Emerging Trends in Antimicrobial Resistance and Novel Therapeutic Strategies

Abstract

Antimicrobial resistance (AMR) is an increasing global health concern that threatens to undermine the effectiveness of many commonly used antibiotics. The emergence of novel and more resistant strains of bacteria, as well as the overuse and misuse of antibiotics, have contributed to the rise of AMR. This has led to an urgent need to identify new therapeutic strategies to combat these pathogens. This review aims to provide an overview of the emerging trends in AMR and novel therapeutic strategies. We will discuss the mechanisms of AMR and the latest developments in diagnostics, prevention, and treatment of resistant infections. This includes the use of alternative antimicrobial agents, such as bacteriophages, peptides, and natural compounds, as well as the development of new drugs and vaccines.

We will also explore the potential of new technologies, such as genomics, proteomics, and nanotechnology, in the fight against AMR. These technologies offer new avenues for the discovery and development of novel antimicrobial agents, as well as for understanding the underlying mechanisms of resistance.

Overall, this review highlights the importance of developing new strategies to combat AMR, as well as the need for a global effort to address this growing threat to public health. We hope that this review will serve as a valuable resource for researchers and clinicians working in the field of infectious diseases and antimicrobial resistance.

INTRODUCTION

Antimicrobial chemotherapy has conferred huge benefits on human health. A variety of microorganisms were elucidated to cause infectious diseases in the latter half of the 19th century. Thereafter, antimicrobial chemotherapy made remarkable advances during the 20th century, resulting in the overly optimistic view that infectious diseases would be conquered in the near future. However, in response to the development of antimicrobial agents, microorganisms that have acquired resistance to drugs through a variety of mechanisms have emerged and continue to plague human beings. In Japan, as in other countries, infectious diseases caused by drug resistant bacteria are one of the most important problems in daily clinical practice. In the current situation, where multidrug-resistant bacteria have options for treatment with antimicrobial agents are limited, and the number of brand new drugs placed the market is decreasing. Since drug-resistant bacteria have been selected by the use of antimicrobial drugs, the proper use of currently available antimicrobial drugs, as well as efforts to minimize the transmission and spread of resistant bacteria through appropriate infection control, would be the first step in resolving the issue of resistant organisms. This paper provides an outline of the history of antimicrobial agents, and thereafter describes resistant organisms that emerged in response to antimicrobial agents and discusses practical clues to prevent microorganisms.

EMERGENCE OF DRUG–RESISTANT BACTERIA

An **antimicrobial** is an agent that kills microorganisms or stops their growth .Antimicrobial medicines can be grouped according to the microorganisms they act primarily against. For example, antibiotics are used against bacteria, and antifungals are used against fungi. They can also be classified according to their function. Agents that kill microbes are **microbicide**s, while those that merely inhibit their growth are called bacteriostatic agents. The use of antimicrobial medicines to treat infection is known as antimicrobial chemotherapy, while the use of antimicrobial medicines to prevent infection is known as antimicrobial prophylaxis.

Main classes of antimicrobial agents are disinfectants (non-selective agents, such as bleach), which kill a wide range of microbes on non-living surfaces to prevent the spread of illness, antiseptics (which are applied to living tissue and help reduce infection during surgery), and antibiotics (which destroy microorganisms within the body). The term "antibiotic" originally described only those formulations derived from living micro organisms but is now also applied to synthetic agents, such as sulfonamides or fluoroquinolones[6]. Though the term used to be restricted to antibacterials (and is often used as a synonym for them by medical professionals and in medical literature), its context has broadened to include all antimicrobials. Antibacterial agents can be further subdivided into bactericidal agents, which kill bacteria, and bacteriostatic agents, which slow down or stall bacterial growth. In response, further advancements in antimicrobial technologies have resulted in solutions that can go beyond simply inhibiting microbial growth. Instead, certain types of porous media have been developed to kill microbes on contact.

GENERAL CLASSIFICATION OF ANTIMICROBIAL AGENTS

Antimicrobial Agents can be classified basically into seven (7) categories;
1).Based on mechanism of action
2).Based on therapeutic use/ organisms affected
3).Based on spectrum of activity
4).Based on type of action
5).Anti-mycobacterial agents
6).Based on source
7).Based on Chemical structure

1**)Based on mechanism of action**

Cell Wall Synthesis inhibitors: Most pathogenic bacteria have a cell wall that provides tensile strength and maintains intracellular osmotic pressure. Its synthesis progresses in three steps:
(a) monomers are synthesized in the cytoplasm from amino acid and sugar building blocks; (b) Bactoperol transfers the monomers across the cytoplasmic membrane where they are polymerized into linear peptidoglycan chains; (c) transpeptidase cross-links peptidoglycan chains into a three-dimensional matrix.
A number of drugs inhibit cell wall synthesis. Most important are vancomycin, which targets monomer polymerization; and the β-lactams,e.g., penicillins and cephalosporins, which block polymer cross-linking. β-lactam antibacterial agents also activate autolysins. Autolysins punch holes in bacterial cell wall and disrupt its integrity. Transpeptidase antagonism and autolysis prevent bacterial self-maintenance, i.e., remodeling and repair; and replication. Other drugs that inhibits cell wall synthesis include Cycloserine, Bacitracin, Monobactam etc
Inhibitors of DNA Synthesis or Integrity: Cell wall inhibitors cannot kill all bacteria because some bacteria lack a cell wall. Other bacteria have unique structures that inherently resist the accumulation or action of cell wall inhibitors. However, bacteria, in preparation for cell division, must replicate their double stranded DNA. To facilitate replication, topoisomerase type II, a bacterial DNA gyrase, must first unwind and separate, and then reassemble the original DNA during the process. In the replication process, bacteria must synthesize folate.Its synthesis begins with the formation of dihydropteroic acid from pteridine and para-aminobenzoic acid (PAPA), a reaction catalyzed by dihydropteroate synthase. Dihydropteroic acid and glutamate condense to form dihydrofolate (DHF). Dihydrofolate reductase (DHFR) reduces DHF to tetrahydrofolate (THF). THF is an essential cofactor in the synthesis of DNA, RNA, and protein. Examples of these drugs include fluoroquinolones, Metronidazole, Antimetabolites (Sulfamethoxazole, Trimethoprim) etc
Inhibitors of Transcription or Translation: Bacteria, like mammalian cells, must synthesize proteins for self-maintenance and replication. DNA serves as the "instruction manual;" it provides the information necessary for protein synthesis. The first step in this process is transcription, the synthesis of a single-stranded ribonucleic acid (RNA) from the DNA template catalyzed by RNA polymerase. The function of the newly synthesized RNA is translation.In the process of translation, RNA serves three functions: (1) as messenger RNA (mRNA), it tells ribosomes which proteins to synthesize; (2) as transfer RNA (tRNA), it transports specific amino acids called for by mRNA codons from the cytoplasm to ribosomes; and (3) as ribosomal RNA (rRNA), it ensures that the amino acid carried by the charged tRNA is the one called for by the corresponding mRNA codon. Protein synthesis is initiated when the mRNA joins with the 30S ribosomal subunit and tRNAlinked formyl methionine (fMet). Examples of these drugs includes; (a). Binding with 50s RNA unit-eg.Chloramphenicol,Tetracyclines, Clindamycin, Macrolides. (b). Binding with 30s RNA unit-eg. Tetracyclines, Aminoglycosides, Spectinomycin (c). Inhibiting elongation factor .
Cell Membrane Synthesis Inhibitors: Regardless of the metabolic state of the bacteria, the existence of the cell membrane is essential for its survival. It provides a selective barrier for the stability of bacterial cells and the conduction of energy and matter. In addition, the membrane also contains about a third of the proteins in the cell and is involved in many important physiological processes. Antibacterial peptides (AMP) produced by some hosts and several bioactive molecules acting on the membrane demonstrate their potential as antibacterial targets. But because of concerns that similar compounds could damage mammalian plasma membranes, traditional antibacterial drug screening efforts have not used bacterial cell membranes as targets for antibiotic development. In recent years, with the successful medical application of membrane-active antibiotics such as daptomycin, telavancin, oritavancin, and dalbavancin, antibacterial drugs targeting cell membranes have been shown to establish bacterial specificity. The key mechanism is that bacterial cell membranes are rich in negatively charged phospholipids (phosphatidylglycerol and cardiolipin) and zwitterionic phosphatidylethanolamine, which can be bound by compounds with a positive charge. For example, daptomycin can oligomerize into a micelle-like amphiphilic structure in the presence of

calcium ions, providing a surface with a false positive charge, thereby increasing its affinity for negative ions. In addition, binding to peptidoglycan precursors and bacterial membrane proteins on the membrane also contributes to the specificity of daptomycin and lipoglycopeptides.other examples of drugs on this group includes; Amphoterecin B, Polymyxin, Nystatin, Meconazole etc.

2.Based on therapeutic use/ organisms affected

2a. Antibacterial i. Penicillin, ii. Chloramphenicol, iii. tetracyclines iv. Aminoglycosides
2b. Antifungal i. AmphotericinB, ii. Griseofulviniii. ketoconazole
2c. Antiviral I. Acyclovirii. Idoxuridineiii. Vidarabineiv. Zidovudinev. Ribavirin
2d. Antiprotozoal i. Metronidazoleii. Quinapyramine, iii. Diminazine
2e. Anthelmintics i. Albendazoleii. Levamisoleiii. Niclosamideiv. praziquantel
2f. Ectoparasiticides i. Cypermethrinii. Lindaneiii. Amitraziv. Ethion

3.Based on Spectrum of Activity

Broad spectruma. Tetracyclines b. Chloramphenicol c. Gentamycind. AmpicillinNarrow spectrum
a. penicillin G b. Streptomycin c. Erythromycind. Vencomycin

4.Based on type of action

Bacteriostaticsa. Erythromycin b. Sulfonamide c. Trimethoprim d. Clindamycin e. ChloramphenicolBactericidala. Penicillin G b. Streptomycin c. Vencomycin d. Bacitracin e. Potentiated sulfonamides f. Cephalexin.

5.Antimycobacterial agentsa. Isoniazideb. Paraamino salisyclic acid.

