

Anti-microbial Drug Resistance: An Evolving Threat to Modern Medicine

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Abstract

Antimicrobial drug resistance (AMR) poses an extreme risk to the efficient prevention and treatment of infectious illnesses and is a major global public health concern. It happens when microorganisms, such as bacteria, viruses, fungi, and parasites, learn to resist exposure to antimicrobial treatments that were once effective against them. A number of factors, including improper antimicrobial usage, self-medication, poor infection prevention practices, poor sanitation, and the widespread use of antimicrobials in agricultural and animal husbandry, contribute to the emergence and spread of AMR. AMR is linked to higher rates of morbidity, mortality, healthcare costs, and extended hospital stays. Antimicrobial resistance continues to be a major challenge to reach sustainable healthcare goals and is estimated to have caused to millions of deaths worldwide. The important resistance mechanisms are enzymatic drug inactivation, target alteration, decreased drug uptake, efflux pump activation, and horizontal gene transfer. The necessary components of a multimodal strategy to combat AMR are antimicrobial stewardship, surveillance, infection prevention and control strategies, public awareness, quick diagnostics, and the creation of novel antimicrobial drugs. To reduce the increasing prevalence of AMR and maintain the efficacy of current antimicrobial treatments for future generations, national and international collaborations must be strengthened.

Keywords: Antimicrobial resistance, drug resistant infections, antibiotic resistance, public health, antimicrobial stewardship

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Introduction

Antimicrobials are medicines that are used to prevent, treat, or control infections caused by microorganisms such as bacteria, viruses, fungi, and parasites. They act by either killing the microorganisms (microbicidal action) or by inhibiting their growth and multiplication (microbiostatic action). Common classes include antibiotics, antivirals, antifungals and antiparasitic agents.

Antimicrobial resistance (AMR) occurs when microorganisms like bacteria, viruses, fungi and parasites no longer respond to antimicrobial medicines. It is the ability of microorganisms to survive and multiply despite exposure to antimicrobial drugs that were previously effective against them.

Antibiotics and other antimicrobial drugs no longer work, and infections are becoming harder or impossible to treat. AMR leads to treatment failure, prolonged illness, increased healthcare costs, and high morbidity and mortality.

There were almost 5 million deaths linked to bacterial AMR in 2019, and if nothing is done, this number is expected to rise significantly by 2050. For instance, the COVID-19 pandemic increased the use of antibiotics and hastened the emergence of disease resistance.^[1] AMR is a natural process that evolves over time through genetic changes in pathogens. Human activities, notably the abuse and overuse of antimicrobials to cure, prevent, or control disease in

humans, animals, and plants, has hastened the emergence and spread of antimicrobial drug resistance.

A global concern

The foundation of contemporary medicine is antimicrobial medications. Pharmaceutical companies withdrew from antibiotic development as a result of the increase in MDR, which reduced the number of effective antibiotics available. Healthcare systems are still under pressure from this perfect storm of rising resistance and a lack of new drug development. Now knowing that common diseases and mild injuries might once again become fatal, we have entered an alarming post-antibiotic period. Millions of people are predicted to die annually from AMR infections if urgent measures are not put in place.^[2]

Both health systems and national economies as a whole bear heavy costs due to AMR. For instance, it reduces agricultural productivity, necessitates more costly and extensive care, and reduces the productivity of patients or their caregivers due to longer hospital stays.

Antimicrobial resistance is driven by multiple interrelated factors that promote survival of resistant microbes and dissemination of resistant genes. Antibiotic abuse and misuse in humans, including needless prescriptions and incomplete treatment regimens, is the primary cause of antimicrobial resistance (AMR). Additionally, it is fueled by the overuse of

antibiotics in agriculture and livestock, inadequate infection control procedures in medical facilities, and the easy access to antibiotics without a prescription. Inadequate diagnostic facilities result in improper empirical therapy, and global travel and the transfer of diseases hasten the development of resistance.^[3]

Key facts

Antimicrobial resistance (AMR) is a major danger to global development and public health.

