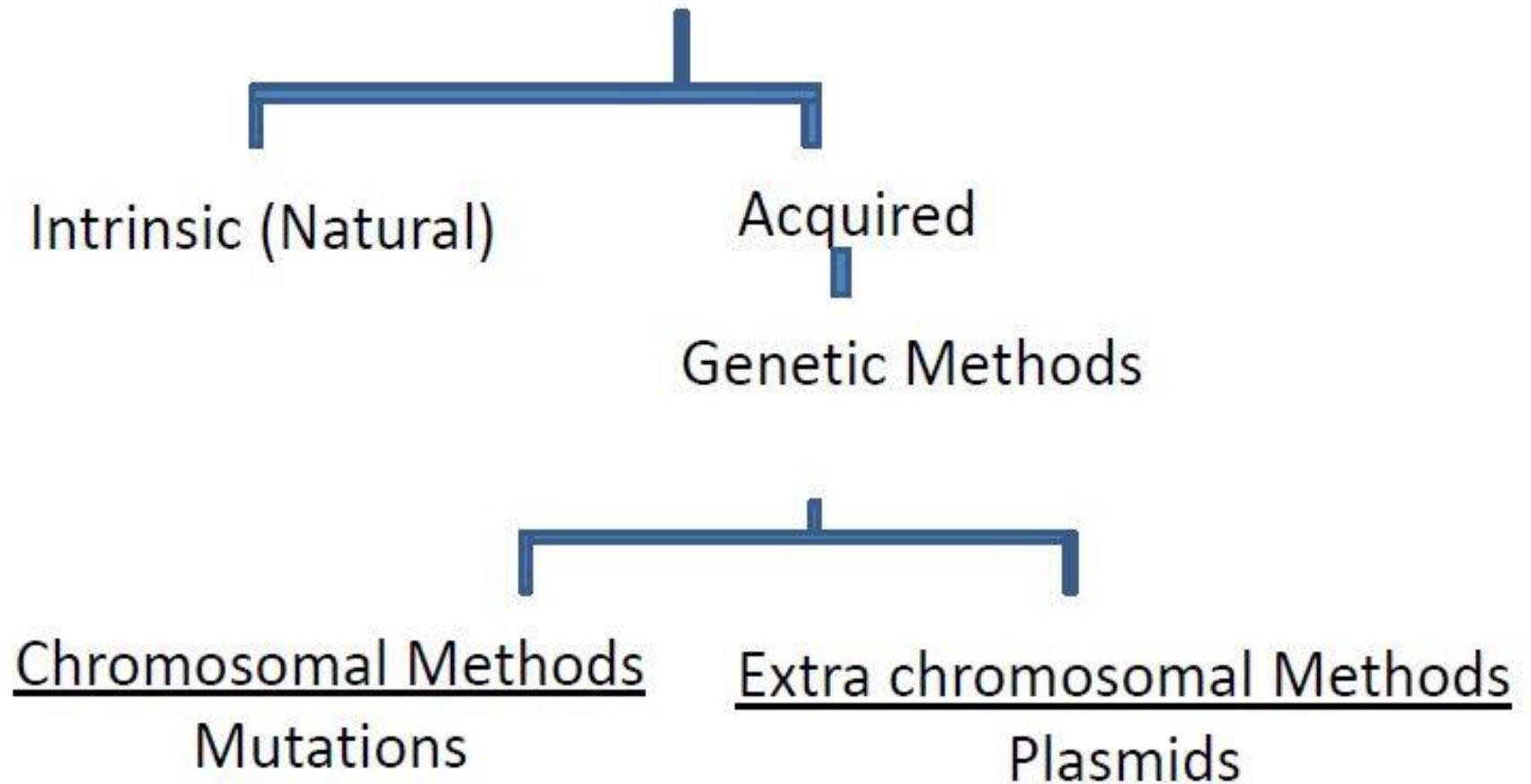
- Drug resistance occurs in :
- **BACTERIA—ANTIBIOTIC RESISTANCE**
- Endoparasites
- Viruses—Resistance to antiviral drugs
- Fungi
- Cancer cells

# BACTERIA—ANTIBIOTIC RESISTANCE

- Antibiotics select out the resistant strain
- Faulty use of antibiotics or widespread use of antibiotics increases the probability of such selection.
- Antibiotic resistant strains appear to be more virulent because we cannot kill them or stop their growth.



# Mechanism Antibiotic Resistance



## Intrinsic Resistance

It occurs naturally.