6.Based on source Fungi
a. Penicillin G b. Cephalexin c. GriseofulvinActinomycetes
a. Erythromycin b. Chloramphenicol c. Streptomycin d. Tetracyclines
Bacteriaa. PolymyxinB b. Colistin, c. BacitracinSynthetica. Sulfonamide b. Trimethoprim c. Quinolones d. Nitrofuranse. Nitroimidazole

7.Based on Chemical structure

a. Sulfonamide group–trimethoprim,ormethoprim, baquiloprim
b. Diaminopyramidine group–Sulphadimidine,sulphadiazine,sulphanilamidec . Quinolones–nalidixic acid, enrofloxin, ciprofloxind. Beta lactam antibiotics–Penicillin G,Ampicillin, cephalexin, Cloxacillin
e. Aminoglycosides –Streptomycin gentamycinf. Tetracycline–Tetracycline,Doxycyclines,oxytetracyclines
g. Macrolides–Erthromycin, azithromycinh. Polypeptide antibiotics–Polymyxin B, Colistin,Bacitracini. Nitrofuran derivatives–Nitrofurantoin,furazolidonej. Nitroimidazoles–Metronidazole, tinidazolek. Polyene antibiotics–AmphotericinB,Nystatinl. Imidazole derivatives–Ketoconazole fluconazole, clotrimazole.

ANTIMICROBIAL RESISTANCE

According to World Health Organisation (WHO) in 2021, antimicrobial resistance (AMR) occurs when bacteria, fungi, viruses and parasites change over time and no longer respond to medications or medicines making infections difficult to treat and increasing the risk of disease spread, severe illness and death. As a result, the medicines become ineffective and infections persist in the body, increasing the risk of spread to others. Antimicrobial resistance (AMR) is said to occur when microbes evolve mechanisms that protect them from the effects of antimicrobial drugs that are used for treating the infection they cause. Every time an antimicrobial agent or medicine is used, it diminishes the effectiveness for all users, because its usage increases the possibility for the microorganism to become resistant. A person(s) cannot become resistant to antimicrobials. Resistance is a property of the microbe, not a person or other organism infected by a microbe. Resistance is usually acquired by the microbes. Antimicrobial resistance threatens the effective prevention and treatment of increasing range of infections, including blood poisoning, pneumonia, diarrhoea, gonorrhoea, tuberculosis, HIV/AIDS and malaria.

All classes of microbes can evolve resistance. Fungi usual evolve anti fugal resistance. Viruses evolve antiviral resistance. Protozoa evolve antiprotozoal resistance, and bacteria evolve antibiotic resistance. Bacteria that are considered extensively drug resistant (XDR) or totally drug-resistant (TDR) are sometimes referred to as a superbug. Although antimicrobial resistance could also be considered as a naturally-occurring process, it is often the result of improper usage of antimicrobial drugs and management of infections caused by microorganisms.

Among all the subsets of antimicrobial resistance, antibiotics resistance,which applies specifically to bacteria that become resistant to antibiotics, is a major and an urgent problem because antibiotics are a cornerstone of modern medicine and most medicinal procedures in both human and animal health rely on.

The treatment of bacterial infections is increasingly complicated by the ability of bacteria to develop resistance to antimicrobial agents. Antimicrobial agents used for the treatment of bacterial infections are often categorized according to their principal mechanism of action. There are six major modes of action:
1. Interference with cell wall synthesis 2. Inhibition of protein synthesis
3. Interference with nucleic acid synthesis 4. Inhibition of a metabolic pathway
5. Inhibition of membrane function 6. Inhibition of ATP Synthase.

WHY ANTIMICROBIAL RESISTANCE IS A GLOBAL CONCERN

Antimicrobial resistance is one of the top ten global public health threats facing humanity. The emergence and spread of antimicrobial-resistant organisms have a direct consequence on the ability to treat common infections.An example could be identified to the global spread of superbugsthat are multi and pan-resistant bacteria, this occurred during the first wave of COVID-19 pandemic which drove a rise in superbug infectionhence wiping out the progress made against the deadly pathogens before the pandemic . This caused infections that cannot be treated by existing antibiotics.

While we need new antibiotics, it is important to change the way antibiotics are being used. If our behavior towards antibiotics do not change, then new antibiotics will also eventually become ineffective.

Antibiotic resistance leads to increased medical costs, longer hospital stays and increased rate of death. The cost of AMR therefore to health systems and national economies is profound.

In 2014, World Health Organisation (WHO) report released stated, "this serious threat is no longer a prediction for the future, it is happening right now in every region of the world and has the potential to affect anyone, of any age, in any country. Antibiotic resistance---when bacteria change so antibiotics no longer work in people who need them to treat infections---is now a major threat to public health."

In 2019, global deathswere attributable to antimicrobial resistance (AMR) numbered 4.95 million including 1.27 million deaths associated with bacterial antimicrobial resistance. That same year, antimicrobial resistance may have contributed to 5 million deaths and one in five people who died due to antimicrobial resistance were children under five years of age.

In 2018, World Health Organisation considered antibiotic resistance to be one of the biggest threats to global health, food security and development. Deaths attributable to AMR vary by area:

Table 1: Abducted from "Global burden of bacterial antimicrobial resistance in 2019: a systematic analysis"

Place	**Deaths per 100,000 attributable to AMR**
North Africa and Middle East	11.2
Southeast and East Asia, and Oceania	11.7
Latin America and Caribbean	14.4
Central and Eastern Europe and Central Asia	17.6
South Asia	21.5
Sub-Saharan Africa	23.7

From patient assessment, morbidity and mortality are important consequences of antimicrobial resistance affecting patients. Compared to non-resistant forms, resistant bacteria will double the chances of developing a serious health issue and triple the chances of death, hence these negative outcomes will be more pronounced with elevation of the severity of the resistant infections and the susceptibility of the host.

Table 2 shows the comparison between mortality rates due to antimicrobial resistance and major causes of mortality worldwide by 2050.

Table2: Adapted from Antimicrobial resistance: tackling a crisis for the health and wealth of nations, 2019.

Cancer	8.2 Million

Cholera	100,000–120,000
Diabetes	1.5 Million
Diarrheal-disease	1.4 Million
Measles	130,000
Road Traffic Accidents	1.2 Million
Tetanus	60,000
Antimicrobial Resistance	10 Million

ORIGINS OF ANTIMICROBIAL RESISTANCE.

In addition to innate and acquired, there are other terms used to describe the characteristics of antibiotic resistance and a distinction is often made between resistances of phenotypic and genotypic origin as seen in the Table above.

The phenotypic change is, by definition, one that does not arise from an alteration in the genes the organism possess; rather, it is one in which the cell in a population, such as pathogenic bacteria an infection site, modify their physical structure or biochemical properties in response to an environmental stress, for example exposure to antibiotic. This is sometimes referred to as 'adaptive resistance', and it is characterized by a more-or-less simultaneous change in most, or all, of the cells, which is usually reversed when the environmental stress is removed, so it is not a permanently inherited trait. Some examples of this adaptive, phenotypic resistance are quite specific to particular organisms and antibiotics, for instance E. coli exhibits greater resistance to aminoglycosides under anaerobic conditions. However, the more important examples are generic, so, for example, there is considerable evidence that bacteria in general tend to exhibit greater resistance to antibiotics and biocides when they are growing as biofilms than when growing as freely suspended (planktonic) cells. There are likely to be several factors contributing to this increased resistance, but the slower growth rate of biofilm cells compared to planktonic ones is generally accepted as crucial. A second major example of phenotypic resistance is the induced synthesis of B-lactamases in response to the presence of a B-lactam antibiotic. Bacteria responding in this way possess the necessary genes all the time, so it is not a genetic change that they are exhibiting; it is merely protective mechanism that they can switch on when required and switch off to avoid wasting energy when the B-lactamase is no longer needed.

1. Resistance arising by mutation

The frequency with which mutants arise in nature is influenced by the size of the bacterial population and its reproduction rate. Even when growing in the body, bacteria can achieve concentrations in excess of 10" colony-forming units per mL of body fluid and this, combined with doubling times of less than one hour and the fact that bacteria are usually haploid (so any mutation that occurs will be expressed rather than masked by a dominant homologous chromosome), means that mutation is a realistic and clinically important source of antibiotic resistance. One of the earliest examples was streptomycin resistance in Mycobacterium tuberculosis, which was reported shortly after the introduction of streptomycin in the late 1940s. Tuberculosis is a relatively difficult infection to eradicate so antibiotic treatment is required for several months, and it is this long period of exposure that gives the organism a protracted opportunity to mutate. The increased risk of resistance arising is similarly seen in other infections with a long period of antibiotic therapy, for example chronic Pseudomonas aeruginosa lung infections in cystic fibrosis patients.

Resistance by enterococci to both vancomycin and aminoglycosides are more recent consequences of mutation. Bacterial species differ in their potential to become resistant by mutation and some antibiotics are more vulnerable to resistance development by this means than others - fusidic acid and rifampicin are two which seem more susceptible than most. A mutation rate is defined as the probability of a mutant arising during a cell division so, for example, if there were 2 x 10' bacteria at the infection site and just one mutant arose after they had all divided, the mutation rate would be 1+2x 10', which equals 5 x 10. Such values are sometimes quoted as if they were an intrinsic property of a drug/organism combination, whereas, in fact, they are influenced both by the concentration of antibiotic to which the bacteria are exposed and by the environmental conditions. Nevertheless, it is generally

accepted that mutation rates to antibiotic resistance are typically 10 to 10 but values as high as 10 and as low as 10 0 may occur. With bacterial concentrations at the infection site as high as 10* or 10° CFU/mL it is clear that tens or hundreds of mutants could arise per cell division, so resistance is a real threat. However, if two different antibiotics are used simultaneously, the chance of a single cell becoming resistant to both at the same time is the product of their mutation rates, not the sum. In other words, if the mutation rate for each antibiotic was 10^-7, the chance of a double mutant arising is 10-4; this is the logic behind the use of multiple antibiotics being used to treat infections requiring a long period of therapy, such as tuberculosis, leprosy and HIV/AIDS

2. Resistance arising by receipt of new genetic information

Essentially, there are three ways in which new genes maybe acquired by a bacterial cell.

Transformation :This describes the situation where a cell dies, disintegrates and releases its genetic information (DNA), which is picked up by another healthy cell that then transports it through its cell membrane and incorporates it into its own chromosome; it is often described as the transfer of 'naked' DNA. The process occurs naturally in only a few bacterial genera, for example Streptococus, Neisseria, Helicobacter and Acinetobacter, and even in these it operates only environmental or nutritional condition dern Organisms that do it naturally are described as competent, and for these species it is a realistic mechanism of acquiring resistance. It is less common and, consequently, less important than other mechanisms, but is very effective in some bacteria-antibiotic combinations such as benzyl penicillin or amoxicillin (and ampicillin) resistance in Streptocous pneumoniae and gonococci.