It is estimated that anti-microbial resistance was directly responsible for 1.14 million deaths in 2021 and 4.71 million deaths were associated with bacterial AMR.^[4] Drug-resistant infections are mostly caused by the abuse and overuse of antibiotics in people, animals, and plants. All regions and all income levels are impacted by AMR. Poverty and inequality worsen its causes and effects, with low- and middle-income countries being the most impacted.

Many of the advances in contemporary medicine are at danger due to AMR. It increases the danger of certain medical procedures and treatments, including surgery, caesarean sections, and cancer chemotherapy, and makes infections more difficult to treat.

Antibiotic access and the pipeline are global issues. In light of growing resistance, there is an inadequate pipeline for research and development, and further steps are desperately needed to ensure fair access to both novel and current vaccines, diagnostics, and medications. AMR has substantial financial costs in addition to death and disability. According to World Bank projections, AMR could cause annual GDP losses of between US\$1 trillion to US\$3.4 trillion by 2030 and an extra US\$1 trillion in healthcare expenses by 2050. Proper use of antibiotics (antimicrobial stewardship programmes) to guarantee the right medication, dosage, and duration are important measures to combat antimicrobial resistance in human health. Reducing the spread of resistant organisms can be achieved by strengthening infection prevention and control techniques such as hand hygiene, immunisation, and hospital sterilisation. Enhancing diagnostic tools allows for targeted treatment rather than the empirical antibiotic use. Misuse is decreased by limiting over-the-counter antibiotic sales and implementing prescription-only regulations. Effective control is further supported by ongoing monitoring of resistance trends and public and healthcare worker awareness campaigns.^[5]

Mechanisms of Resistance to Antimicrobial Agents

When antimicrobial drugs were originally introduced into clinical practice, they were thought to be miraculous treatments. But as soon as penicillin was discovered, it became clear that resistance would arise and lessen the miracle's impact. The end of the antimicrobial era is threatened by this grave development, which is present with every new antimicrobial agent. Significant resistance is now linked to every major class of antibiotic. The development of antibiotic resistance is linked to two main factors: evolution

and clinical/environmental practices. A microbial species' genome will randomly undergo mutations that allow it to survive when it is under pressure from an existing threat, whether chemical or otherwise. When we submit pathogens to chemical warfare, they will adapt to become resistant. The indiscriminate use of antibiotics in agriculture and animal husbandry, as well as poor methods of treatment by medical professionals, have contributed significantly to this progression.^[6]

Antimicrobial resistance can arise at any one or more stages of a drug's delivery to interaction with its target. Thus resistance development may occur due to reduced entry of the drug into the microorganism, enhanced antibiotic export through efflux pumps, production of enzymes by the microorganism which destroy the antibiotic, modification of the target proteins, creation of alternative pathways for those that the antibiotic inhibits. The different mechanisms of antimicrobial drug resistance are shown in Figure 1.

Resistance due to reduced entry of drug into pathogen

Gram-negative bacteria have a semipermeable outer membrane that keeps big polar molecules out of the cell. Porins are protein channels that allow small polar compounds, such as many antibiotics, to enter cells. Drug entrance into a cell can be slowed down or completely stopped by the absence, mutation, or loss of a preferred porin channel. This will reduce the drug concentration at the target site. Resistance may result from a mutation or phenotypic alteration that reduces or eliminates the drug's active transport across the cell membrane if the target is intracellular. For instance, suramin and pentamidine are used to treat *Trypanosoma brucei* in its early phases, whereas melarsoprol and eflornithine are used when CNS illness (sleeping sickness) is evident.^[7]

Resistance due to drug efflux

Antibiotics that the bacteria would ordinarily be vulnerable to can be expelled by microorganisms that overexpress efflux pumps. For bacteria, fungi, and parasites, efflux pumps are a common defence mechanism. *Plasmodium falciparum*'s development of drug resistance is one of the terrible outcomes of resistance emergence. *P. falciparum* multidrug resistance gene 1 (*pfmdr1*) encodes an ABC transporter that mediates drug resistance to the majority of antimalarial medications, including chloroquine, quinine, mefloquine, halofantrine, lumefantrine, and the combination of artemether and lumefantrine. Chemotherapy failure and drug resistance are caused by point mutations in the *pfmdr1* gene.^[8]

Resistance due to destruction of antibiotic

One typical mechanism of drug resistance is drug inactivation. The generation of an aminoglycoside-modifying enzyme or beta-lactamase is typically the cause of bacterial resistance to aminoglycosides and beta-lactam antibiotics.

