ANTIMICROBIAL RESISTANCE

–*What a primary care physician needs to know*

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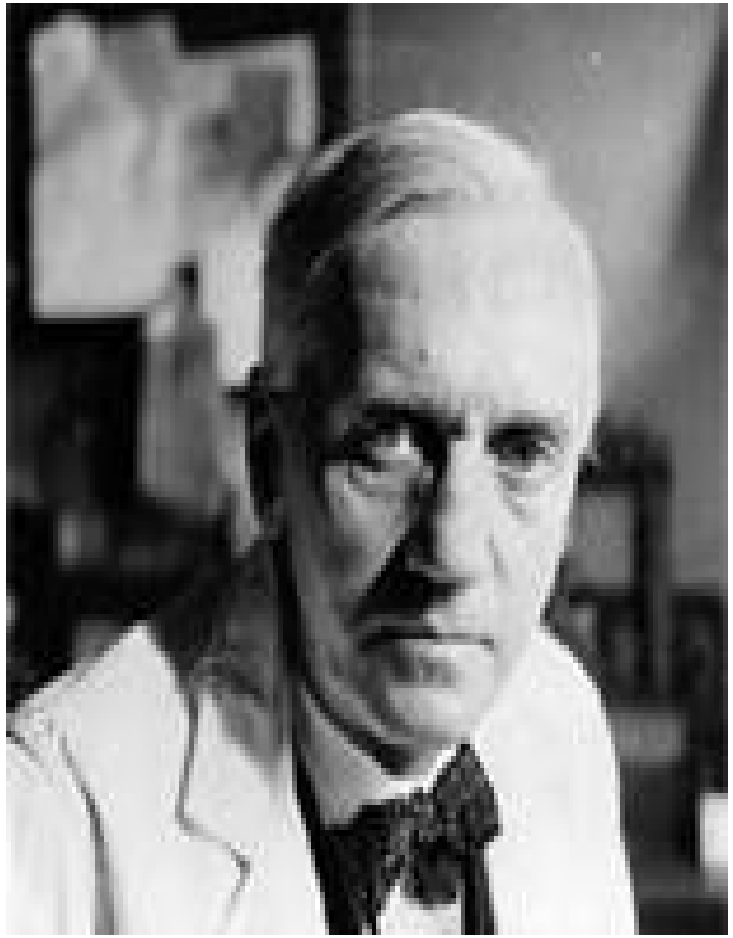
OBJECTIVES

- Magnitude of the problem of AMR.
- Major mechanisms of antimicrobial resistance.
- Methods of detection of AMR
- Identify the contributing factors
- Strategies to prevent AMR.

Disclosures-NONE

Introduction

- In 1928 at St.Mary's Hospital ,London ,Sir Alexender Fleming discovered penicillin.
- This led to the introduction of antibiotics which has since shaped human history.
- However over the years unsustainable use of antimicrobials have led to growing resistance to them leading to an unprecedented global crisis.
- Antimicrobial resistance (AMR) is a global health threat that occurs when microbes like bacteria, viruses, fungi, and parasites evolve to become resistant to antimicrobials, making infections difficult to treat and raising the risk of severe illness and death.



AMR-THE SILENT PANDEMIC

- Globally 700,000 deaths every year are attributable to AMR.
- If not contained 10,000,000 lives a year are estimated to be at risk by 2050, 90% of which will be in Asia and Africa.
- 1·27 million deaths were directly attributable to resistance. 4·95 million deaths were associated with bacterial AMR Lancet 2022; 399: 629–55
- Huge impact on Global economy. AMR was ranked as **5th** out of 10 threats to global health in 2019 by WHO.

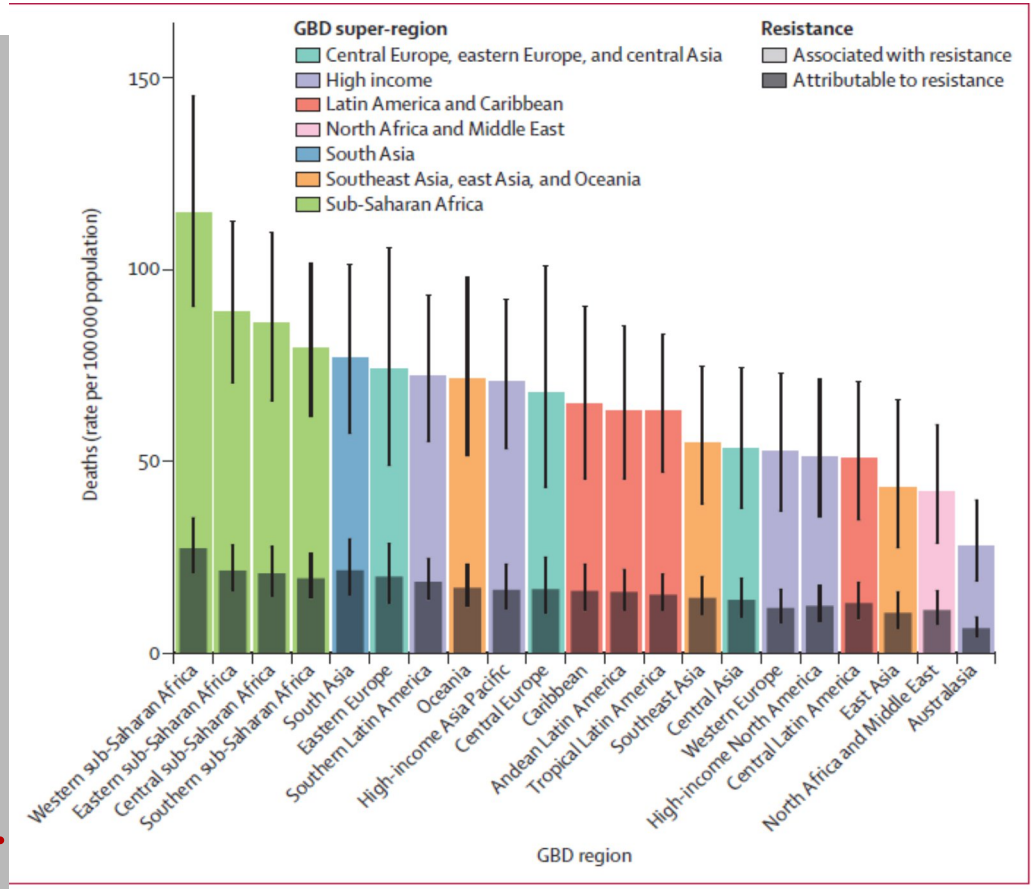


Figure 2: All-age rate of deaths attributable to and associated with bacterial antimicrobial resistance by GBD region, 2019

SOURCE-LRTI, BSI and Intra abdominal infections accounted for 78·8% of deaths attributable to AMR in 2019

BUGS-Together, six pathogens were responsible for 929000 of 1·27 million deaths attributable to AMR & 3·57 million of 4·95 million deaths associated with AMR Lancet 2022; 399: 629–55