Transduction:Here, a bacterial cell is infected by a bacteriophage which does not immediately kill it but becomes dormant inside the bacterial host (referred to as lysogeny) and its nucleic acid becomes incorporated into that of the host. The lysogenic state does not last indefinitely and may cease when the cell is exposed to an appropriate stimulus (for example chemicals or sub lethal ultraviolet radiation); this causes the phage to be replicated, leading to death and lysis of the bacterial cell. The new phage particles are released and are free to infect new hosts, but they may carry with them small sections of bacterial DNA including antibiotic resistance genes from the original cell, and these may ultimately become incorporated into the chromosome of the new host. The bacteriophage acts, therefore, as a vector for the transmission of genetic information. Transduction is species-specific so it is not a mechanism whereby resistance can be transmitted between dissimilar bacteria, and probably the most important example is that of B-lactamase genes transferred between strains of Staphylococus aureus. It is worth noting here that transduction is important in other respects too: it is, for example, the means by which virulence factors, such as genes for toxin production, may be transferred from one cell to another.

Conjugation :Conjugation is the most important mechanism of horizontal gene transfer. Plasmids can be regarded as mini-chromosomes (typically about 19% of the size of the main bacterial chromosome) which contain genes that are not essential for normal growth and replication of the cell but which may confer an advantage to it under certain environmental conditions. The ability to produce toxins,fimbriae (to facilitate attachment of the cell to surfaces), and antibiotic resistance are just three of many characteristics determined by plasmid-encoded genes. Plasmids are replicated independently of the main chromosome and so a cell may contain many copies. Plasmids can be passed from one cell to another by a process of conjugation in which the donor and recipient cells are temporarily attached to each other by means of a sex(conjugation or F - for fertility) pilus.The sex pilus possessed by the donor cell acts like a lasso and locates the recipient then retracts to draw the two cells sufficiently close to cach other to permit membrane fusion. The plasmid(s) inside the donor cell are replicated and a copy is passed to the recipient cell. In addition to the genes conferring antibiotic resistance, plasmids usually possess the genetic information to enable the cell containing them to make the sex pilus itself, in which case they are termed self-transmissible plasmids. Non-self- transmissible plasmids have to rely on the formation of a sex pilus by other, self-transmissible, plasmids present in the same bacterial cel.Two important features of horizontal gene transfer by conuion are that that distinguish it from transformation and transduction at the d donor cell does not die in the process and there is a much lower degree of species specificity. This means that conjugation can occur not merely between the same strains of a species or between different species of a genus, but between genera, so antibiotic resistance genes can be transferred between, say, the various gut bacteria like E. coli and species of Salmonella, Shigella, Proteus and Klebsiella with relative case. A consequence of this is that even bacteria that are regarded as nonpathogenic may represent a problem if they are harbouring antibiotic resistance plasmids. This is because resistance can e transmitted to pathogens following mating between the bacteria in the body (particularly in the colon where bacterial concentrations in excess of 10° CFU/mL can occur, so cells are close together and collisions are relatively common).A further characteristic of plasmid-transmissible resistance is that the plasmids often carry genes conferring resistance to two or more dissimilar antibiotics at the same time. Such a plasmid is only of benefit to the bacterial cell when it is being exposed to one of the antibiotics: in an antibiotic-free environment the plasmid may even be a disadvantage to the cell because it has to expend energy making something that is of no value. Consequently it is often found that the plasmids may be spontancously lost if the relevant antibiotic is not used -

which is the logic behind the antibiotic cycling strategies that are part of stewardship programmes. If genes for, say, three different antibiotics are contained on the plasmid,only one of the three needs to be in regular use in the h hospital ward for the plasmid to be retained and the bacterium would still exhibit resistance to the other two.

Antibiotic resistance genes may also be transferred between plasmids and chromosomes within cells by means of mobile gene sequences called transposons. These are sometimes described as 'jumping genes' to explain their potential to move from one location within the cell's DNA to another. Like plasmids, they can also promote the transfer of genes between bacteria by conjugation ,but they difer from plasmids in that the genes required to initiate the conjugation process are located on the chromosome of the cell.

The mechanisms of antibiotic resistance at cellular level

Enzyme inactivation and modification, Modification of the antibiotics target site

Overproduction of the target ,Replacement of the target site

Efflux and reduced permeability

1.A ENZYME INACTIVATION.

One of the first mechanisms of resistance to be discovered was resistance to penicillin (a β-lactam antibiotic). Penicillin resistant strains of Staphylococcus aureus were found to have acquired an enzyme known as a β-lactamase (originally known as a penicillinase).

β-lactamase enzymes target a part of β-lactam antibiotics known as the β-lactam ring, this is found in all β-lactam antibiotics. The β-lactamase enzyme breaks this ring open, preventing the antibiotic from binding to their target. β-lactamases are a family of enzymes (there are thousands of different versions) found in many bacterial pathogens. They have different activities, meaning some will work against specific members of the β-lactam family, while others will not. Certain members of the β-lactamase family, known as Carbapenemases, are the most problematic because they break down all members of the β-lactam family of antibiotics, including carbapenems, severely limiting treatment options.

1.B ENZYME MODIFICATION.

Two other mechanisms of resistance are mediated by bacteria acquiring enzymes. Firstly, bacteria can acquire enzymes that chemically modify the target of the antibiotic in the bacteria by adding additional chemical groups. An example of this is the erm (erythromycin ribosomal methylation) gene that provides resistance against macrolide antibiotics like erythromycin. This enzyme methylates (adds a methyl group: CH_3) to part of the ribosome, which is the target of erythromycin. This means that erythromycin can no longer bind to the target, meaning the bacteria can continue to thrive in the presence of the antibiotic.

The second type of enzyme acts by chemically modifying the antibiotic itself, which prevents the antibiotic binding to its target site. An example of this is aminoglycoside-modifying enzymes such as N-acetyltransferases, which add an additional acetyl group (CH_3CO) to aminoglycoside antibiotics such as kanamycin. , this stops it binding to the ribosome, meaning the bacteria becomes resistant. There are many different types of these enzymes which have different activities against antibiotics from many different classes of antibiotics including aminoglycosides, tetracyclines, phenicols and lincosamides.

2. MODIFICATION OF THE ANTIBIOTIC TARGET SITE.

A common mechanism that bacteria use to become resistant to antibiotics is by modifying the target of the antibiotic. As bacteria grow and replicate they copy their genetic material (the genome). When they do this, occasionally mistakes in the DNA sequences get included (e.g. an A gets replaced with a C). These mistakes only happen very rarely, but the very large population sizes (billions and trillions) of bacteria, means that this happens frequently enough that occasionally these mutations are present in bacterial populations in the presence of antibiotics. If one of these mutations happens to be at a location of a gene that encodes for a protein that is the target of an antibiotic, then sometimes these mutations mean that the antibiotic can no longer bind to the target. This means that the bacteria with the mutation will have a growth advantage and will survive the antibiotic while the rest of the population will die.

This is a common mechanism for resistance to penicillin in Streptococcus pneumoniae, where the acquisition of mutations in the penicillin binding proteins (PBP) which are the target of penicillin. The presence of the mutations in the PBPs mean that penicillin can no longer bind and kill the bacteria.

Similarly resistance in many bacterial pathogens to fluoroquinolone antibiotics such as ciprofloxacin is mediated by mutations in the DNA gyrase and DNA topoisomerase IV genes, which are the target of ciprofloxacin.

3. REPLACEMENT OF THE TARGET SITE.

While bacteria like Streptococcus pneumoniae mutate the targets of the antibiotics, another similar mechanism of resistance is to gain an additional copy of the gene that encodes a protein that still retains activity (e.g. the antibiotic can't bind to it) in the presence of the antibiotic. This is how the pathogen Staphylococcus aureus becomes resistant to most β-lactam antibiotics such as penicillin. Methicillin-resistant Staphylococcus aureus (MRSA), which is the

name given to S. aureus that is resistant to β-lactam antibiotics, becomes resistant by gaining an extra copy of penicillin binding protein 2, which is the target of β-lactam antibiotics. This additional version known as penicillin binding protein 2a (PBP2a) can still function in the presence of β-lactam antibiotics.

4. OVERPRODUCTION OF THE TARGET.

Bacteria can also overproduce the target of the antibiotics, meaning there is an excess of the protein target of the antibiotics compared to the antibiotic itself. this means that there is enough of the target protein for it to continue its role in the cell in presence of antibiotics; this is a mechanism of resistance to trimethoprim in escherichia coli and haemophilus influenzae. the overexpression is sometimes found in combination with mutations that lower the ability of the antibiotic to bind to its target. (note: trimethoprim is typically used with sulfamethoxazole, a combination known as co-trimoxazole or sxt).

The most often used class of antibiotics in clinical practicetoday is the versatile betalactam antibiotics,which was first employed in medicine approximately 60 years ago. This class of antibiotics consists of a betalactam ring which is a cyclic amide wherein the nitrogen atom on the amide ring is attached to the beta carbon atom relative to the carbonyl in the beta lactam structure. This group of antibiotics includes; penicillin, cephalosporins; carabapenems and monobactam.

Beta-lactam antibiotics are known to have bacteriocidal activity against gram positive, gram negative bacteria and some anaerobic organisms wherein they bring about this action via inhibition of the enzyme transpeptiase or peniciilin binding proteins[PBP_S] by covalently binding to the active site of the enzyme, at the late stage of of peptidoglycan synthesis.

Resistance to betalaam agents is common being the widely used antimicrobal agent, and its resistance is caused by one or more mechanism listed below; wherein the resistant gene expressed in the bacteria

Produces proteins that modifys the PBP_S.

Produces proteins that reduces the uptake of the beta lactam antibiotics into the cell [Efflux mechanism]

Produces enzymes that inactivate the betalactam antibiotics[Betalacatamases].

Prevention of drug entry

MECHANISM OF RESISTANCE VIA EFFLUX PUMP

Using a special transmembrane spanning active transporter protein known as the efflux pump, mostly gram negative bacteria pumps out intracellular betalactam antimicrobial agent[penicillins, cephalosporins, carbapenem [mostly the imipenem example] from their cellular interior to the extern4al environment. This mechanism of resistance helps to reduce the plasma concentration of the betalactam agent in the cells of the bacteria, rendering the agents ineffective as its bactericidal activity is not expressed.