### 1. Lack target :

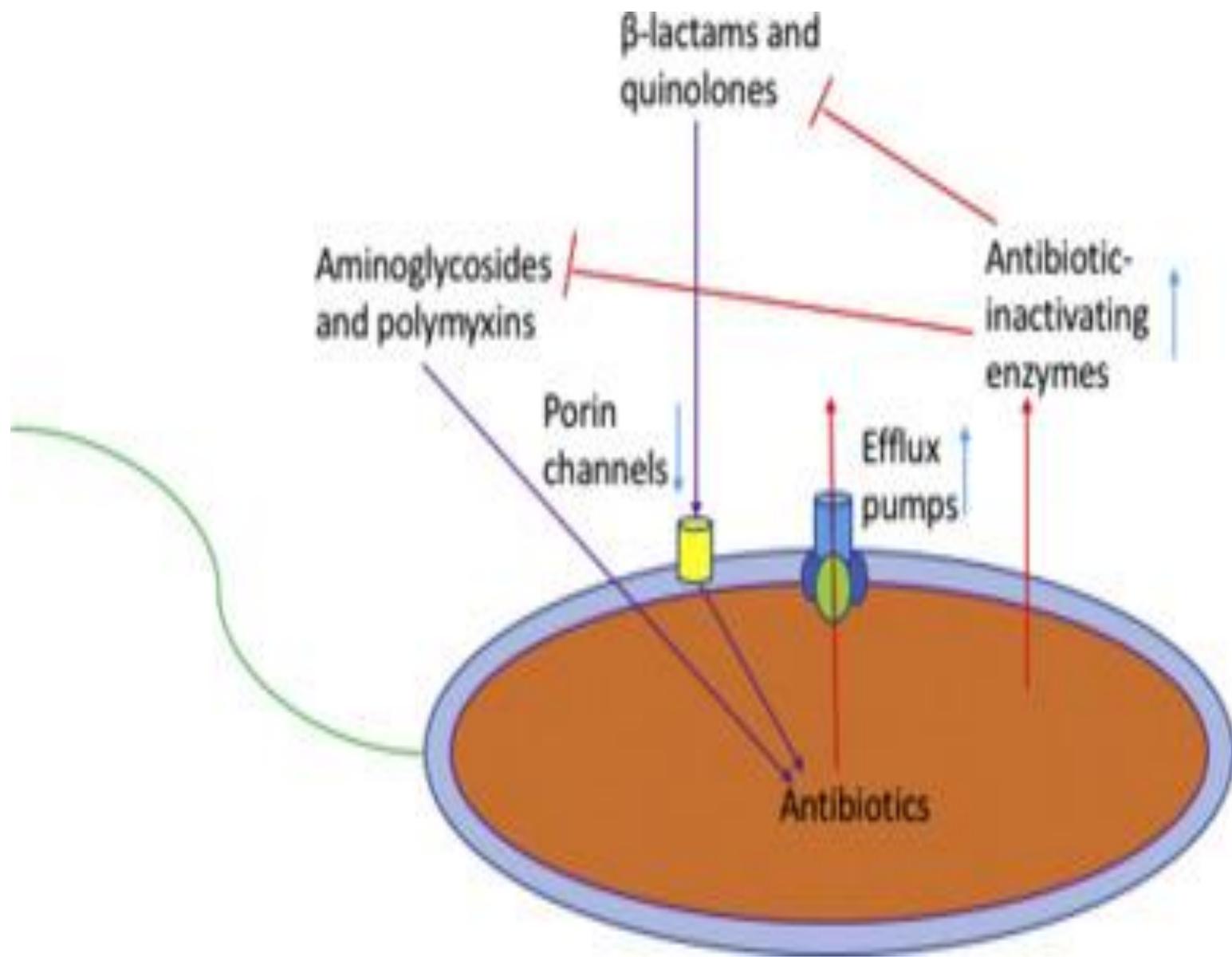
- No cell wall; innately resistant to penicillin

### 2. Innate efflux pumps:

- Drug blocked from entering cell or ↑ export of drug (does not achieve adequate internal concentration). Eg. *E. coli*, *P. aeruginosa*

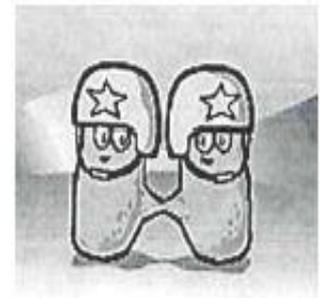
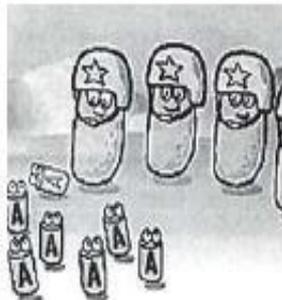
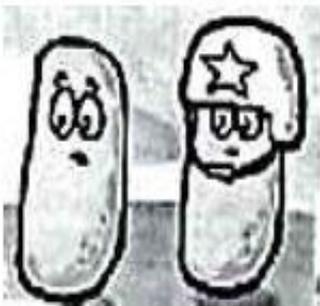
### 3. Drug inactivation:

- Cephalosporinase in *Klebsiella*



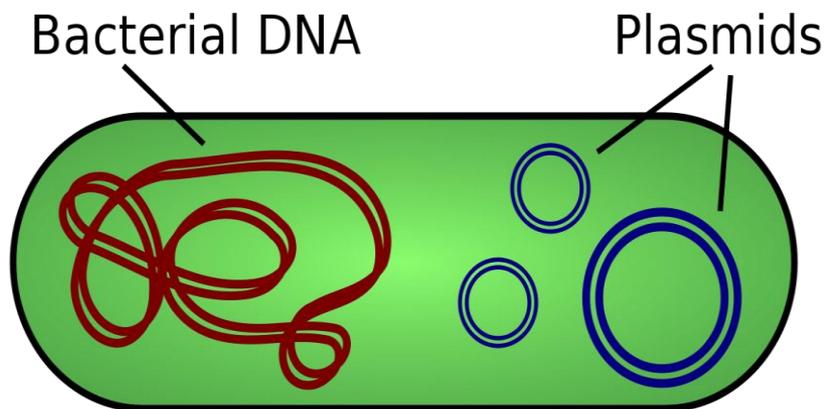
# Acquired resistance

- Mutations:
- It refers to the change in DNA structure of the gene.
- Occurs at a frequency of one per ten million cells.
- Eg. *Mycobacterium tuberculosis*, *Staphylococcus aureus*.
- Often mutants have reduced susceptibility



# Plasmids

- Extra chromosomal genetic elements can replicate independently and freely in cytoplasm.
- Plasmids which carry genes resistant (*r-genes*) are called **R-plasmids**.
- These *r-genes* can be readily transferred from one R-plasmid to another plasmid or to chromosome.
- Much of the drug resistance encountered in clinical practice is plasmid mediated

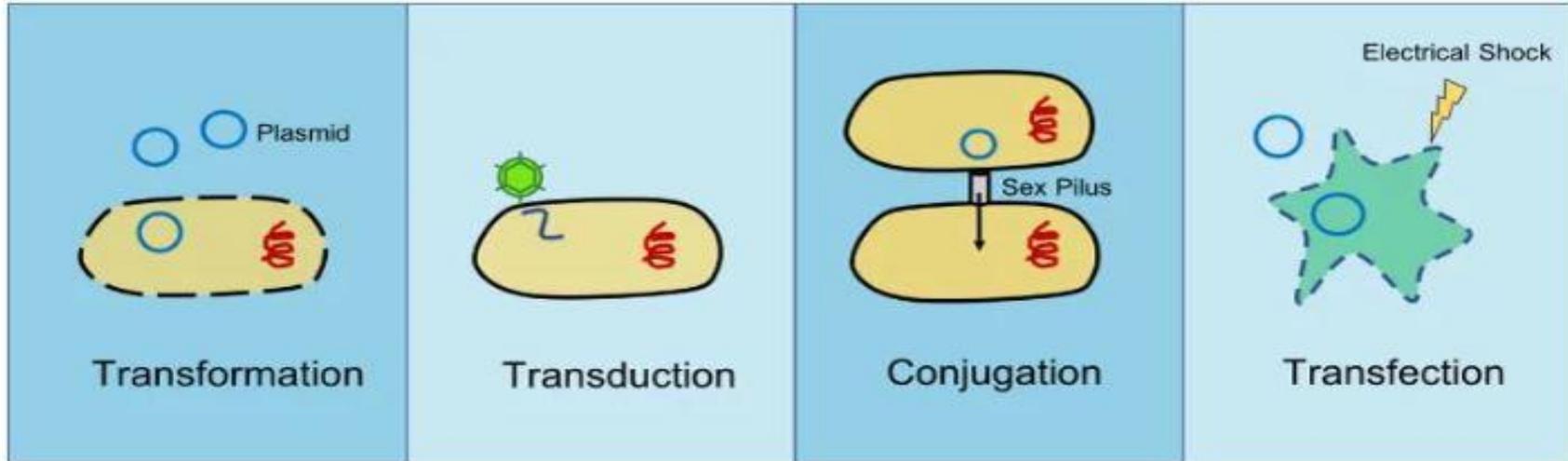


## Mechanisms of Resistance Gene Transfer

- **Transfer of r-genes from one bacterium to another**
  - Conjugation
  - Transduction
  - Transformation
- **Transfer of r-genes between plasmids within the bacterium**
  - By transposons
  - By Integrons

## Transfer of r-genes from one bacterium to another

- **Conjugation** : Main mechanism for spread of resistance  
The conjugative plasmids make a connecting tube between the 2 bacteria through which plasmid itself can pass.
- **Transduction** : Less common method  
The plasmid DNA enclosed in a **bacteriophage** is transferred to another bacterium of same species.  
Seen in Staphylococci , Streptococci
- **Transformation** : least clinical problem.  
Free DNA is picked up from the environment (i.e..  
From a cell belonging to closely related or same strain.