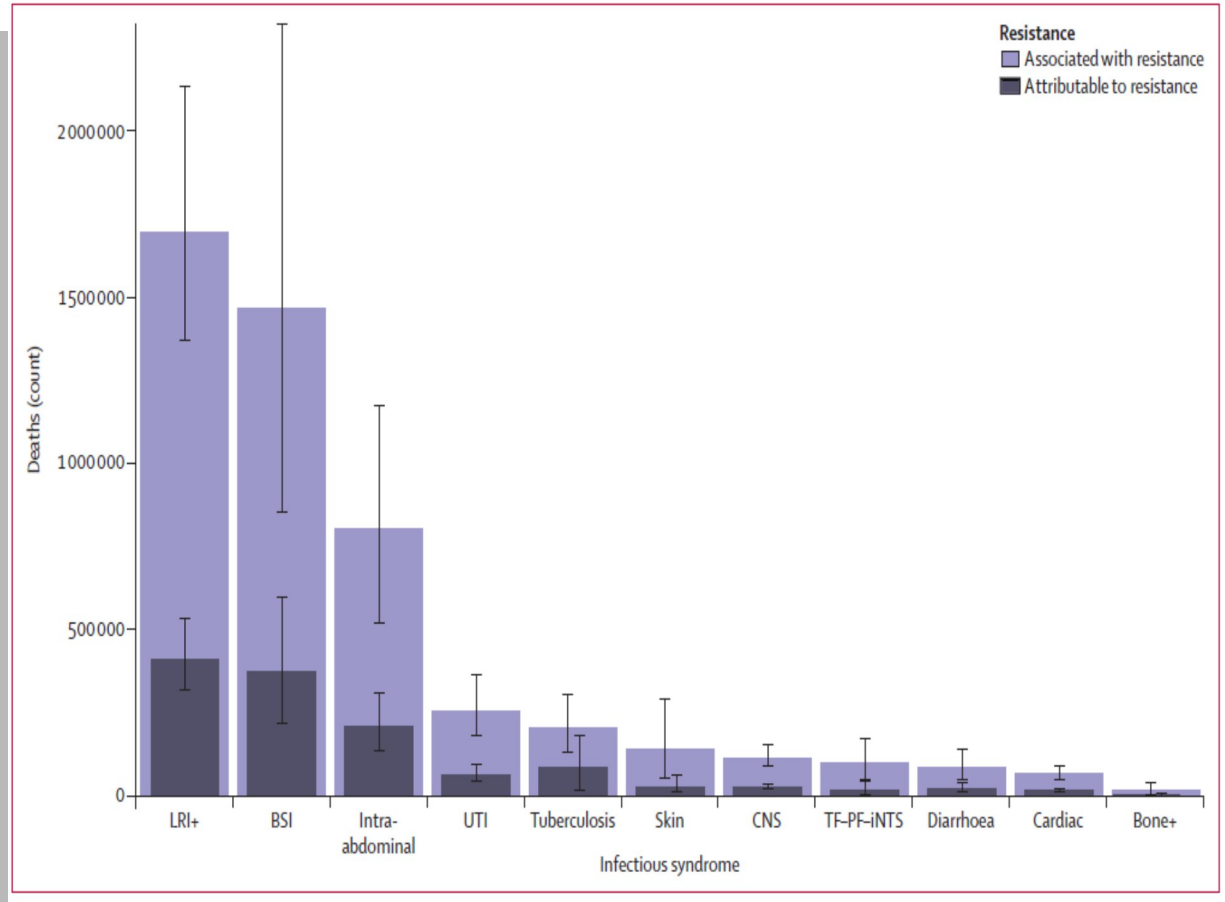
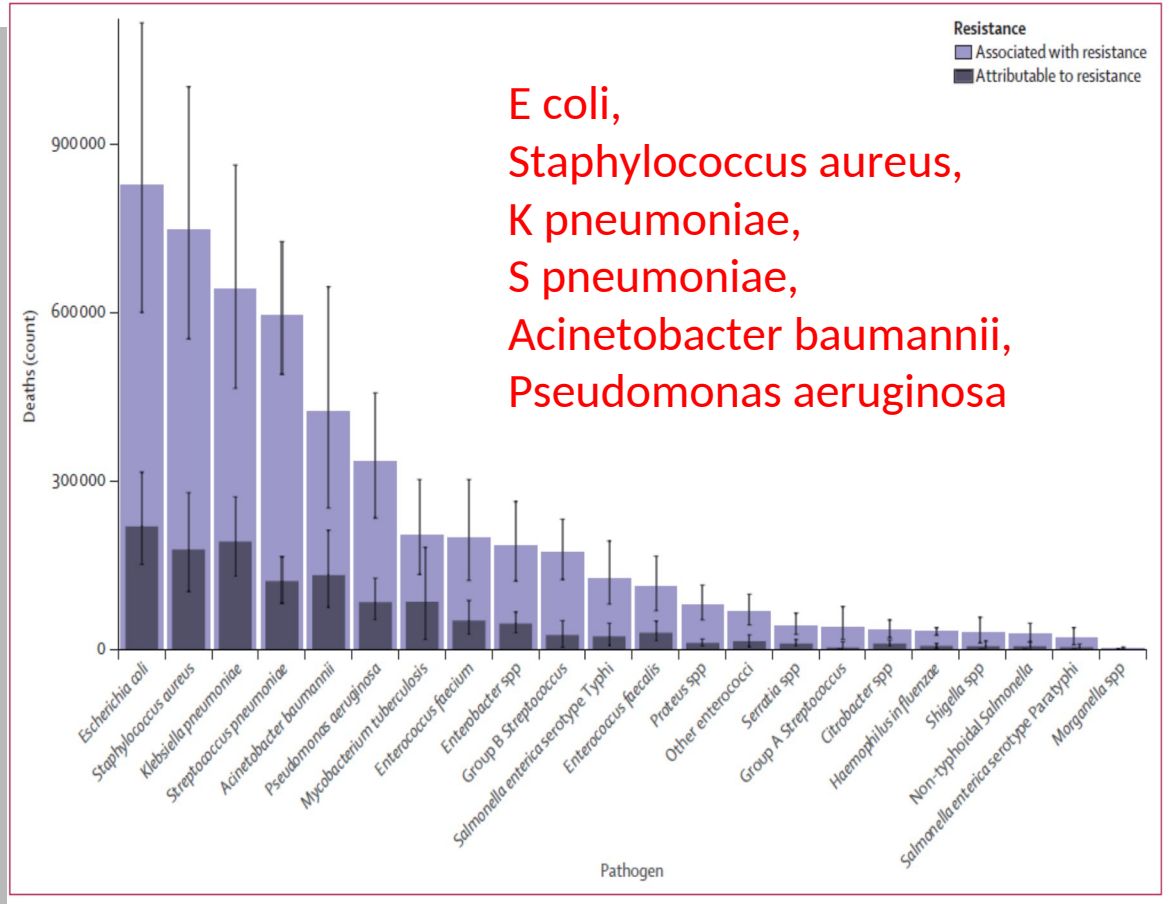


Figure 3: Global deaths (counts) attributable to and associated with bacterial antimicrobial resistance by infectious syndrome, 2019



E coli,
Staphylococcus aureus,
K pneumoniae,
S pneumoniae,
Acinetobacter baumannii,
Pseudomonas aeruginosa

Figure 4: Global deaths (counts) attributable to and associated with bacterial antimicrobial resistance by pathogen, 2019

Overuse of antibiotics led to 60% of sepsis deaths in India: Lancet study

ANURADHA MASCARENHAS
Pune, September 16

WHEN A 60-YEAR-OLD patient with leukaemia was admitted to the emergency department with high fever and low blood pressure, he was immediately started on broad-spectrum antibiotics. However, the drugs didn't work, complicating his condition. A blood culture later revealed a drug-resistant Klebsiella infection, which required a combination of drugs to bring it under control.

"The patient's condition deteriorated because of antimicrobial resistance (AMR), a condition where bacteria and parasites become resistant to medicines that were previously effective against them," said Dr Abdul Ghafur, infectious diseases expert at Apollo Hospital, Chennai.

Overuse or wrongful use of antibiotics is exacting a toll on the health of Indians, with a latest *Lancet* study showing that 60% of the 2.9 million sepsis deaths in the country in 2019 were caused by antimicrobial resistance. While about 290,000 sepsis deaths that year were directly attributable to bacterial AMR, nearly one million deaths were linked to it.

Sepsis deaths occur when one's immune system has a dangerous reaction to a bacterial infection and without treatment, can lead to organ failure.

"AMR is the result of overuse of antibiotics earlier in the patient's lifetime or wrongful use. With rising rates of drug-resistant bacteria in India, treatment options are becoming increasingly limited, posing a public health challenge," said Dr Ghafur.

Already widely recognised as a major global health challenge, AMR is anticipated to worsen in the coming decades with *Lancet* predicting that more than 39 million people around the world could die from antibiotic-resistant infections over the next 25 years. The report, based on a new study by the Global Research on Antimicrobial Resistance (GRAM) Project, is the first global analysis of antimicrobial resistance trends over time.

"Until now, no study has assessed historical trends of AMR and provided in-depth forecasts of future global impacts. Understanding how trends in AMR deaths have changed over time, and how they are likely to shift in future, is vital to make informed decisions to help save lives," said Dr Mohsen Naghavi, team leader of the AMR Research Team at the Institute of Health Metrics, University of Washington, US.

IN NUMBERS

2.9 million
sepsis deaths in the country in 2019; 60% were due to wrongful use of antibiotics

290,000
sepsis deaths that year were directly attributable to bacterial antimicrobial resistance

39 mn
people around the world could die from antibiotic-resistant infections over next 25 years