MECHANISM OF RESISTANCE VIA MODIFICATION OF PBP_S

PBPS are important proteins involved in the construction of peptidogylcan a major component of bacterial cell wall, this enzyme PBPS catalyzes the transgylcosylation and cross linking between glycan chains.

Modification of PBPS a resistance mechanism of the betalactam is used almost exclusively by gram positive bacteria, and this occurs via the alteration in the structure or number of PBPS wherein this alteration [either by increasing or decreasing the PBPS from the normal drug binding] tends to impact on the amount of the drug that binds to the target site or totally inhibit the drug binding to the site, when this occurs the drug administerd those not exhibits its pharmacological action as it ose not bind to the active site or the amount that binds is not enough to ellict a therapeutic effect.

MECHANISM OF RESISTANCE VIA ACTIVATION OF THE ENZYME BETA LACTAMASES

In this class, with the exception of the carbapenems and monobactams, which are comparatively resistant to beta lactamases, beta lactamase is a broad class of enzymes produced by bacteria that helps in the inactivation of the betalactam ring [by opening of the ring] rendering them ineffective to carry out their bactericidal effect and thus confering resistance to betalactam antibiotics. Beta lactamases may be chromosomal or plasmid borne, inducible or constructive and are classified into class a-d based on the peptide sequence present in their structure,where class a,c and d are found to posses a serine ring at the active site and d having four zinc atoms at their active site and are called mettallo-beta-lactamases. class of a beta lactamase are found to be highly active against benzylpenicillin; class b enzyme active against

penicillin and cephalosporins. class c enzyme are usually inducible, but mutation can lead to overexpression . class d enzyme is highly active against oxacillin a sub type of penicillin.

MECHANISM OF RESISTANCE VIA PREVENTING DRUG ENTRY

modification in the frequency, size, and selectivity of the porin channels, which are located on the surface of the bacteria cell wall, hinders beta lactam drugs from entering the bacteria cell to carry out its pharmacological action. thus enabling the bacteria to become resistant to the beta lactam drugs such as [cefepime, cefpirome [of the cephalosoprin class] and imipenem [of the carbapenem class].

TABLE 3; Table showing various resistance mechanism and the class of beta lactam affected.

MECHANISM OF RESISTANCE	CLASS OF BETALACTAM AFFECTED
Efflux pump	Carbapenem, cephalosoprin, penicillin
Prevention of drug entry	Cephalosoprin, carbapenem
Modification of PBP	Penicillin and cephalosporin
Activation of beta lactamase	Penicillin and cephalosporin

RESISTANCE TO GLYCOPEPTIDE

Glycopeptides are a class of antimicrobial used in the treatment of bacterial infections, particularly enteroccal infections and those brought on by gram positive bacteria that are resistant to other antimicrobial agents, antimicrobal called glycopeptides function by preventing bacteria from synthesizing their cell walls, by inhibiting peptidoglycan synthesis The D-alanyl-D-alanine terminus, a component of the cell wall, serves as its target, preventing the invasive bacteria from replicating and growing. Adittionally, glyopeptides have bactericidal properties, which means they can poison bacterial and prevent them from multiplying. This group of antimicrobial includes;

First generation glycopeptides which are; Vancomycin, Teicoplanin and Ramoplanin.

Second generation semi synthetic glycopeptide which are; Oritavancin, Dalbavancin, and Televancin.

Of the examples of the glycopeptide listed above, vancomycin and teicoplanin are the glycopeptides that is of clinical importance, they are not active against gram negative organism because of the presence of an outer membrane. Vancomycin use, increase dramatically in response to the increasing incidence of methicillin resistance Staphylococcus aureus [MRSA] and resistance was first reported in Enterococci in 1988. Vancomycin now account for about 20 percent of all enterococcal infections. Clinically five types of resistance is known; VAN A-E have been reported of which phenotypic VAN A is the most common and confers high level resistance to vancomycin and teicoplanin. VAN-A resistance mediated by seven-gene cluster on the transposable genetic element.

RESISTANCE TO VANCOMYCIN

Vancomycin forms an intricate network of hydrogen bonds with the d-Ala-d-Ala region of Lipid II, interfering with the peptidoglycan layer maturation process. Resistance to vancomycin involves degradation of this natural precursor and its replacement with d-Ala-d-lac or d-Ala-d-Ser alternatives to which vancomycin has low affinity.

Resistance to vancomycin occurs via a sensor histidine kinase [VanS] and a response regulator [VanR]. VanH encodes a D-lactate dehydrogenase\ alpha-keto acid reductase and generates D-lactate, which is the substrate for VanA, a D-Ala-D-Lac ligase. The result is cell wall precusors terminating in D-Ala-D-Lac to which vacomycin binds with very low affinty, thus leading to reduced concentration of vancomycin in the cell of the bacteria, enabling the bacteria to confer resistance to vancomycin. This change in affinity is mediated by one hydrogen bond lose. The bond formed between vancomycin and the D-Ala-D-Ala is stabilized by five hydrogen bonds, whereas only four hydrogen bonds is formed between vancomycin and d - Ala - d - Lac and the complex is unstable.

RESISTANCE TO AMINOGLYCOSIDE ANTIBIOTICS

Resistance to Aminoglycosides can be seen in some micro organisms such as *Acinetobacter baumannii* which can cause severe health care-associated infections (HAIs) of the skin and soft tissue, wound infections, urinary tract infections, pneumonia and secondary meningitis. The highest mortality rates, however, are seen in ventilator-associated pneumonia and bloodstream infections especially in intensive care units.

Acinetobacter may develop antibiotic resistance very rapidly. A significant element of *Acinetobacter baumannii* empowering its endurance and spread inside the health care system, is its capacity to upregulate which is the ability to increase the amount of receptors inherently as well as to gain outside components of antimicrobial resistance. They also had the ability to acquire a wide variety of antibiotic resistance genes and rapid development of multidrug-resistant (MDR), extensively drug-resistant (XDR) and even pan drug-resistant (PDR) strains. MDR *Acinetobacter baumannii* strains are resistant to beta-lactams, aminoglycosides, carbapenems and fluoroquinolones.Decreased membrane permeability due to loss of porins, acquisition of extended-spectrum β -lactamase, and multidrug efflux systems are mechanisms claimed for *Acinetobacter baumannii* multidrug resistance.

The bactericidal activity of aminoglycosides depends on their concentration rather than on the exposure duration to inhibitory concentrations of them.

Development of resistance to newer semisynthetic aminoglycosides such as tobramycin, isepamicin, amikacin and sisomicin are being described in many countries worldwide. The resistance mechanisms of A. baumannii to aminoglycoside agents includes aminoglycoside-modifying enzymes (AME) production, which might be classified into aminoglycoside phosphotransferases (APH),aminoglycoside acetyltransferases (AAC),besides aminoglycoside nucleotidyltransferases (ANT). The genes of those enzymes are carried on plasmids and transposons and are transferred easily among *the Acinetobacter baumannii* population.

The main mechanism of aminoglycoside resistance is enzymatic alteration of amino-or hydroxyl-groups of aminoglycosides. Aminoglycoside enzymatic modification results in decreased binding to the ribosome of the aminoglycoside molecule. Previous studies suggested several mechanisms of aminoglycoside resistance in Acinetobacter spp.Enzymatic inactivation by AAC, ANT, and APH is the most prevalent resistance mechanism.

Although aminoglycosides present nephrotoxicity risks and other side effects, they are considered to be important antimicrobial agents and are used to treat HAIs. The high rates of aminoglycoside resistance could cause a serious issue for combination therapy of aminoglycoside with broad-spectrum β-lactams including cephalosporins and carbapenems against A. baumannii infections

Other microorganism that shows Aminoglycoside resistance are the *Campylobacter jejuni* and *Campylobacter coli* which are the main pathogens that cause sporadic gastroenteritist(4).Among the known mechanisms of acquired aminoglycoside resistance, the enzymatic modification is the most common mechanism for the inactivation of aminoglycosides in many bacterial species, including Campylobacter spp.The aminoglycoside-modifying enzymes are divided into three main classes based on the reactions they catalyze as: aminoglycoside acetyltransferases (AAC), aminoglycoside nucleotidyltransferases, and aminoglycoside phosphotransferases (APH).(5).

In summary, the mechanismof resistance can be due to;

Type of microorganism such as the anaerobes which are inherently resistant to aminoglycosides. Aminoglycosides require an active transport system (oxygen dependent) for the uptake of drugs inside bacterial cell. This type of oxygen dependent transport system is absent in anaerobes.

Mutation in the gene responsible for deletion or alteration of the receptor protein can also leads to development of resistance towards aminoglycosides.

Alteration of cell surface that interfere with penetration or uptake of drug in bacteria can also leads to resistance.

Production of enzyme such as aminoglycoside acetyltransferase, aminoglycoside phosphoryltransferase, aminoglycoside adenyltransferase etc by resistant bacteria that inactivates the aminoglycoside either by phosphorylation or adenylation or acetylation. This can also cause resistance to aminoglycosides.

RESISTANCE TO TETRACYCLINES

Tetracyclines exhibit anti microbial activity against a wide range of microorganisms which includes gram-positive and gram-negative bacteria, chlamydiae, mycoplasmas, rickettsiae, and protozoan parasites. They are inexpensive antibiotics, which have been used extensively in the prophlylaxis and therapy of human and animal infections and also at subtherapeutic levels in animal feed as growth promoters. Tetracycline resistance is now common in an increasing number of pathogenic, opportunistic, and commensal bacteria. The presence of tetracycline-resistant pathogens limits the use of these agents in treatment of disease. Tetracycline resistance is often due to the acquisition of new genes, which code for energy-dependent efflux of tetracyclines or for a protein that protects bacterial ribosomes from the action of tetracyclines. A limited number of bacteria acquire resistance by mutations, this mutations alter the permeability of the outer membrane porins and sometimes the lipopolysaccharides in the outer membrane, it can also change the regulation of innate efflux systems, or alter the 16S rRNA.

The mechanism of resistanceof these microorganisms can be summarized as;

(a) blocking tetracyclines from binding to the ribosome
(b) binding to the ribosome and distorting the structure to still allow t-RNA binding while tetracycline is bound
(c) binding to the ribosome and dislodging tetracycline.