- Transformation is the **uptake of genetic material from the environment** by bacterial cells. In nature, this genetic material often comes from adjacent lysed bacteria and can include plasmid DNA or fragmented DNA released into the environment.
- Transduction occurs when foreign DNA or RNA is introduced into bacterial or eukaryotic cells **via a virus or viral vector**.
- One example are bacteriophages that attach to bacterial membranes and inject their genetic material into the cell.
- During conjugation, genetic material is transferred from a donor bacterium to a recipient bacterium through **direct contact**.

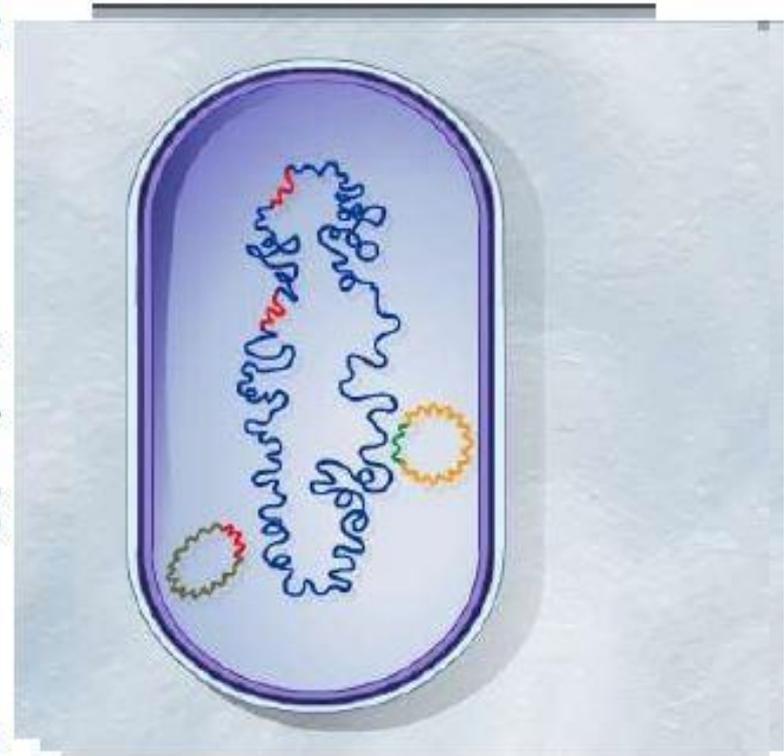
## Transfection:

- Unlike the last three methods which can be used in prokaryotes, transfection is only done in eukaryotic cells.
- Transfection is the process by which foreign DNA is deliberately introduced into a eukaryotic cell **through non-viral methods** including both chemical and physical methods in the lab.
- Chemicals like calcium phosphate and diethylaminoethyl (DEAE)-dextra neutralize or even impart an overall positive charge on DNA molecules so that it can more easily cross the negatively charged cell membrane.
- Physical methods such as electroporation or microinjection actually pokes holes in the cell membrane so DNA can be introduced directly into the cell.

# Mechanisms of Resistance Gene Transfer

## Transposons

- Transposons are sequences of DNA that can move around different positions within the genome of single cell.
- The donor plasmid containing the Transposons, co-integrate with acceptor plasmid. They can replicate during cointegration
- Both plasmids then separate and each contains the r-gene carrying the transposon.



- Eg ; Staphylococci, Enterococci

# Mechanisms of Resistance Gene Transfer

## **Integrans**

- Integron is a large mobile DNA can spread Multidrug resistance
- Each Integron is packed with multiple gene cassettes, each consisting of a resistance gene attached to a small recognition site.
- These genes encode several bacterial functions including resistance and virulence.

# Biochemical mechanisms of antibiotic resistance

- Prevention of drug accumulation in the bacterium
- Modification/protection of the target site
- Use of alternative pathways for metabolic / growth requirements
- By producing an enzyme that inactivates the antibiotic
- Quorum sensing

## By producing enzymes that inactivates antibiotic

### a) Inactivation of $\beta$ -lactam antibiotics

- *S. aureus*, *N. gonorrhoea*, *H. influenza*, Produce  $\beta$ -lactamase which cleaves  $\beta$ -lactam ring

### b) Inactivation of Chloramphenicol

- Inactivated by chloramphenicol acetyltransferase .
- Gram-ve (enzyme present constitutively hence higher resistance) gram +ve bacteria (enzyme is inducible )

### c) Inactivation of Aminoglycosides

- Inactivated by acetyl, phospho & adenylyl transferases  
Present in gram +ve and gram -ve .