1 mn deaths were linked to bacterial AMR

MECHANISM OF ANTIBIOTIC RESITANCE

Basic concepts of antimicrobial resistance

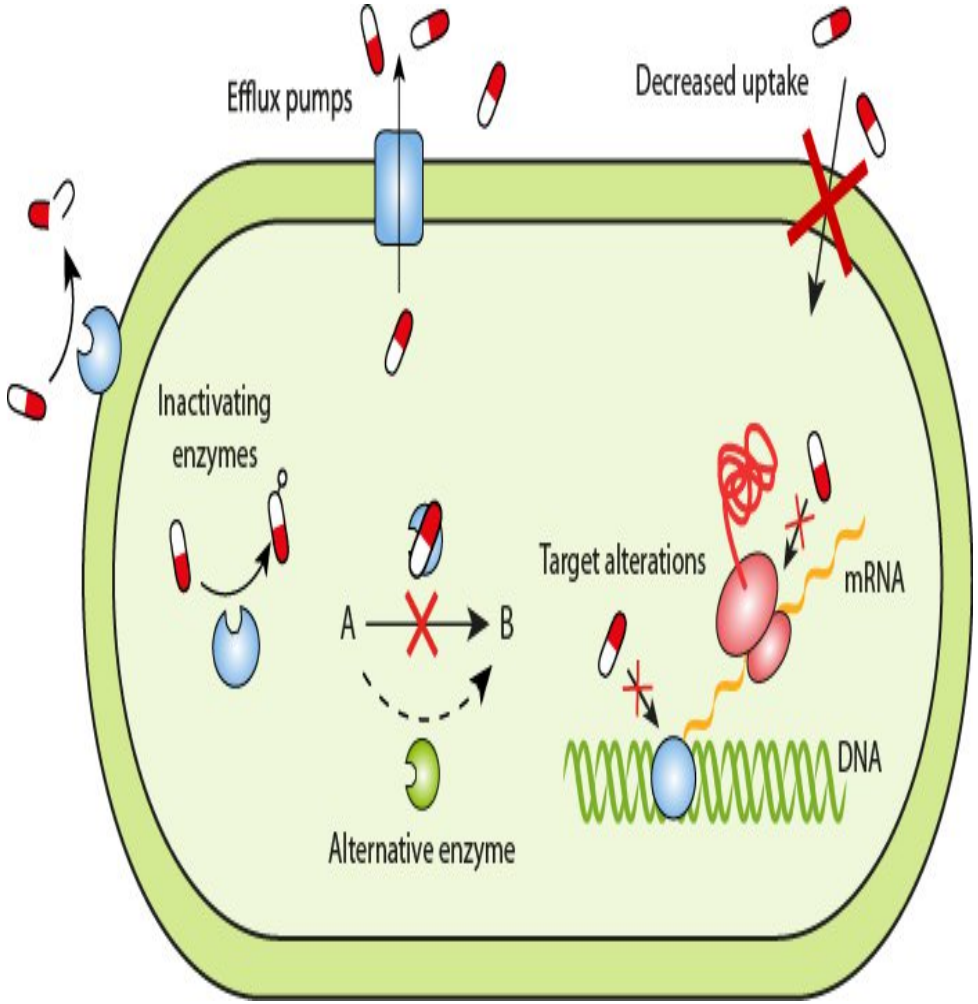
- **INTRINSIC RESISTANCE**-is inherent resistance to an antimicrobial that all or almost all members of a species display, rendering susceptibility testing unnecessary
- **AQUIRED RESISTANCE**: development of resistance to an antimicrobial to which members of the wild-type bacterial population are susceptible
- **Constitutively expressed resistance** mechanisms are expressed continuously.
- **Inducible expression occurs** following exposure to a particular inciting agent
- **Heteroresistance**-A phenomenon where subpopulations of seemingly isogenic bacteria exhibit a range of susceptibilities to a particular antibiotic.

INTRINSIC RESISTANCE

ANTIBIOTIC	BACTERIA
Aztreonam	Gram positive bacteria
Aminoglycosides, Cephalosporins	Enterococci
Vancomycin	Gram negative bacteria
Sulphonamides,TMP,tetracyclines, chloramphenicol	P.aeruginosa
Ampicillin	Klebsiella spp
Imipenem	S.maltophila
Aminoglycosides	Anaerobic bacteria
Metronidazole	Aerobic bacteria

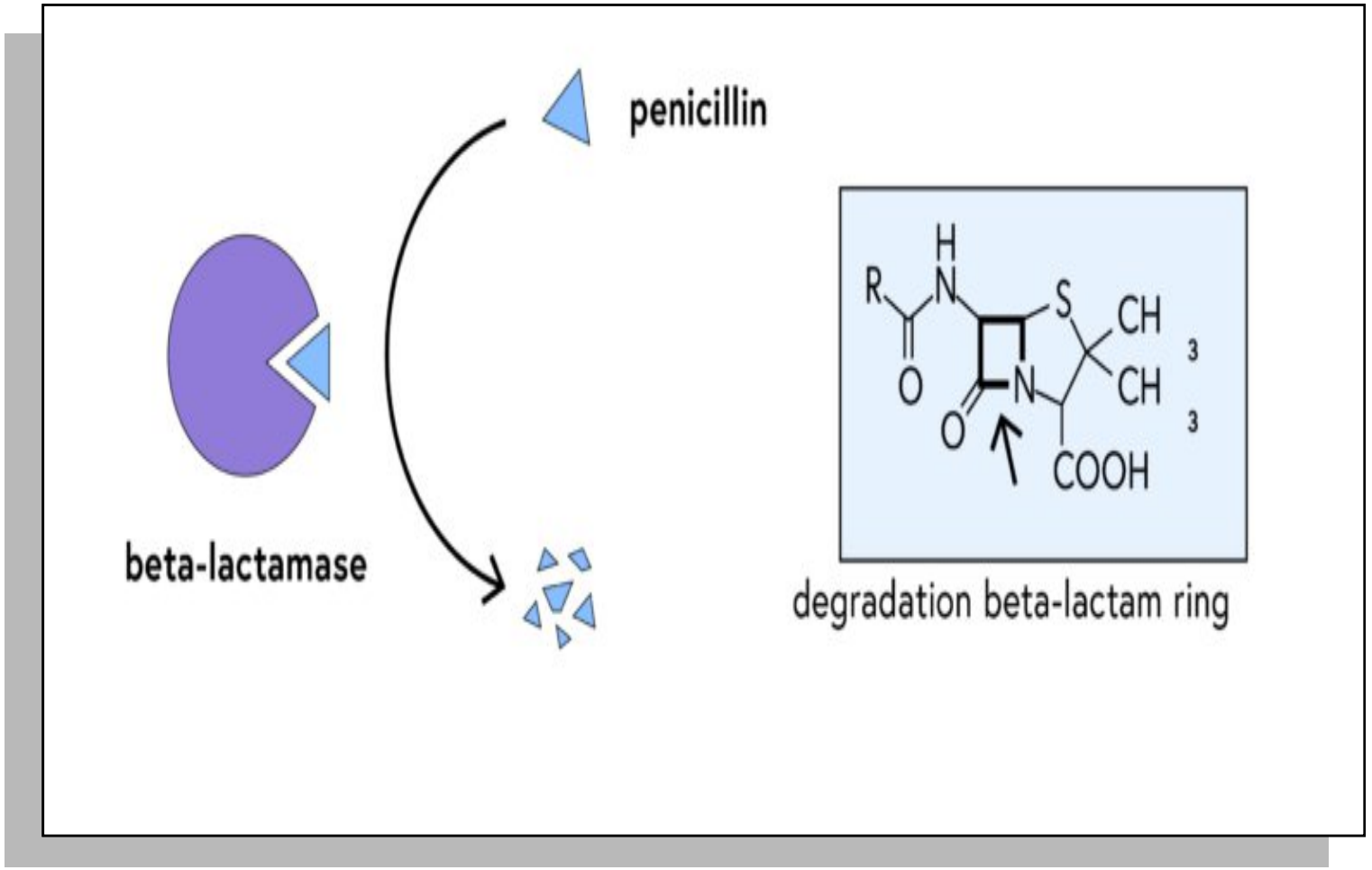
Mechanisms of antibiotic resistance

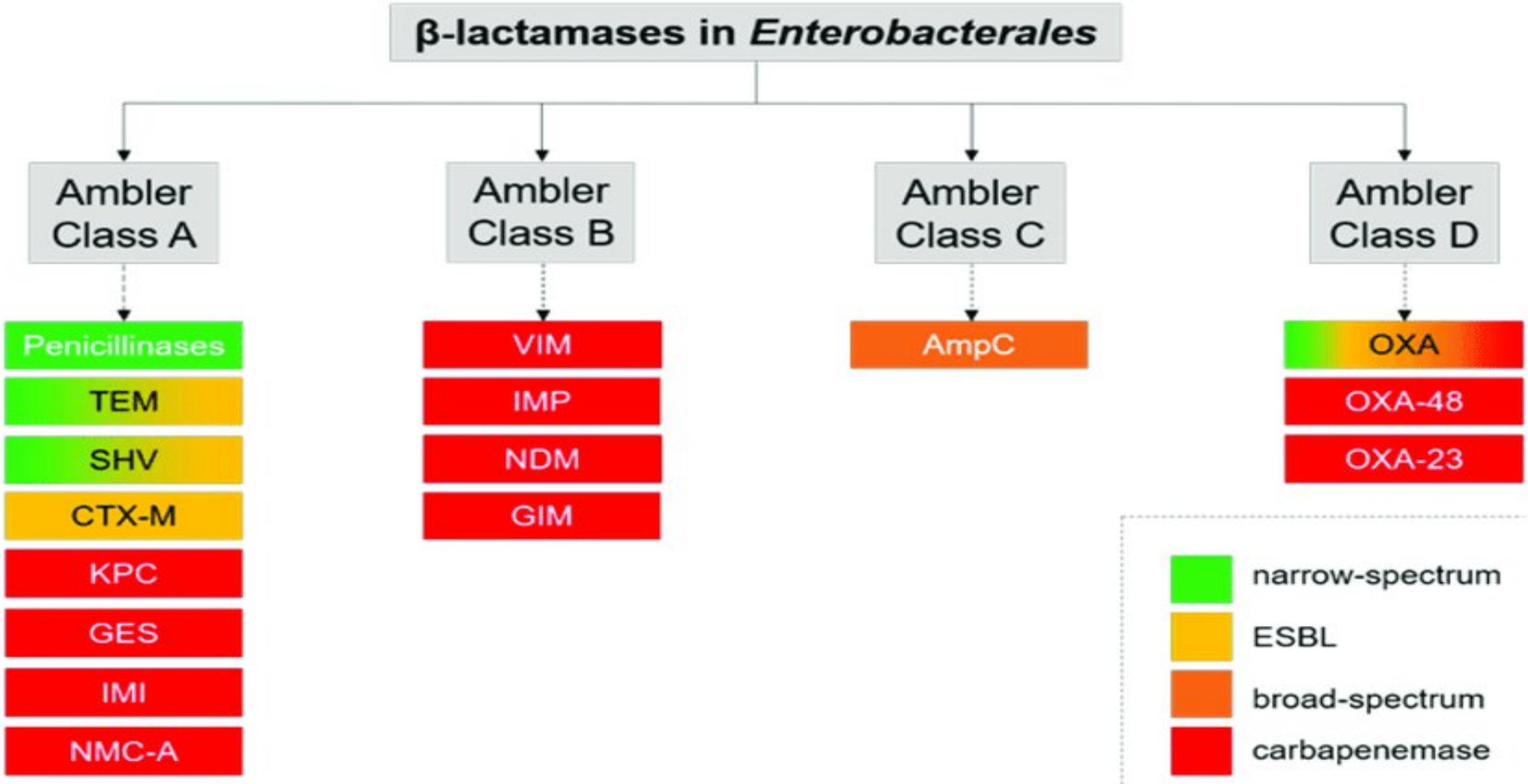
- Inactivating enzymes
- Modification of target site
- Replacement of target site
- Decreased uptake
- Efflux