MECHANISMS OF RESISTANCE TO MACROLIDES AND LINCOSAMIDES

Resistance to macrolides and lincosamides is increasingly reported in clinical isolates of gram-positive bacteria. The multiplicity of mechanisms of resistance, which include ribosomal modification, efflux of the antibiotic, and drug inactivation, results in a variety of phenotypes of resistance. There is controversy concerning the clinical relevance of in vitro macrolide resistance. Recent data, however, have shown that eradication of bacteria correlates with clinical outcome of acute otitis media in children and that macrolide therapy results in delayed eradication of macrolide-resistant pneumococci. These results support the need for in vitro detection of macrolide resistance and correct interpretation of susceptibility tests to guide therapy.

Macrolide and lincosamide antibiotics are chemically distinct but share a similar mode of action. They have a spectrum of activity limited to gram-positive cocci (mainly staphylococci and streptococci) and bacilli, to gram-negative cocci, and intracellular bacteria (Chlamydia and Rickettsia species). Gram-negative bacilli are generally resistant, with some important exceptions (i.e., Bordetella pertussis, Campylobacter, Chlamydia, Helicobacter, and Legionella species).

Bacteria resist macrolide and lincosamide antibiotics in 3 ways:

1. Through target-site modification by methylation or mutation that prevents the binding of the antibiotic to its ribosomal target.
2.Efflux of the antibiotic
3. By drug inactivation.

These mechanisms have been found in the macrolide and lincosamide producers, which often combine several approaches to protect themselves against the antimicrobial that they produce. In pathogenic microorganisms, the impact of the 3 mechanisms is unequal in terms of incidence and of clinical implications. Modification of the ribosomal target confers broad-spectrum resistance to macrolides and lincosamides, whereas efflux and inactivation affect only some of these molecules.

An Emerging Mechanism: Target Mutation

In vitro selection of Escherichia coli mutants that are highly resistant to erythromycin has been of considerable value for characterization of the binding site of this antibiotic to the ribosome. The clinical importance of this mechanism was only recently recognized with identification of mutations at either A2058 or A2059 in domain V of rRNA; A2058 and A2059 confer MLSB and ML resistance, respectively . Depending on the species, bacteria possess from 1 to several rrn operons encoding 23S rRNA. In general, the mutations are observed in pathogens with 1 or 2 rrn copies, often with each copy carrying the mutation. This mechanism is responsible for clarithromycin resistance in the vast majority of, if not all, strains of Mycobacterium avium and Helicobacter pylori . Similar mutations have also been reported in Treponema pallidum and Propionibacterium species. Clinical strains and laboratory mutants have recently been identified in S. pneumoniae, which harbors 4 rrn copies [17].Mutations in ribosomal proteins L4 and L22 that confer erythromycin resistance have been documented in laboratory and clinical isolates of S. pneumoniae . The changes are clustered in a highly conserved sequence of L4 and confer resistance to macrolides but not to clindamycin. Although these types of resistance are considered, by definition, to be nontransferable, the ability displayed by pneumococci to acquire extrinsic genes easily by transformation followed by homologous recombination might then lead to spread.The prevalence and clinical importance of the pneumococcal mutants are not known. In particular, the in vivo conditions that lead to selection of mutant strains have not been studied. Because attention has been brought on these new types of resistance only recently, however, we believe that, so far, their importance has been underestimated.

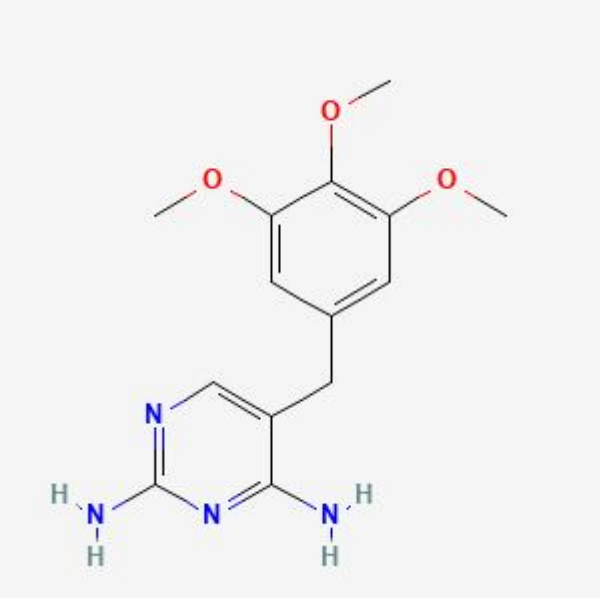
Antibiotic Efflux

In gram-negative bacteria, chromosomally encoded pumps contribute to intrinsic resistance to hydrophobic compounds, such as macrolides. The pumps often belong to the resistance/nodulation/division family composed of proteins with 12 membrane-spanning regions. In gram-positive organisms, acquisition of macrolidemacrolide resistance by active efflux is caused by 2 classes of pumps, members of the ATP-binding-cassette (ABC) transporter superfamily and of the major facilitator superfamily (MFS).To date, the only efflux proteins conferring acquired macrolide resistance characterized in Staphylococccus species are ABC transporters encoded by plasmidborne msr(A) genes .The msr(A) resistance determinant was originally detected in Staphylococcus epidermidis, and, since then, it has been found in a variety of staphylococcal species, including S. aureus. ABC transporters require ATP to function and are usually formed by a channel composed of 2 membrane-spanning domains and 2 ATP-binding domains located at the cytosolic surface of the membrane.The msr(A) gene encodes a protein with 2 ATP-binding domains characteristic of ABC transporters. The nature of the transmembrane component of the MsrA pump

remains unknown. The efflux system appears to be multicomponent in nature, involving msr(A) and chromosomal genes to constitute a fully operational efflux pump that has specificity for 14- and 15-membered macrolides and type B streptogramins (the MSB phenotype) . The resistance is inducibly expressed. Erythromycin and other 14- and the 15-membered macrolides are inducers, whereas streptogramins B are not. Therefore, the strains are resistant to streptogramins B only after induction with erythromycin. Clindamycin is neither an inducer nor a substrate for the pump, and thus the strains are fully susceptible to this antimicrobial.

RESISTANCE TO TRIMETHOPRIM

(1)Trimethoprim is a synthetic derivative of trimethoxybenzyl-pyrimidine with antibacterial and antiprotozoal properties. As a pyrimidine inhibitor of bacterial dihydrofolate reductase, trimethoprim binds tightly to the bacterial enzyme, blocking the production of tetrahydrofolic acid from dihydrofolic acid. The antibacterial activity of this agent is potentiated by sulfonamides.



Scheme 1: Chemical structure of Trimethoprim

Common side effects of trimethoprim include:
Aseptic meningitis, BUN and creatinine increased, Cholestatic jaundice
Erythema multiforme, Exfoliative dermatitis, High blood potassium (hyperkalemia)
Hypersensitivity reactions, Itching (common)

RESISTANCE TO TRIMETHOPRIM

Bacteria may develop trimethoprim resistance by several mechanisms, which can be chromosome or plasmid mediated. Clinically,the most important mechanism is plasmid-mediated trimethoprim resistance

Clinical resistance to trimethoprim is increasing and may be due to selection of bacterial cells with altered permeability, loss of drug-binding capacity, overproduction of or alterations in DHFR, or a combination of these factors.

Distinctive DHFRs mediated by*dfr*genes have been described in Enterobacteriaceae,*P. aeruginosa, H. influenzae,* Streptococcus pneumoniae, *S. aureus,* and Campylobacter spp. that may be chromosomally resistant to high trimethoprim concentrations. These resistant enzymes often may be plasmid mediated and disseminated by highly mobile transposons (e.g., Tn7) with wide host species ranges. Outbreaks caused by trimethopri

N m-resistant conjugative plasmids have been noted in multiple centers in Europe, Asia, and the Americas. Many of the outbreaks occurred in immunocompromised hosts, with organisms manifesting resistance to multiple other antibiotic groups. DHFR variants in*P. jiroveci* pneumonia isolates may be associated with resistance to TMP-SMX.

Variable local increases in trimethoprim resistance, particularly among Enterobacteriaceae, have been reported. Recent surveys have found trimethoprim resistance steadily increasing among*E.coli*uropathogens. Whether the clinical use of trimethoprim alone in some countries has resulted in increasing resistance to TMP-SMX is unclear.

(4)A study that demonstrates the molecular detection of *dfrA* genes
was carried out to determine the susceptibility/resistance of *E. coli* and *Klebsiella* spp. isolates (n = 124) to trimethoprim using urine samples(n = 16).

Resistance to trimethoprim was observed in 37/124 (29.8%) *E. coli and Klebsiella* spp. isolates with an MIC90 > 32 mg/L. *DfrA* genes were detected in 29/37 (78.4%) trimethoprim-resistant isolates. Detection of *dfrA* was highly sensitive (93.6%) and specific (91.4%) in predicting phenotypic trimethoprim resistance among *E. coli and Klebsiella* spp. isolates. The *dfrA* genes analysed were detected using a culture-

independent PCR method in all urine samples. Phenotypic trimethoprim resistance was apparent in isolates cultured from 15/16 (94%) *dfrA*-positive urine samples. There was a significant association ($P < 0.0001$) between the presence of *dfrA* and trimethoprim resistance in urine samples containing Gram-negative bacteria (Sensitivity = 75%; Specificity = 96.9%; PPV = 93.8%; NPV = 86.1%).

This study demonstrates that phenotypic trimethoprim resistance can be rapidly and reliably predicted by molecular detection of *dfrA*genes in isolates and urine samples. Timely and appropriate initiation of antimicrobial therapy is key to effective antimicrobial stewardship policies. Rapid detection of trimethoprim resistance, prior to prescription of an antibiotic, could help avoid the risk of treatment failure, longer hospitaliza

Mupirocin, sold under the brand name **Bactroban** among others, is a topical antibiotic useful against superficial skin infections such as impetigo or folliculitis. It may also be used to get rid of methicillin-resistant *S. aureus* (MRSA) when present in the nose without symptoms.Due to concerns of developing resistance, use for greater than ten days is not recommended.It is used as a cream or ointment applied to the skin. Common side effects include itchiness and rash at the site of application, headache, and nausea.Long term use may result in increased growth of fungi. Use during pregnancy and breastfeedingappears to be safe. Mupirocin is in the carboxylic acid class of medications. It works by blocking a bacteria's ability to make protein, which usually results in bacterial death.