MECHANISMS OF ANTIMICROBIAL DRUG RESISTANCE

Bacteria develop resistance through diverse mechanisms that prevent antibiotics from reaching their target, inactivate the drug, alter the target, or bypass the inhibited pathway.

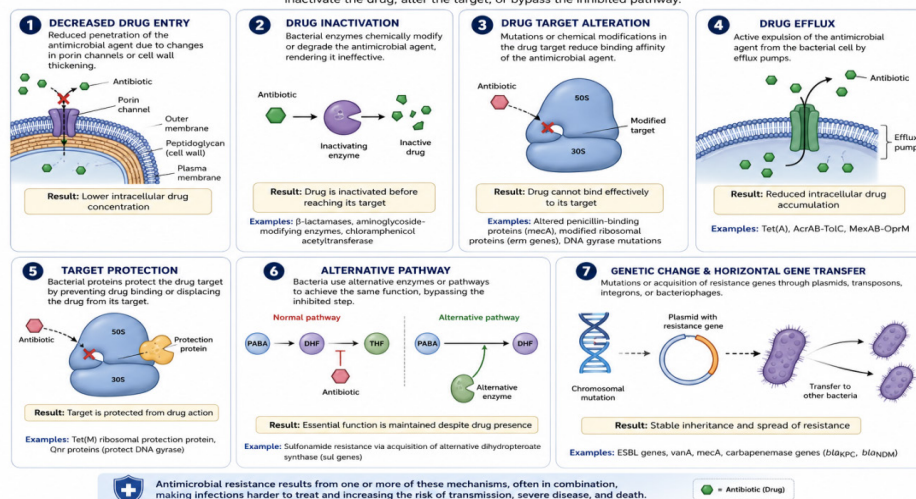


Figure 1: Mechanisms of drug resistance.

Resistance due to altered target structure

Changes in the amino acid composition and structure of the target protein of an antibiotic are frequently the result of single or multiple point mutations. This change can lead to reduced affinity of drug for its target, e.g. ribosomal protection type of resistance to macrolides and tetracyclines. Mutations linked to decreased affinity for protease inhibitors, integrase inhibitors, fusion inhibitors, and non-nucleoside reverse transcriptase inhibitors are seen in HIV resistance.^[9]

Resistance due to development of alternative pathways for metabolic requirements

Instead of producing folic acid from PABA absorbed from the medium, certain sulfonamide-resistant bacteria adapt to using preformed folic acid.

Figure 1 illustrates the major mechanisms by which microorganisms develop resistance to antimicrobial agents, including reduced membrane permeability, enzymatic drug inactivation, alteration of drug targets, active efflux of antimicrobial agents, target modification, use of alternative pathway, horizontal gene transfer leading to dissemination of resistant genes.^[10] [Figure created with the assistance of ChatGPT (open AI)]

Development of resistance

Gene transfer or mutation can result in resistance

A mutation is a persistent, heritable genetic alteration that happens randomly and spontaneously in microorganisms. Another name for this is vertical transfer of resistance.

Mutation is of two types

Single step

A high level of resistance may be conferred by a single gene mutation. It appears quickly, such as enterococci to streptomycin.

Multiple steps

Sensitivity eventually declines in a stepwise fashion due to several gene modifications. Many organisms develop resistance to erythromycin, tetracyclines and chloramphenicol in this way.^[11]

Gene transfer

Horizontal transfer of resistance refers to the transmission of the resistance-carrying gene from one organism to another (infectious resistance). The different mechanisms of horizontal gene transfer are shown in Figure 2.