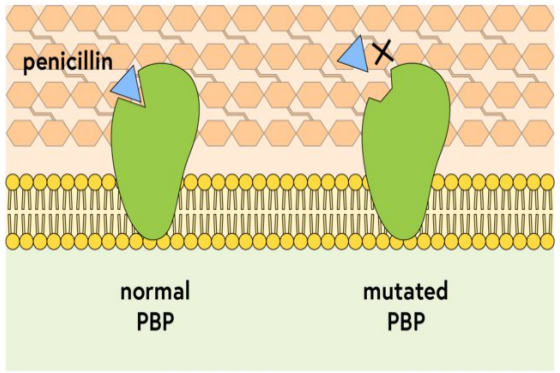
Inactivation by a bacterial enzyme

- Production of beta-lactamases is a major mechanism of resistance to the beta-lactam antibiotics in clinical isolates.



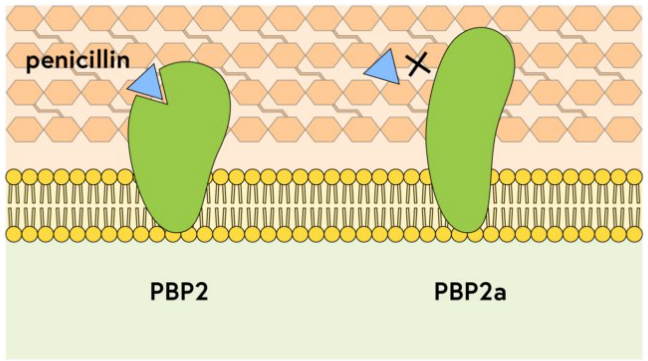

β-lactamases in *Enterobacterales*
Ambler Class A
Ambler Class B
Ambler Class C
Ambler Class D
Penicillinases
TEM
SHV
CTX-M
KPC
GES
IMI
NMC-A
VIM
IMP
NDM
GIM
AmpC
OXA
OXA-48
OXA-23
narrow-spectrum
ESBL
broad-spectrum
carbapenemase

Modification of the antibiotic target site



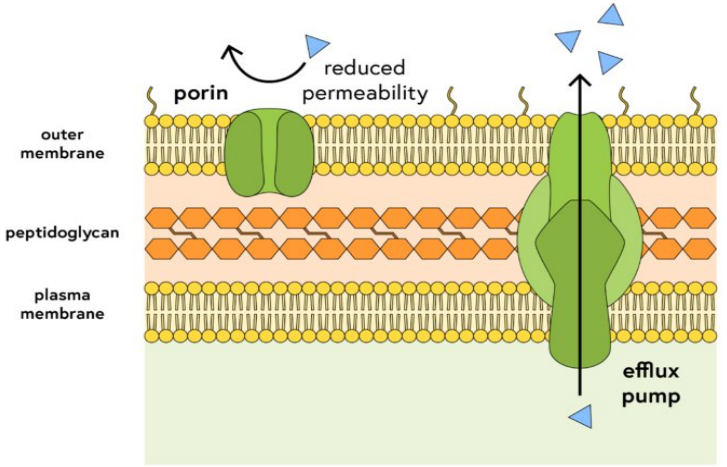
The target sites for the beta-lactams are the PBPs in the cytoplasmic membrane.
Alterations in PBPs may influence their binding affinity for beta-lactam antibiotics and therefore the sensitivity of the altered bacterial cell to inhibition by these antibiotics.eg Penicillin resistance in Streptococcus Pneumonae

Replacement of the antibiotic target site



PBP2a is encoded by the mecA gene, which is carried on a mobile genetic element called SCC mec.
PBP2a has a lower affinity for beta-lactams, which allows the cell wall to continue to be built even when the antibiotic is present.
This is the mechanism by which MRSA is able to persist despite treatment with multiple beta-lactam antibiotics.

Decreased penetration to the target site and efflux



Mutations that result in decreased amounts of porin channels, those that increase the amounts of native active efflux pumps, or both can contribute to acquired resistance to beta-lactams.
Found typically in pseudomonas and Acinetobacter,it inactivates ticarcillin, higher generations of cephalosporins ,FQ, AG, Carbapenems, tigecycline etc

Other mechanisms of Antibiotic resistance

- Topoisomerase modification and gyrase modifications-found in pseudomonas, Enterobactereciae, Acinetobacter .They inactivate fluroquinolones.

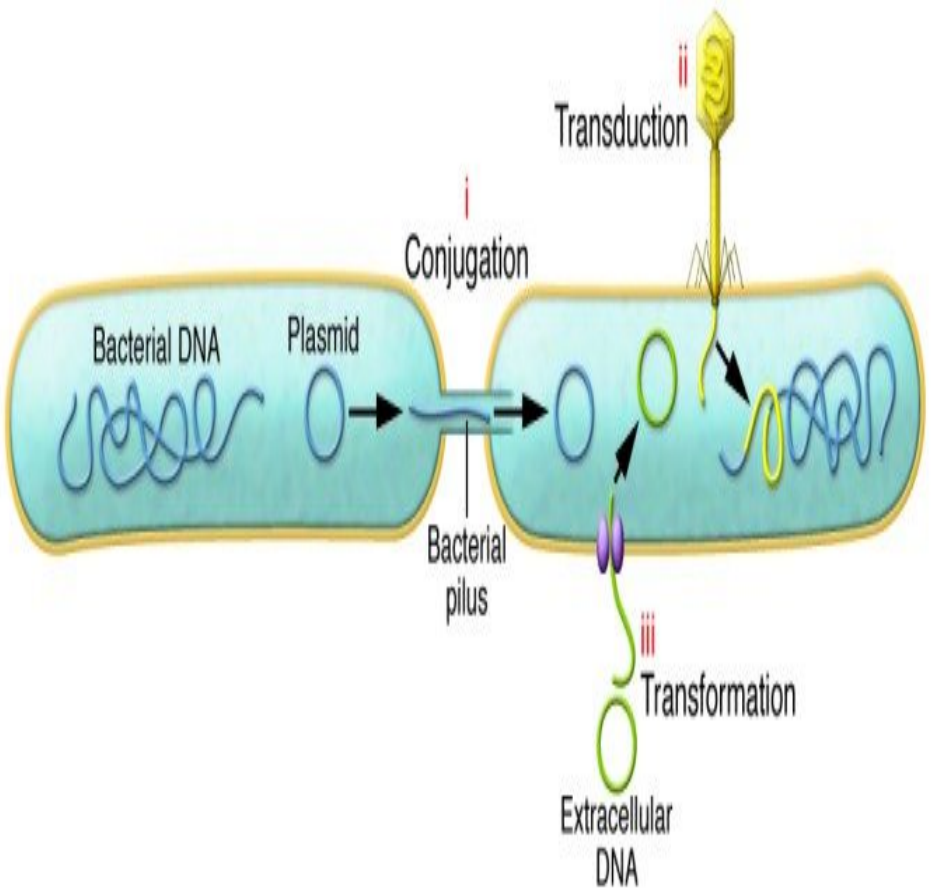
- Aminoglycoside modifying enzymes(AME)-Produced in Enterobacteriaceae, Acinetobacter, etc. They inactivae aminoglycosides.