Mechanism of action

Pseudomonic acid inhibits isoleucine tRNA synthetase in bacteria, leading to depletion of isoleucyl-tRNA and accumulation of the corresponding uncharged tRNA. Depletion of isoleucyl-tRNA results in inhibition of protein synthesis. The uncharged form of the tRNA binds to the aminoacyl-tRNA binding site of ribosomes, triggering the formation of (((p)ppGpp, which in turn inhibits RNA synthesis. The combined inhibition of protein synthesis and RNA synthesis results in bacteriostasis. This mechanism of action is shared with furanomycin, an ((analog of isoleucine.

(6)Resistance

The first MUP-resistant *S. aureus* was reported in 1987 during MRSA treatment at St. Thomas' hospital, London. The MUP resistance frequency varies (0–65%) in different MRSA strains. Globally, MUP resistance is increasing in the *S. aureus* species, especially MRSA, due to an increase in over-the-counter, unjustified, and long-term usage, leading to the potential efficacy being hampered. The prevalence of MUP resistance in *S. aureus* depends on various factors such as selection of patient population (community, hospital, or ICU), surveillance nature, e.g., active surveillance in previously MUP-treated patients vs. passive surveillance of isolates from all the patients, and associated resistance profile. Based on the minimum inhibitory concentration (MIC), MUP possesses two types of resistance: low-level resistance (LLR) and high-level resistance (HLR). LLR (MIC $\leq$ 8–256 μg/mL) is a more common chromosomal resistance that usually arises due to the spontaneous point mutation of the Ile-tRNA synthetase gene, leading to the retardation of the binding affinity of MUP to the Ile-tRNA synthetase enzyme. LLR resistance is clinically insignificant and non-transferable, but further mutations can lead to HLR via the acquisition of a pSK41-like plasmid (staphylococcal multi-resistant conjugative plasmids) . HLR (MIC > 500 μg/mL) is a plasmid-coded resistance that possesses two resistance mechanisms. The first mechanism comprises the acquisition of plasmid-mediated *mup*A or the Ile-tRNA synthetase-2 gene. Moreover, the *mupA* gene is self-transmissible, leading to creating resistance to other antibiotics such as clindamycin, erythromycin, gentamicin, tetracycline, levofloxacin, and trimethoprim. Molecular studies revealed that the *mupA* gene is mainly responsible for HLR in almost all *S. aureus* isolates. The second mechanism is due to the synthesis of another paralog *mupB* that shares 45.5% sequence identity with Ile synthetase and 65.5% identity with *mupA*. Additionally, some aminoacyl-tRNA synthetases paralogs are also responsible for MUP resistance.

RESISTANCE TO ANTIFUNGAL AGENTS

Antifungal resistance occurs when an antifungal medication no longer works to treat a fungal infection. The fungus can fight off the medicine's effects.This problem is a type of antimicrobial resistance. It occurs when fungi, viruses, bacteria and parasites don't respond to medications developed to treat them. Your body doesn't develop antifungal resistance — fungi do. Today, while antifungal medicines may still help you, fewer drugs can treat drug-resistant fungi.Antifungal resistance is becoming a significant concern to clinicians who are charged with caring for patients at high risk for invasive mycoses. Resistance to currently available antifungal agents can develop secondary to acquired mechanisms following exposure to these drugs. Recent trends in acquired antifungal resistance include increased azole resistance among non-*Candida albicans*isolates, azoles resistance in *Aspergillus fumigatus*, and echinocandin resistance in *C. glabrata*. In contrast, some fungal species are intrinsically resistant to certain drugs (e.g., *C. krusei* and fluconazole, or *C. lusitaniae* and amphotericin B), while others demonstrate microbiologic resistance to all clinically available antifungals

(e.g., *Lomentospora*[formerly *Scedosporium*] *prolificans* and *Fusariumsolani*).[Citation4–Citation6] New species are also emerging that may demonstrate resistance to multiple class of available agents (e.g., *C. auris*). Superbugs like Candida auris don't respond to antifungals, which limits treatment options. Drug resistance is a serious global health problem.

Resistance

Antifungal resistance can occur for many reasons. It sometimes develops spontaneously. Or it may result from antibiotic overuse or misuse of antifungal medicines. People with compromised immune systems are most at risk for developing fungal infections that can lead to antifungal resistance. Some fungi, known as superbugs (certain strains of fungi that have become more resistant to antifungal medicines), don't respond to standard antifungal treatments.These fungi continue to multiply and cause infections even when you take medication. There are only three classes of antifungal medicines: **azoles, echinocandin and polyenes**. A fungus that develops resistance to one drug may not respond to any available treatments. Fungal infections with superbug status include:

Resistance in *Aspergillus fumigatus*

This mold causes a lung infection called aspergillosis. Approximately 200,000 people worldwide develop aspergillosis every year. They typically get it from breathing in the mold spores. The infection is becoming more resistant to azole antifungals.

Resistance in *Candida*

This yeast naturally occurs on the skin and inside the body. *Candida* can enter the bloodstream, causing a potentially life-threatening infection called candidemia. This infection no longer responds well to azole medicines.***Candida glabrata***affects the urinary system. It's becoming more resistant to azoles and echinocandins. That leaves people with few safe treatment options.***Candida auris* (*C. auris*)** is a relatively new fungal superbug that first appeared in 2009. It quickly caused problems worldwide and is becoming more common in the United States. Antifungals that typically work on *Candida* infections don't always work against this strain. Some strains are multi-drug resistant. These *C. auris* infections don't respond to any antifungal drugs. The fungus causes bloodstream infections that can affect the heart and brain. When this happens, more than 1 in 3 infected people die. The fungus spreads easily in hospitals and nursing homes. People get it through contact with an infected person or contaminated surfaces. It can live on surfaces for several weeks and is difficult to get rid of.

Resistance in non-*C. albicans*

Azole resistance

Although *C. albicans* is the most common *Candida* species cultured from patients with candidiaisis, infections caused by other species within this genus are becoming more important in various regions around the world, including *C. glabrata, C. parapsilosis*, and *C. tropicalis*, and the species can vary between different geographic regions. This is of importance, as resistance has been shown to be increasing in many of the non-*C. albicans*species in different institutions and geographic regions.As reported by the World Health Organization, fluconazole resistance is indeed more common in non-*C. albicans* species . This is of concern, since fluconazole is a relatively inexpensive and well-tolerated medication that is easily administered orally. Furthermore, resistance to fluconazole may also mean resistance to other azoles, since mechanisms that reduce fluconazole susceptibility, such as point mutations within the *ERG11* gene that encodes lanosterol 14a-demethylase, the target of the azoles (e.g., itraconazole, voriconazole, posaconazole, and isavuconazole), increase transcription of this gene, leading to increased amounts of the enzyme, or the efflux pumps, such as Cdr1 and Cdr2, also affect this class of antifungals.

Echinocandin resistance

The echinocandins are recommended as the first line of therapy against invasive candidiasis in immunocompromised patients and in those who have had prior azole exposure due to the fear of resistance. Because the mechanism of action is different from that of the azoles, the echinocandins, including anidulafungin, caspofungin, and micafungin, have been shown to maintain potent in vitro activity against many *Candida*isolates that have developed resistance to fluconazole and the other triazoles.However, resistance to the echinocandins can develop with exposure to the members of this class, and this occurs via point mutations within highly conserved regions (i.e., hot spots 1 and 2) of the *FKS1* and *FKS2* genes, which encode subunits of the glucan synthase enzyme.

Resistance in Aspergillusspecies

Recent attention has also begun to focus on azole-resistant *Aspergillus* species, with particular interest in resistant *A. fumigatus* isolates. As in *Candida* species, resistance to the mold active triazoles, itraconazole, posaconazole, voriconazole, and isavuconazole can develop with prolonged clinical exposure. This has been well documented in the literature and can occur in patients with chronic pulmonary aspergillosis, where azole therapy is often administered to patients for years.' This acquired resistance in *A. fumigatus* is caused by point mutations in the *CYP51A* gene, which encodes the Cyp51 enzyme responsible for the conversion of lanosterol to ergosterol. Different mutations can differentially affect the azoles, with some causing resistance to voriconazole and isavuconazole, some causing resistance to posaconazole and itraconazole, and others causing pan-azole resistance

MULTI DRUG RESISTANCE

During the last few decades, the incidence of microbial infections has increased dramatically. Continuous deployment of antimicrobial drugs in treating infections has led to the emergence of resistance among the various strains of microorganisms. Multidrug resistance (MDR) is defined as insensitivity or resistance of a microorganism to the administered antimicrobial medicines (which are structurally unrelated and have different molecular targets) despite earlier sensitivity to it.

Classification of MDR

Despite of administration of appropriate doses of drugs for a specific duration of time, survival of various microbial strains recommends the high levels of resistance developed in them. This clinical failure is due to not only the antimicrobial resistance but also the suppressed immune function, poor/deprived drug bioavailability, or increased rate of drug metabolism. Persistence of microbes after conventional/standard treatments points out different types of antimicrobial drug resistance which is an expanding problem in medical world. MDR can be classified as primary or secondary resistance.

Flow chart 1. Classification of MDR

Primary Resistance

It occurs when the organism has never encountered the drug of interest in a particular host.