- Methylation of 16 ribosomal subunit-found in enterobactereriaceae, inactivate Plazomycin

- Lipid A modification, mcr gene mutation and Pmr A and B modifications-Found in Klebsiella, Pseudomonas, Acinetobacter and Enterobacteriaceae. They Inactivate Polymixins.

Genetic basis of AMR

- From an evolutionary perspective, bacteria use two major genetic strategies to adapt to the antibiotic.
- Spontaneously occurring **mutations** in gene(s)conferring resistance and **vertically** transmitted due to multiplication as its competitor is killed by the antibiotic.
- Acquisition of foreign DNA coding for resistance determinants through **horizontal gene transfer (HGT)**
- Classically, bacteria acquire external genetic material through three main strategies: (i) transformation (incorporation of naked DNA), (ii) transduction (phage mediated), and (iii) conjugation (bacterial "sex").



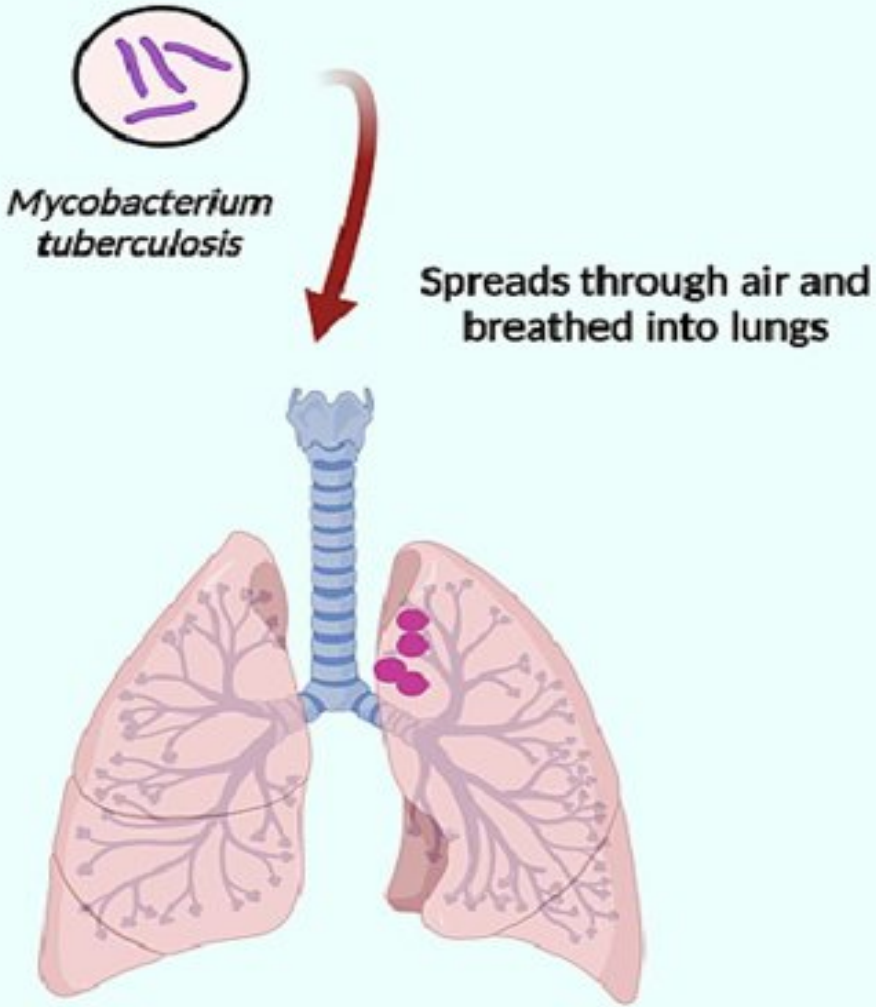
SPECTRUM OF RESISTANCE

I

- If the resistance is against only one type of antimicrobial (structurally and mechanistically similar), it is simply called **resistance to that particular class**.

- If resistant to at least *"one antimicrobial in three or more categories*" of structurally unrelated antimicrobials, then it is called **"multi-drug resistance (MDR).**

- MDR is further classified as "**Extensively Drug-Resistant (XDR**)", and "**Pan Drug-Resistant (PDR)".** XDR organisms will be susceptible to antimicrobials in at most two structurally unrelated antimicrobial classes. PDR organisms will be resistant to all available antimicrobials.



Drug Resistant TB

Multi-Drug Resistant TB (MDR-TB)

- Manifest resistance to both Isoniazid and Rifampicin
- Globally, around 3.4% of the new TB patients and 20% of patients with a history of preceding medication for TB were identified as MDR-TB

Extensively-Drug Resistant TB (XDR-TB)

- MDR strains that offer additional resistance to any fluoroquinolone
- Plus at least one of the following: Linezolid or Bedaquiline

Drug Resistance caused by

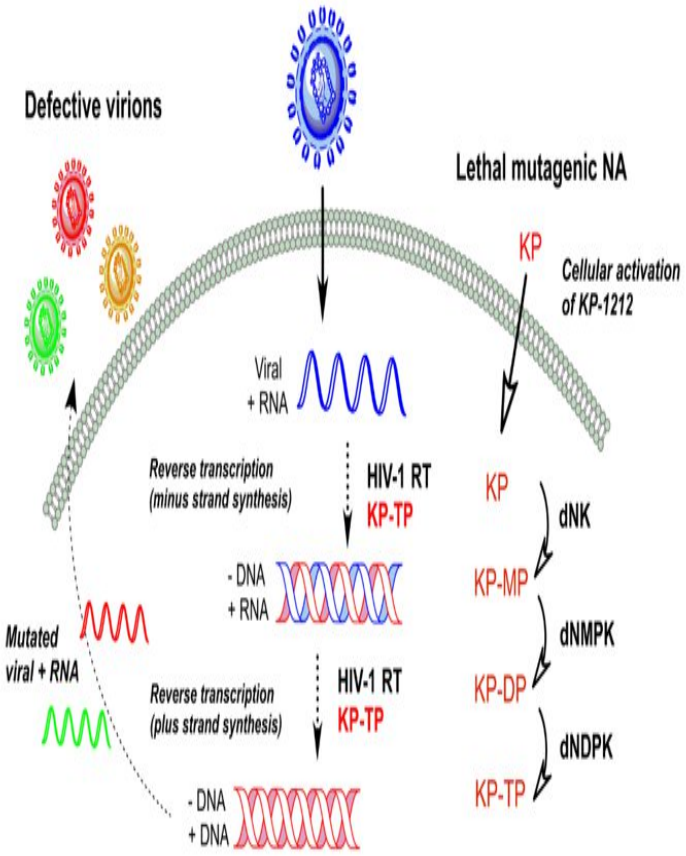
- Incorrect prescribing
- Irregular supply of drug
- Patient non-adherence
- Low-grade quality of drugs

ANTI-VIRAL RESISTANCE

- Antiviral drug resistance is an increasing concern in immuno-compromised patient populations, where ongoing viral replication and prolonged drug exposure lead to the selection of resistant strains.

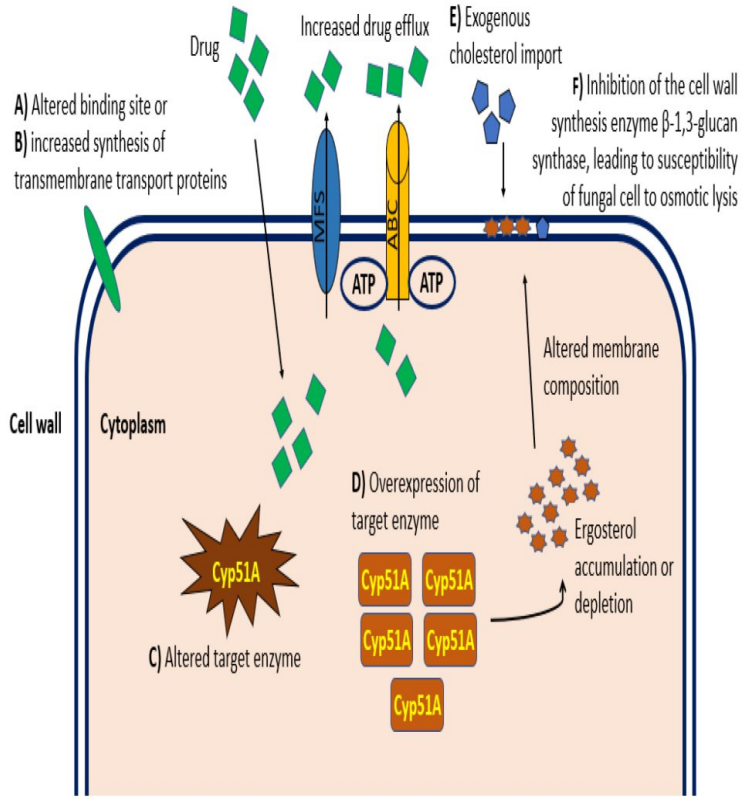
- Various modes of resistance in six exemplary viruses including RNA viruses HCV ,influenza A virus (IAV), DNA viruses (HSV) and human cytomegalovirus (HCMV), retrovirus HIV, and unconventionally replicating HBV have been studied.

- Knowledge of genetic mechanisms and associated viral mutations has allowed for development of genotypic techniques for the timely diagnosis of resistance.



ANTI FUNGAL RESISTANCE

- The frequent use of antifungal agents has led to the development of robust resistance in medically important fungi. Resistance to azoles and echinocandins is well documented, while resistance to polyenes remains rare.
- Antifungal resistance can develop through a number of mechanisms, including:
- **Altering the drug target**:
- **Reducing intracellular drug levels**:
- **Decreased access to the drug target**: .
- **Point mutations**: This can include mutations in the FKS1 gene.
- **Activation of stress responses**

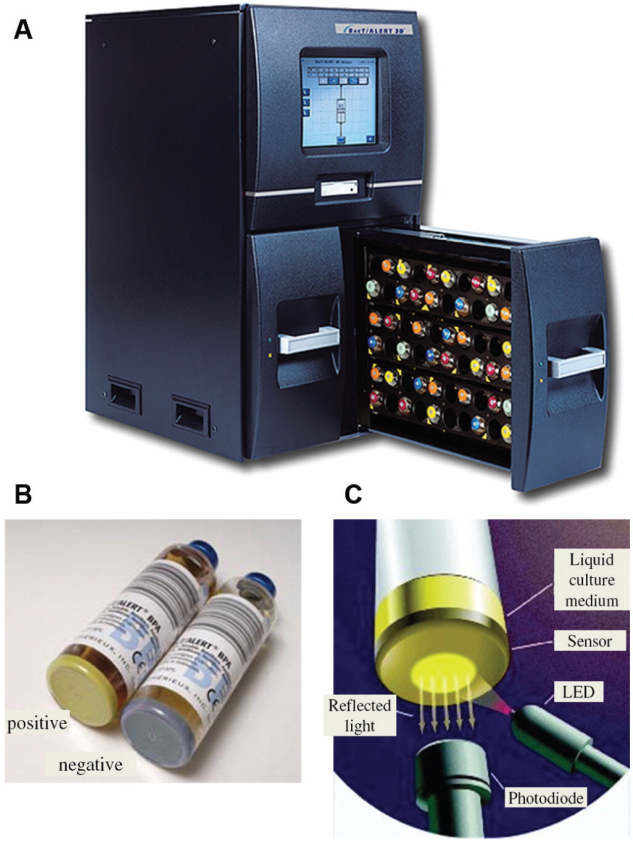


DETECTING AMR

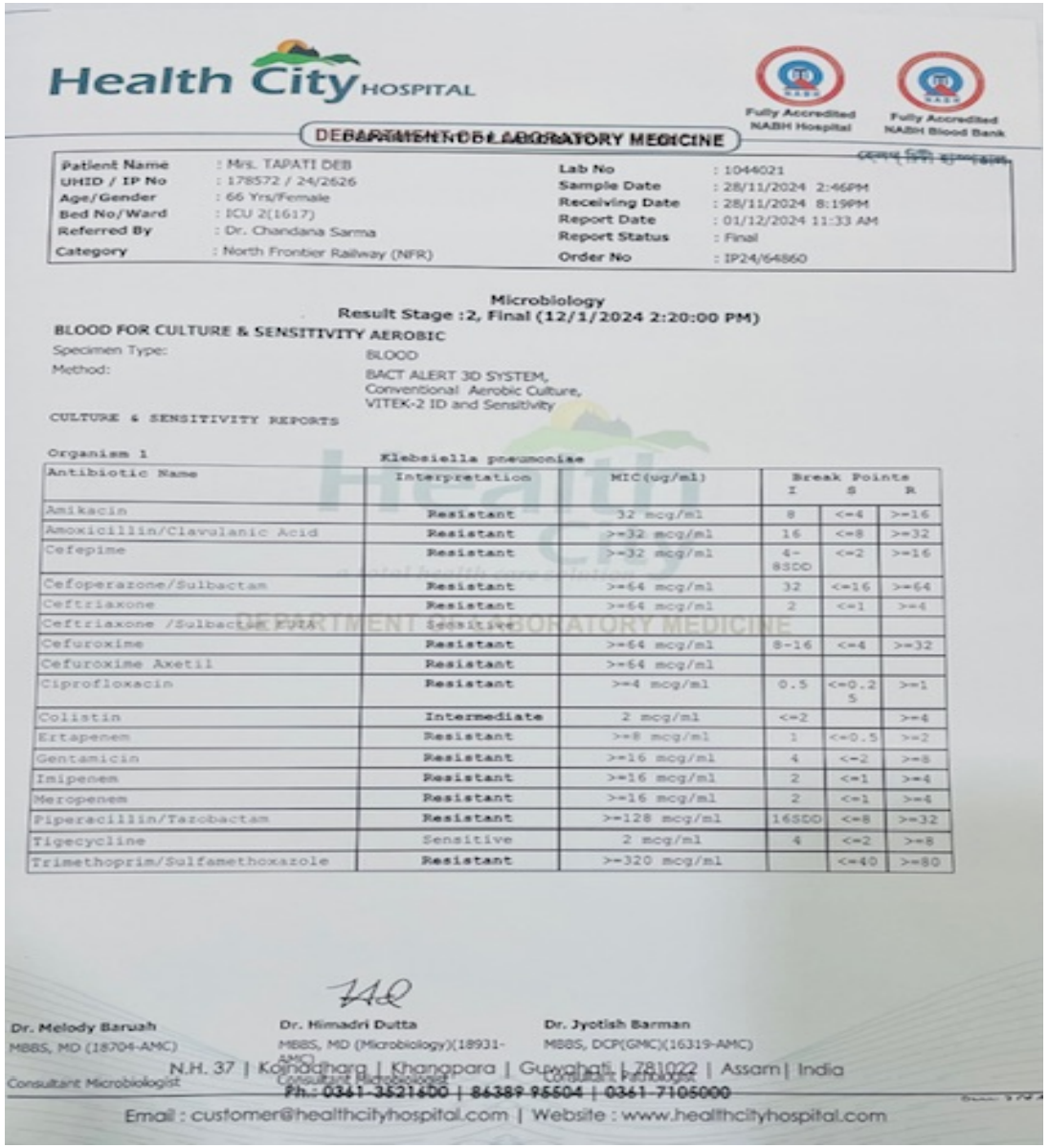
- **Phenotypic methods** These methods are cheaper and more reliable, but they involve culturing, subculturing, and plating steps, which can be time-consuming. Examples include- broth dilution, gradient diffusion, and disc diffusion.

- **Automated systems** include Vitek2 (BioMérieux), MicroScan WalkAway (Beckman Coulter),or Phoenix (Becton Dickinson).

- **Molecular methods** These methods can detect AMR genes in microbes. Examples include: PCR: A technique that can amplify target DNA sequences ,DNA microarray technology: A method that can detect the presence or absence of genes ,Whole-genome sequencing (WGS): A method that can detect genetic determinants of AMR



INTERPRETING AN ANTIMICROBIAL SUSCEPTIBILITY REPORT



Health City HOSPITAL

Fully Accredited NABH Hospital | Fully Accredited NABH Blood Bank

DEPARTMENT OF LABORATORY MEDICINE

Patient Name	: Mrs. TAPATI DEB	Lab No	: 1044021
UHID / IP No	: 178572 / 24/2626	Sample Date	: 28/11/2024 2:46PM
Age/Gender	: 66 Yrs/Female	Receiving Date	: 28/11/2024 8:19PM
Bed No/Ward	: ICU 2(1617)	Report Date	: 01/12/2024 11:33 AM
Referred By	: Dr. Chandana Sarma	Report Status	: Final
Category	: North Frontier Railway (NFR)	Order No	: IP24/64860

Microbiology

Result Stage :2, Final (12/1/2024 2:20:00 PM)

BLOOD FOR CULTURE & SENSITIVITY AEROBIC

Specimen Type: BLOOD

Method: BACT ALERT 3D SYSTEM, Conventional Aerobic Culture, VITEK-2 ID and Sensitivity

CULTURE & SENSITIVITY REPORTS

Organism 1 Klebsiella pneumoniae

Antibiotic Name	Interpretation	MIC(ug/ml)	Break Points I	S	R
Amikacin	Resistant	32 mcg/ml	8	<=4	>=16
Amoxicillin/Clavulanic Acid	Resistant	>=32 mcg/ml	16	<=8	>=32
Cefepime	Resistant	>=32 mcg/ml	4-8SDD	<=2	>=16
Cefoperazone/Sulbactam	Resistant	>=64 mcg/ml	32	<=16	>=64
Ceftriaxone	Resistant	>=64 mcg/ml	2	<=1	>=4
Ceftriaxone /Sulbactam EUCAST	Sensitive				
Cefuroxime	Resistant	>=64 mcg/ml	8-16	<=4	>=32
Cefuroxime Axetil	Resistant	>=64 mcg/ml			
Ciprofloxacin	Resistant	>=4 mcg/ml	0.5	<=0.25	>=1
Colistin	Intermediate	2 mcg/ml	<=2		>=4
Ertapenem	Resistant	>=8 mcg/ml	1	<=0.5	>=2
Gentamicin	Resistant	>=16 mcg/ml	4	<=2	>=8
Imipenem	Resistant	>=16 mcg/ml	2	<=1	>=4
Meropenem	Resistant	>=16 mcg/ml	2	<=1	>=4
Piperacillin/Tazobactam	Resistant	>=128 mcg/ml	16SDD	<=8	>=32
Tigecycline	Sensitive	2 mcg/ml	4	<=2	>=8
Trimethoprim/Sulfamethoxazole	Resistant	>=320 mcg/ml		<=40	>=80