Secondary Resistance

Also known as "acquired resistance," this term is used to describe the resistance that only arises in an organism after an exposure to the drug . It may further be classified as follows.(i)*Intrinsic resistance:* it refers to the insensitivity of all microorganisms of a single species to certain common first-line drugs, which are used to treat diseases based on the clinical evidence of the patient. It is also known as multidrug resistance (MDR), for example, *Mycobacterium tuberculosis* to rifampicin and isoniazid or *Candida* spp. to fluconazole .(ii)*Extensive resistance:* it defines the ability of organisms to withstand the inhibitory effects of at least one or two most effective antimicrobial drugs. Also termed as XDR, this seemed to arise in patients after they have undergone a treatment with first line drugs, for example, XDR-TB resistance against fluoroquinolone

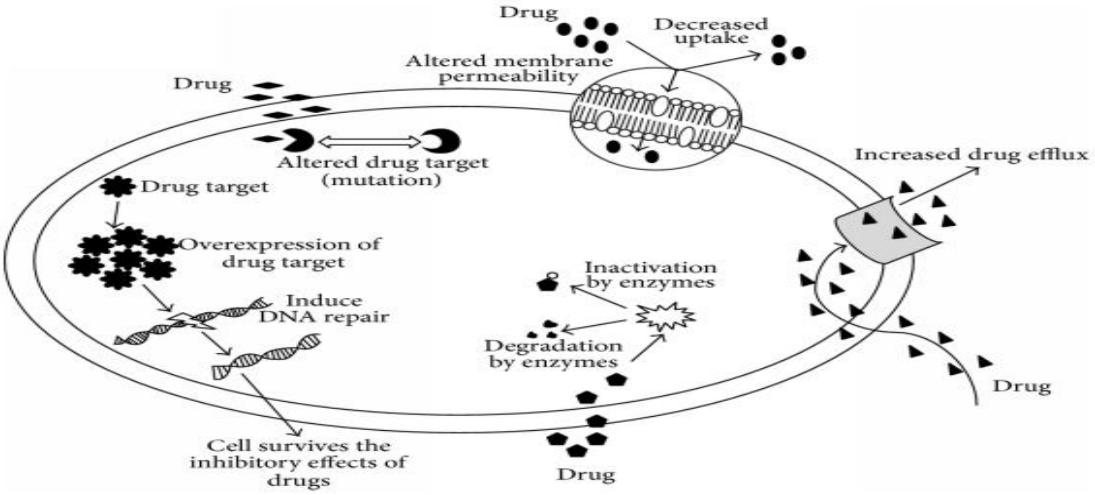
Clinical Resistance

In addition to the above-mentioned types, clinical resistance is defined by the situation in which the infecting organism is inhibited by a concentration of an antimicrobial agent that is associated with a high likelihood of therapeutic failure or reappearance of infections within an

organism due to impaired host immune function. In other words, the pathogen is inhibited by an antimicrobial concentration that is higher than could be safely achieved with normal dosing

Mechanisms of MDR

Resistance is the term referred to as the insensitivity of a microbe to an antimicrobial drug when compared with other isolates of the same species. Although several new drugs have been introduced commercially, this development of resistance among infectious microorganisms is increasing especially in patients under prolonged drug exposure . Antimicrobial drugs generally act on the microbes either by inhibiting a metabolic pathway like nucleotide synthesis which in turn leads to the inhibition of DNA/RNA synthesis and further protein synthesis and disruption of the cell membrane or by competing with the substrate of any enzyme involved in cell wall synthesis (e.g., chitin synthase) Microorganisms have evolved a multitude of mechanisms to overcome the effectiveness of drugs, thereby surviving exposure to the drugs. This section will mainly describe the resistance mechanisms that the microbes develop to avoid getting killed by the drugs



Flow chart 2. Mechanisms of MDR

Mechanisms of MDR

Cell wall, in both bacteria and fungi, plays a crucial role in their survival. As discussed above, drugs inhibit the cell wall synthesis by binding with the peptidoglycan layer in bacteria or affecting ergosterol synthesis (e.g., polyenes) in fungi, thus, blocking the cell growth and division. These organisms undergo certain chromosomal mutations or exchange of extrachromosomal DNA elements through conjugation or transformation (horizontal gene transfer) such as in *K. pneumoniae* , which can cause alteration in the cell membrane composition (e.g., a reduction in the ergosterol content in fungal plasma membrane) resulting in decreased permeability and uptake of drugs into the cell [1,]. Altered membrane composition (such as *β*-1,3-glucan and lipid content in fungal cell membrane) also leads to lack of active target sites for the drugs (e.g., echinocandins in fungi [38]) to bind. Mutations in the genes encoding for the target cause modifications at the molecular level and retain cellular function by reducing susceptibility to inhibition [1, 5, 37, 41].

Another mechanism of MDR was found to be an overexpression of drug target enzymes leading to target bypass due to modification in certain metabolic pathways (e.g., azoles and allylamines in fungi [38]), which causes production of alternate target molecules and interference in some protein synthesis. This can influence the access of drugs to the target sites.

MDR mediated by drug efflux pumps remains the predominant mechanism of MDR. The overexpression of genes encoding for ATP-binding cassette (ABC) transporter membrane proteins (e.g., P-glycoprotein (Pgp)), also known as the multidrug efflux pumps which are responsible for the export or expulsion of drugs out of the cell [3, 39, 42], usually generates MDR and continues cellular functions without any interference.

FACTORS THAT FACILITATE EMERGENCE AND SPREAD OF ANTIMICROBIAL RESISTANCE

Antimicrobial resistance (AMR) is one of the most serious global public health threats in this century. The first World Health Organization (WHO) Global report on surveillance of AMR, published in April 2014, collected for the first time data from national and international surveillance networks, showing the extent of this

phenomenon in many parts of the world and also the presence of large gaps in the existing surveillance. In this review, we focus on antibacterial resistance (ABR), which represents at the moment the major problem, both for the high rates of resistance observed in bacteria that cause common infections and for the complexity of the consequences of ABR. We describe the health and economic impact of ABR, the principal risk factors for its emergence and, in particular, we illustrate the highlights of four antibiotic-resistant pathogens of global concern – *Staphylococcus aureus, Klebsiella pneumoniae,* non-typhoidal *Salmonella and Mycobacterium tuberculosis* – for whom we report resistance data worldwide. Measures to control the emergence and the spread of ABR are presented.

Antimicrobial resistance (AMR) has emerged as one of the principal public health problems of the 21st century that threatens the effective prevention and treatment of an ever-increasing range of infections caused by bacteria, parasites, viruses and fungi no longer susceptible to the common medicines used to treat them. The problem of AMR is especially urgent regarding antibiotic resistance in bacteria. Over several decades, to varying degrees, bacteria causing common or severe infections have developed resistance to each new antibiotic coming to market. Faced with this reality, the need for action to avert a developing global crisis in health care is imperative.

The World Health Organization (WHO) has long recognised the need for an improved and coordinated global effort to contain AMR. In 2001, the WHO Global Strategy for Containment of Antimicrobial Resistance has provided a framework of interventions to slow the emergence and reduce the spread of antimicrobial-resistant microorganisms; In 2012, WHO published The Evolving Threat of Antimicrobial Resistance – Options for Action proposing a combination of interventions that include strengthening health systems and surveillance; improving use of antimicrobials in hospitals and in community; infection prevention and control; encouraging the development of appropriate new drugs and vaccines; and political commitment.

Following the indication of a primary role for surveillance, in April 2014, WHO published the first global report on surveillance of AMR collecting experiences from national and international surveillance networks. .This report shows that surveillance data, where available, can be very useful for orienting treatment choices, understanding AMR trends, identifying priority areas for interventions, and monitoring the impact of interventions to contain resistance. The lack of adequate surveillance in many parts of the world leaves large gaps in existing knowledge of the distribution and extent of this phenomenon.

Our review examines the main factors contributing to the development of antibiotic resistance and the consequences for human health focussing on the impact of resistance in species commonly associated with infection (i.e. *Staphylococcus aureus, Klebsiella pneumoniae,* non-typhoidal *Salmonella*) in different settings and in the treatment of tuberculosis.

Impact of Antibiotic Resistance

The impact of antibiotic resistance in terms of mortality and of the public health cost is quite difficult to estimate, and there are few studies addressing this issue. The US Center for Disease Control and Prevention (CDC) conservatively estimated that, in the US, more than two million people every year are affected with antibiotic-resistant infections, with at least 23 000 dying as a result of the infection.

In Europe each year, the number of infections and deaths due to the most frequent multidrug-resistant bacteria (*S. aureus*, *Escherichia coli*, *Enterococcus faecium*, *Streptococcus pneumoniae*, *Klebsiella pneumoniae* and *Pseudomonas aeruginosa*) was estimated at ~400 000 and 25 000, respectively, in 2007.

Several fields of modern medicine depend on the availability of effective antibiotic drugs; chemotherapy for cancer treatment, organ transplantation, hip replacement surgery, intensive care for pre-term newborns and many other activities could not be performed without effective antibiotics. In fact, infections caused by multidrug-resistant bacterial strains are among the main factors influencing morbidity and mortality in patients undergoing these procedures. A report from the University of Texas, published in 2014, showed high antibiotic resistance rates in infections in cancer patients with chemotherapy-related neutropenia. A recent study from the Medical University of Warsaw, on infections after orthotopic liver transplantation, showed a high proportion of isolates of antibiotic-resistant bacteria.

Common infections in neonatal intensive care are increasingly becoming extremely difficult, and sometimes impossible, to treat.*Staphylococcal* species, most notably *S. epidermidis* and *S. aureus*, cause ~60%–70% of infections, and numerous outbreaks of methicillin-resistant *S. aureus* (MRSA) have been reported in these units.

Also the economic impact of antibiotic resistance is difficult to quantify, as several types of consequences must be taken into account. Increased resistance leads to elevated costs associated with more expensive antibiotics (when infections become resistant to first-line antimicrobials, treatment has to be switched to second- or third-line drugs, which are nearly always more expensive), specialised equipment, longer hospital stay and isolation procedures for the patients. Societal costs include death and loss of productivity. In Europe, the overall crude economic burden of antibiotic resistance was estimated to be at least 1.5 billion euros with more than 900 million euros corresponding to hospital costs. Productivity loss due to absence from work or death from infection accounted for 40% of the total estimated cost. However, the estimate was based on antibiotic resistance surveillance data collected in 2007 and may underestimate the present burden of antibiotic resistance, which is a constantly evolving phenomenon.

In the US, the CDC estimated the cost of AMR as $55 billion per year overall: $20 billion in excess for direct healthcare costs, with additional society costs for lost productivity as high as $35 billion a year.**Antimicrobial resistance.**

Key facts

Antimicrobial resistance (AMR) is a global health and development threat. It requires urgent multisectoral action in order to achieve the Sustainable Development Goals (SDGs).

WHO has declared that AMR is one of the top 10 global public health threats facing humanity.

Misuse and overuse of antimicrobials are the main drivers in the development of drug-resistant pathogens.

Lack of clean water and sanitation and inadequate infection prevention and control promotes the spread of microbes, some of which can be resistant to antimicrobial treatment.

The cost of AMR to the economy is significant. In addition to death and disability, prolonged illness results in longer hospital stays, the need for more expensive medicines and financial challenges for those impacted.

Without effective antimicrobials, the success of modern medicine in treating infections, including during major surgery and cancer chemotherapy, would be at increased risk.