Dr. Melody Baruah, MBBS, MD (18704-AMC), Consultant Microbiologist

Dr. Himadri Dutta, MBBS, MD (Microbiology)(18931-AMC), Consultant Microbiologist

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Email : customer@healthcityhospital.com | Website : www.healthcityhospital.com

RIVAARA LABS

Test Report

Patient Name	: Mrs. Gopa Goswami	Registration ID	: 0823600021
Age / Gender	: 56 Years / Female	Sample Coll Dt	: 20-Aug-2023 04:44 PM
Barcode No	:	Sample Reg Dt	: 21-Aug-2023 01:51 PM
Referred By	: Dr. RESHU GUPTA	Reported Date	: 21-Aug-2023 11:29 PM
Client Name	:	Report Status	: Final
		Passport No	:

Human Bocavirus	NOT DETECTED	ND
Drug Resistance		
Methicillin-resistance gene (mecA)	NOT DETECTED	ND
Methicillin-resistance gene (mecC)	NOT DETECTED	ND
NDM	NOT DETECTED	ND
OXA 48	NOT DETECTED	ND
OXA 23	**DETECTED**	ND
KPC	NOT DETECTED	ND
VIM	NOT DETECTED	ND
IMP	NOT DETECTED	ND

Remarks: Acinetobacter baumannii, OXA 23 detected in the present sample.

*** End Of Report ***

Dhrubajyoti Sarma
Lab Head

Page 2 of 2

This Test was performed by Rivaara Labs, Nemcare Super Speciality Hospital, GMC Hospital Road, Bhangagarh, Guwahati, Assam

Registered office: 17th Floor, 17th Floor, Hoechst House, Nariman Point, MUMBAI, Maharashtra 400021, IN

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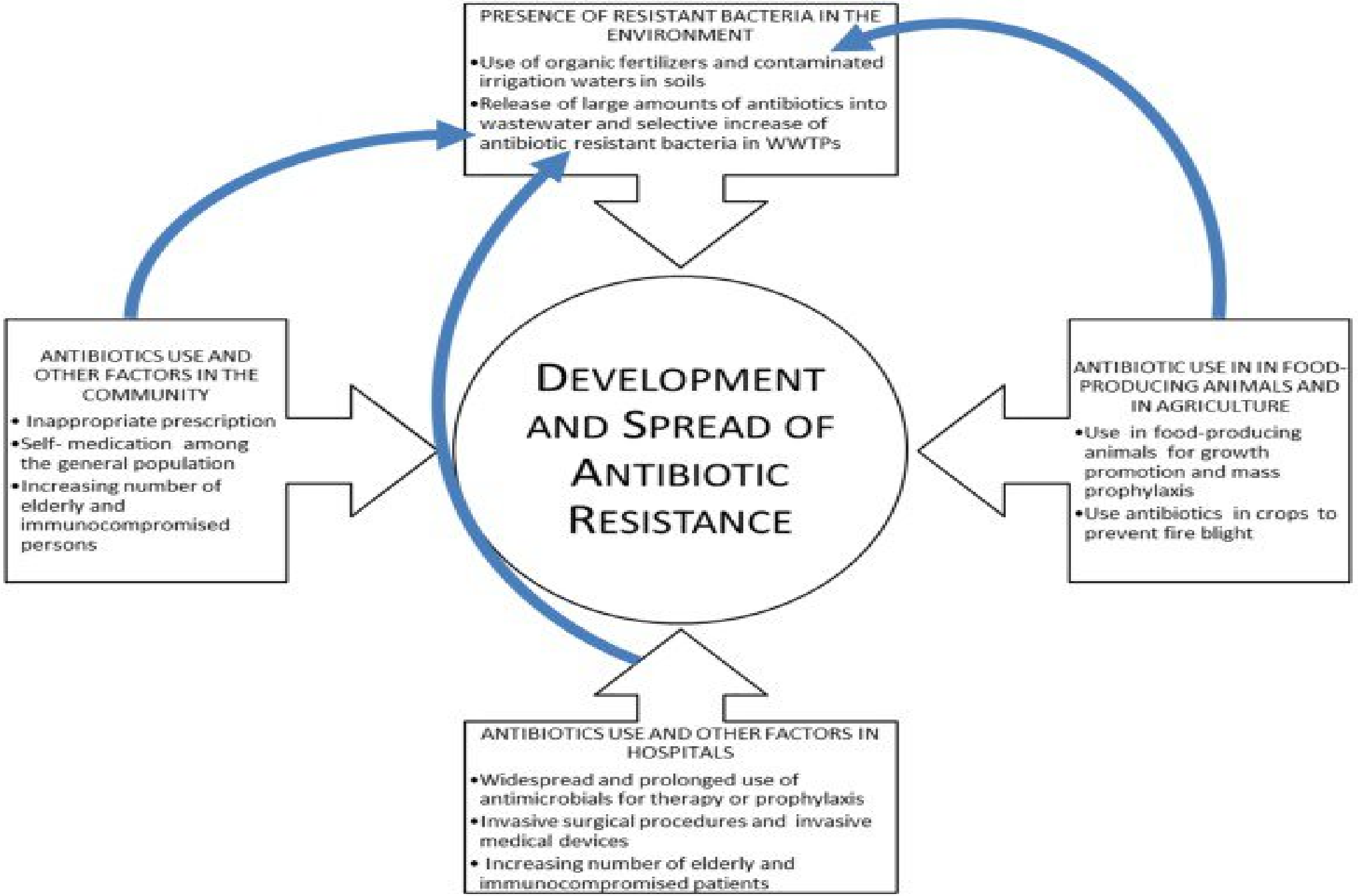
WHAT ARE THE MAJOR CONTRIBUTING FACTORS OF AMR?