The emergence and spread of drug-resistant pathogens that have acquired new resistance mechanisms, leading to antimicrobial resistance, continues to threaten our ability to treat common infections. Especially alarming is the rapid global spread of multi- and pan-resistant bacteria (also known as “superbugs”) that cause infections that are not treatable with existing antimicrobial medicines such as antibiotics.

The clinical pipeline of new antimicrobials is dry. In 2019 WHO identified 32 antibiotics in clinical development that address the WHO list of priority pathogens, of which only six were classified as innovative. Furthermore, a lack of access to quality antimicrobials remains a major issue. Antibiotic shortages are affecting countries of all levels of development and especially in health- care systems.

Antibiotics are becoming increasingly ineffective as drug-resistance spreads globally leading to more difficult to treat infections and death. New antibacterials are urgently needed – for example, to treat carbapenem-resistant gram-negative bacterial infections as identified in the WHO priority pathogen list. However, if people do not change the way antibiotics are used now, these new antibiotics will suffer the same fate as the current ones and become ineffective.

The cost of AMR to national economies and their health systems is significant as it affects productivity of patients or their caretakers through prolonged hospital stays and the need for more expensive and intensive care.

Without effective tools for the prevention and adequate treatment of drug-resistant infections and improved access to existing and new quality-assured antimicrobials, the number of people for whom treatment is failing or who die of infections will increase. Medical procedures, such as surgery, including caesarean sections or hip replacements, cancer chemotherapy, and organ transplantation, will become more risky.

What accelerates the emergence and spread of antimicrobial resistance?

AMR occurs naturally over time, usually through genetic changes. Antimicrobial resistant organisms are found in people, animals, food, plants and the environment (in water, soil and air). They can spread from person to person or between people and animals, including from food of animal origin. The main drivers of antimicrobial resistance include the misuse and overuse of antimicrobials; lack of access to clean water, sanitation and hygiene (WASH) for both humans and animals; poor infection and disease prevention and control in health-

care facilities and farms; poor access to quality, affordable medicines, vaccines and diagnostics; lack of awareness and knowledge; and lack of enforcement of legislation.

Need for coordinated action

AMR is a complex problem that requires a united multisectoral approach. The One Health approach brings together multiple sectors and stakeholders engaged in human, terrestrial and aquatic animal and plant health, food and feed production and the environment to communicate and work together in the design and implementation of programmes, policies, legislation and research to attain better public health outcomes.

Greater innovation and investment is required in operational research, and in research and development of new antimicrobial medicines, vaccines, and diagnostic tools especially those targeting the critical gram-negative bacteria such as carbapenem-resistant Enterobacteriaceae and *Acinetobacter baumannii*. The launch of the Antimicrobial Resistance Multi Partner Trust Fund (AMR MPTF), the Global Antibiotic Research & Development Partnership (GARDP), AMR Action Fund and other funds and initiatives could fill a major funding gap. Various governments are piloting reimbursement models including Sweden, Germany, the USA and the United Kingdom. More initiatives are needed to find lasting solutions.

Global Action Plan on Antimicrobial Resistance (GAP)

Globally, countries committed to the framework set out in the Global Action Plan[1] (GAP) 2015 on AMR during the 2015 World Health Assembly and committed to the development and implementation of multisectoral national action plans. It was subsequently endorsed by the Governing Bodies of the Food and Agriculture Organization of the United Nations (FAO) and the World Organisation for Animal Health (OIE). To ensure global progress, countries need to ensure costing and implementation of national action plans across sectors to ensure sustainable progress. Prior to the endorsement of the GAP in 2015, global efforts to contain AMR included the WHO global strategy for containment of Antimicrobial Resistance developed in 2001 which provides a framework of interventions to slow the emergence and reduce the spread of AMR.

Tripartite Joint Secretariat on Antimicrobial Resistance

The political declaration at the UN High Level Meeting on AMR, committed to by Heads of State at the United Nations General Assembly in New York in September 2016, confirmed a strong focus on a broad, coordinated approach that engages all including the human, animal, plant and environmental health sectors. WHO is working closely with FAO and OIE in a 'One Health' approach to promote best practices to reduce the levels of AMR and slow its development.

The Interagency Coordination Group (IACG) on AMR was convened by the Secretary-General of the United Nations after the UN High-Level Meeting on Antimicrobial Resistance in 2016. The IACG brought together partners across the UN, international organizations and individuals with expertise across human, animal and plant health, as well as the food, animal feed, trade, development and environment sectors, to formulate a plan for the fight against antimicrobial resistance. The Interagency Coordination Group on AMR submitted its report " No time to wait: Securing the future from drug-resistant infections" to the UN Secretary-General in April 2019. Its recommendations are now being implemented.

World Antimicrobial Awareness Week (WAAW)

WAAW was previously called World Antibiotic Awareness Week. Since 2020, it has been called World Antimicrobial Awareness Week. This reflects the broadened scope of WAAW to include all antimicrobials including antibiotics, antifungals, antiparasitics and antivirals. Held annually since 2015, WAAW is a global campaign that aims to raise awareness of antimicrobial resistance worldwide and encourage best practices among the general public, health workers and policy makers to slow the development and spread of drug-resistant infections. The Tripartite Executive Committee decided to set all future WAAW dates as 18 to 24 November. The overarching slogan used for the last 5 years was "Antibiotics: Handle with Care." This was changed to "Antimicrobials: Handle with Care" in 2020.

The Global Antimicrobial Resistance and Use Surveillance System (GLASS)

WHO launched the Global Antimicrobial Resistance and Use Surveillance System (GLASS) in 2015 to continue filling knowledge gaps and to inform strategies at all levels. GLASS has been conceived to progressively incorporate data from surveillance of AMR in humans, surveillance of the use of antimicrobial medicines, AMR in the food chain and in the environment. GLASS provides a standardized approach to the collection, analysis, interpretation and sharing of data by countries, territories and areas, and monitors the status of existing and new national surveillance systems, with emphasis on representativeness and quality of

data collection. Some WHO regions have established surveillance networks that provide technical support to countries and facilitate enrollment into GLASS.

Global Research and Development priority setting for AMR

In 2017, to guide research and development into new antimicrobials, diagnostics and vaccines, WHO developed the WHO priority pathogens list. It will be updated in 2022. On an annual basis, WHO reviews the pre-clinical and clinical antibacterial pipelines to see how the pipeline is progressing with respect to the WHO priority pathogens list. A critical gap remains in research and development, in particular for antibacterial targeting of the gram-negative carbapenem resistant bacteria.

Global Antibiotic Research and Development Partnership (GARDP)

GARDP is a not-for-profit global partnership developing treatments for drug-resistant infections that pose the greatest threat to health. GARDP works across sectors to ensure equitable access to treatments and promote their responsible use.

Factors contributing to the emergence of antibiotic resistance

Antibiotic resistance is a natural phenomenon that occurs when microorganisms are exposed to antibiotic drugs. Under the selective pressure of antibiotics, susceptible bacteria are killed or inhibited, while bacteria that are naturally (or intrinsically) resistant or that have acquired antibiotic-resistant traits have a greater chance to survive and multiply. Not only the overuse of antibiotics but also the inappropriate use (inappropriate choices, inadequate dosing, poor adherence to treatment guidelines) contribute to the increase of antibiotic resistance.

PREVENTION AND CONTROL OF ANTIBIOTIC RESISTANCE

Preventing infections from developing reduces the amount of antibiotics used. This reduction in antibiotic use, in turn, slows the pace of antibiotic resistance. Preventing infections also prevents the spread of resistant bacteria. Antibiotic resistance is a growing public health concern worldwide. When a person is infected with an antibiotic-resistant bacterium, not only is treatment of that patient more difficult, but the antibiotic-resistant bacterium may spread to other people.

When antibiotics don't work, the result can be:

longer illnesses

more complicated illnesses

more doctor visits

the use of stronger and more expensive drugs

more deaths caused by bacterial infections

Examples of the types of bacteria that have become resistant to antibiotics include those that cause skin infections, urinary tract infections, meningitis, sexually transmitted diseases and respiratory tract infections such as pneumonia.

In cooperation with other government agencies, the Food and Drug Administration (FDA) has launched several initiatives to address antibiotic resistance.

Antibiotics are meant to be used against bacterial infections. For example, they are used to treat strep throat, which is caused by streptococcal bacteria, and skin infections caused by staphylococcal bacteria.

Although antibiotics kill bacteria, they are not effective against viruses. Therefore, they will not be effective against viral infections such as colds, most coughs, many types of sore throat, and influenza (flu).

Using antibiotics against viral infections;

will not cure the infection

will not keep other individuals from catching the virus

will not help a person feel better

may cause unnecessary, harmful side effects

may contribute to the development of antibiotic-resistant bacteria

Patients and health care professionals alike can play an important role in combating antibiotic resistance. Patients should not demand antibiotics when a health care professional says the drugs are not needed. Health care professionals should prescribe antibiotics only for infections they believe to be caused by bacteria.

BY INDIVIDUALS

There are many steps that individuals can take to protect themselves and families:

Wash Your Hands, Know the Symptoms, Ask Questions, Learn the Right Ways to Use Antibiotics, Never Share or Use Leftover Antibiotics, Prepare Food Safely

Get Vaccinated, All drugs have side effects, Do not skip doses, Do not save antibiotics
Do not take antibiotics prescribed for someone else, Take the antibiotics as prescribed

BY HEALTH PROFESSIONALS

In environments like hospitals where the likelihood of bacterial exposure is higher than usual, antibiotic resistance is an even more significant issue.

But, what should health care professionals do to curb antibiotic resistance? Are they responsible for engaging in the fight and making antibiotic resistance less problematic? If so, what can and should they do? They can prevent antimicrobial resistance in the following ways:

Prescribing necessary antibiotics, Using the CDC dedicated network

BY AGRICULTURAL SECTOR

Globally, antimicrobials are widely used in animal production not only to improve animal health and animal welfare, but also to enhance animal growth rates and raise animal productivity. The use of antimicrobials, however, can lead to the emergence of resistance and the transmission of resistant genes and resistant bacteria between species. Access to effective and cost-efficient antimicrobials is critical for human and animal health, animal welfare and food security. The potential consequences of antimicrobial resistance include reduced food production, reduced food security, greater food safety concerns, higher economic losses to farm households, and contamination of the environment.

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