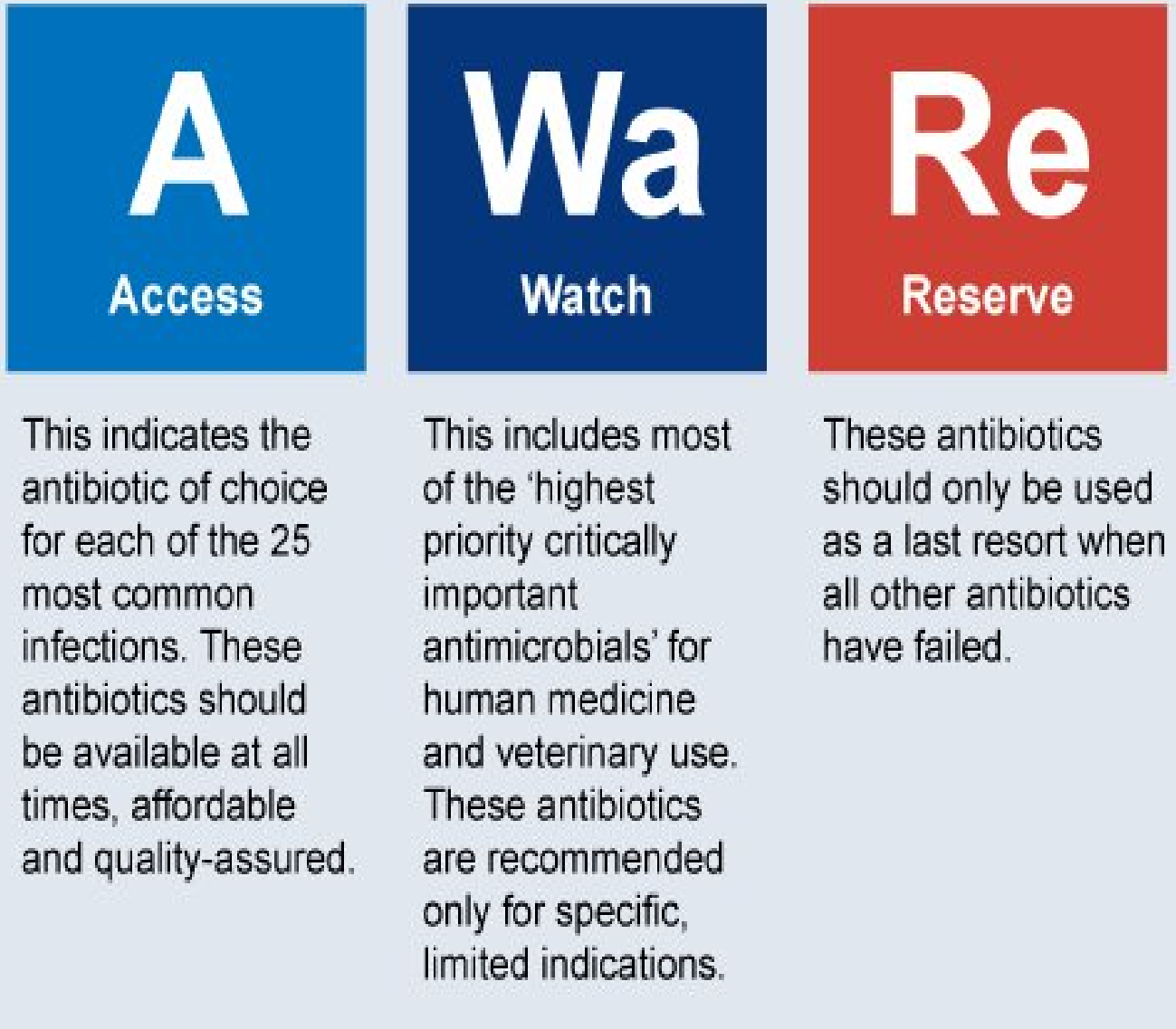

PRESENCE OF RESISTANT BACTERIA IN THE ENVIRONMENT
•Use of organic fertilizers and contaminated irrigation waters in soils
•Release of large amounts of antibiotics into wastewater and selective increase of antibiotic resistant bacteria in WWTPs
ANTIBIOTICS USE AND OTHER FACTORS IN THE COMMUNITY
• Inappropriate prescription
•Self- medication among the general population
•Increasing number of elderly and immunocompromised persons
DEVELOPMENT AND SPREAD OF ANTIBIOTIC RESISTANCE
ANTIBIOTIC USE IN IN FOOD-PRODUCING ANIMALS AND IN AGRICULTURE
•Use in food-producing animals for growth promotion and mass prophylaxis
•Use antibiotics in crops to prevent fire blight
ANTIBIOTICS USE AND OTHER FACTORS IN HOSPITALS
•Widespread and prolonged use of antimicrobials for therapy or prophylaxis
•Invasive surgical procedures and invasive medical devices
• Increasing number of elderly and immunocompromised patients

WHAT ARE THE SOLUTIONS ?

Restricted Antibiotics

The AWaRe Classification of antibiotics was developed in 2017 by the WHO Expert Committee

Antibiotics are classified into three groups - Access, Watch and Reserve



ANTIMICROBIAL STEWARDSHIP

- **ANTIMICROBIAL STEWARDSHIP** is a set of actions and commitments to improve how antibiotics are used and prescribed, with the goal of improving patient safety and reducing adverse events. It involves ensuring that antibiotics are only used when necessary and appropriate.
- **ANTIBIOGRAM-** The hospital antibiogram is a periodic summary of antimicrobial susceptibilities of local bacterial isolates to aid in selecting empiric antibiotic therapy, to monitor resistance trends over time within an institution and compare susceptibility rates across institutions and track resistance trends.
- **ANTIBIOTIC POLICY** -Generally, the hospital antibiotic policy should concur or align with the national antibiotic policy except for a few changes as warranted by the local antimicrobial resistance profiles

Rational antibiotics

	Type 1 (CAI)	Type 2 (HCAI)	Type 3 (NI)
Health Care Contact(last 90days)	No	Yes	Prolonged
Procedures	No	Minimum	Major invasive Procedures
Antibiotic Rx History	No in last 90 days	Yes in last 90 days	Repeat multiple antibiotics.
Patients Characteristics	Young – No co-morbid conditions.	Elderly Few Co-morbid conditions.	**Immunocompromised, or with many co-morbid conditions.**
Causative Pathogen could be	**Susceptible to Common narrow spectrum antibiotics**	**ESBLs**	**ESBLs / Pseudomonas /Acinetobacter MRSA**
Possible Antibiotic recommendations	- **No Need for Broad spectrum antibiotics**	- **Use Non-Pseudomonal broad spectrum antibiotics**	- **Use Anti-pseudomonal Broad spectrum antibiotics**

Ref: Based on stratification criteria suggested by Dr Yehuda Carmelli

Antibiotics for surgical prophylaxis

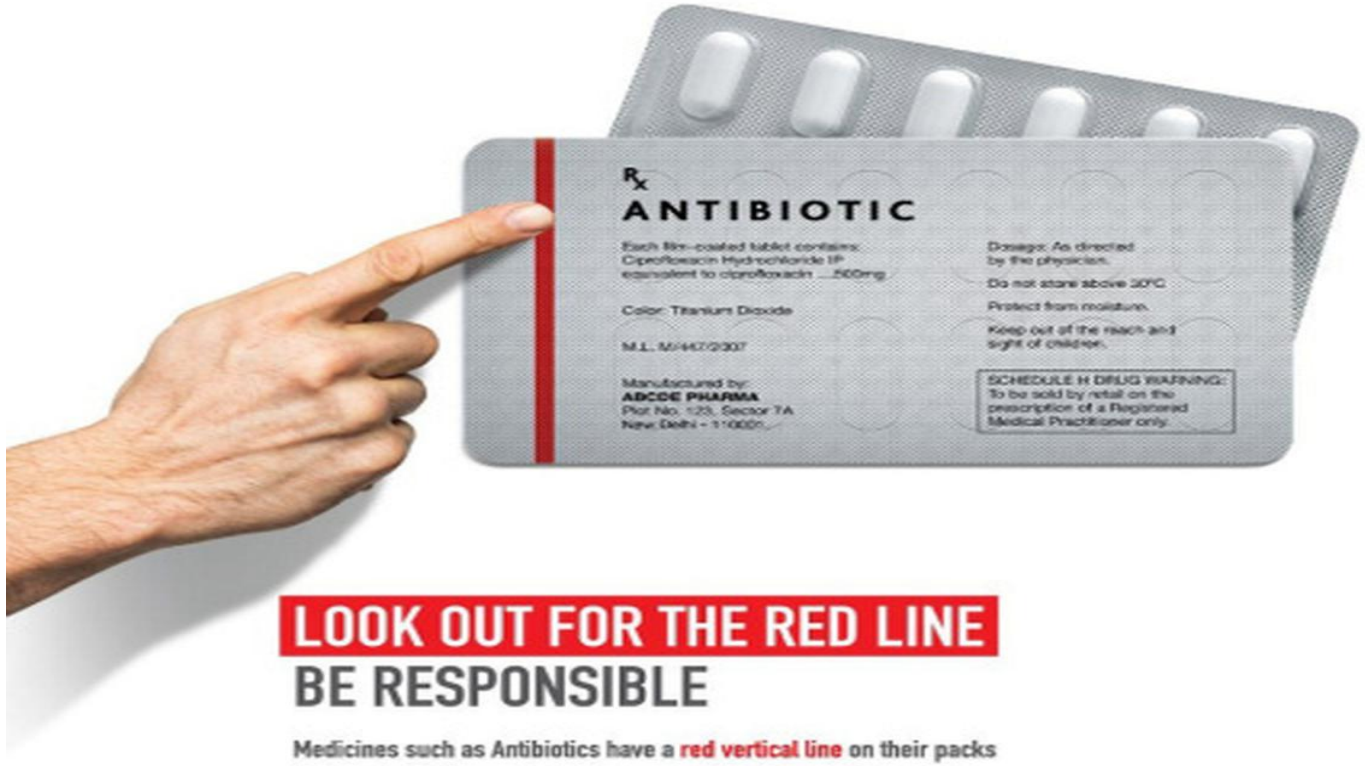
- Antibiotics should be given **1 hour** before proceeding with incision (at induction of anesthesia).
- Second dose may be given … if surgery prolongs **> 4 hours** - readministered every 4 hours (exception - vancomycin, aminoglycosides, and fluroquinolones).
- Prophylactic antibiotic should be **discontinued within 24hours** of the end of surgery.

IDSA guidelines - 2013

Conclusion

- AMR is due to unstainable practices and overlapping ecosystems of animal , environmental and human health.
- Reduce the misuse and overuse of antibiotics in livestock, aquaculture and crops.
- Effective management of waste from food systems, pharmaceutical manufacturing and health care systems .
- Antibiotic stewardship is important for preserving existing antibiotics and improving patient outcomes.
- Vaccination can reduce the use of antimicrobials.
- It needs guidance from policymakers and strong will from all clinicians to achieve control over misuse of antibiotic and reduce development of resistance.

DO YOU KNOW?
MEDICINES WITH A RED LINE ON THE STRIP SHOULD NEVER BE CONSUMED WITHOUT DOCTOR'S PRESCRIPTION



LOOK OUT FOR THE RED LINE
BE RESPONSIBLE

Medicines such as Antibiotics have a **red vertical line** on their packs to indicate that these should be consumed only on doctor's advice. Always complete the full course as prescribed by the doctor.

Ministry of Health
& Family Welfare
Government of India

ANTIBIOTICS: USE WITH CARE

THANK YOU