Methods of gene transfer

Conjugation

Gram-negative bacilli of the same or different species frequently engage in sexual interaction by forming a bridge or sex pilus. Both chromosomal and extrachromosomal DNA (plasmid) may be involved. Another bacterium receives the gene that carries the "resistance" or "R" factor. For instance, streptomycin resistance in *E. coli* and chloramphenicol resistance in typhoid bacilli.^[12]

Transduction

This is the transmission of resistance-carrying genes via a bacteriophage. The phage absorbs the R factor and transports it to another bacterium that it infects. For example, several cases of erythromycin, chloramphenicol, and penicillin resistance.

Transformation

When a resistant bacterium releases resistance-carrying DNA into the media, another susceptible organism may absorb it and stop responding to the medication. Most likely, this mechanism has no therapeutic significance.

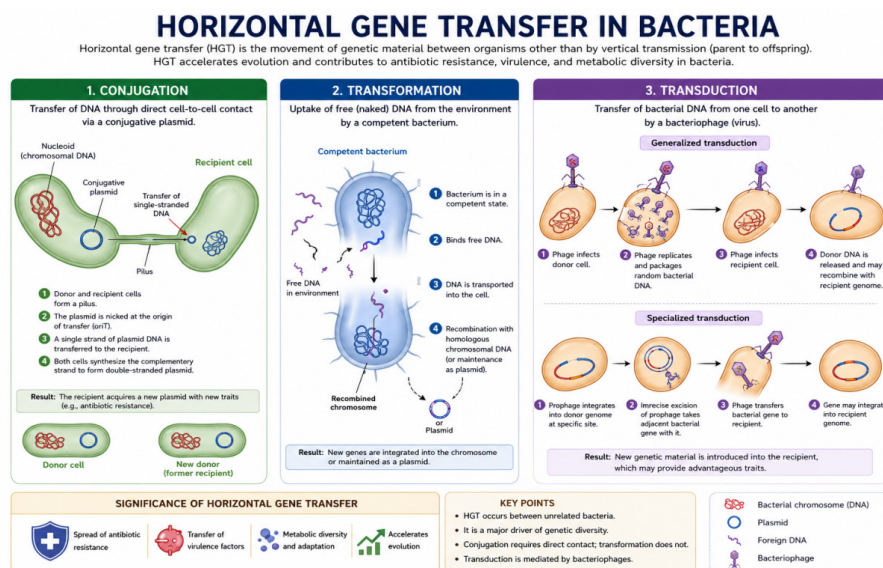


Figure 2: Horizontal gene transfer in bacteria

Figure 2 is a schematic illustration of the three major mechanisms of horizontal gene transfer in bacteria: conjugation, involving direct cell to cell transfer plasmids through a conjugative pilus; transformation involving the uptake of free extracellular DNA; and transduction, mediated by bacteriophages transferring genetic material between bacterial cells.^[13] [Figure created with the assistance of ChatGPT (OpenAI)].

What is the present situation in India

The situation of Antimicrobial resistance in India is rapidly worsening and is now considered among the highest globally.

Rising resistance in common pathogens

Recent surveillance shows increasing resistance in frequently isolated bacteria: *Escherichia coli* (UTIs, bloodstream infections), *Klebsiella pneumoniae* (pneumonia, sepsis), *Acinetobacter baumannii* (ICU infections). These organisms are showing declining sensitivity to first line and even second line antibiotics.^[14]

Increasing resistance to critical antibiotics

India is reporting high resistance to key drug classes: Fluoroquinolones, 3rd generation cephalosporins, Piperacillin-tazobactam, Carbapenems (last resort drugs). Indian Council of Medical Research (ICMR) data indicate that these antibiotics are becoming less effective in hospital acquired infections, especially in Gram-negative bacteria.

Carbapenem resistance is a major concern

A significant recent trend is the rise of carbapenem-resistant Enterobacterales (CRE) due to enzymes like New-Delhi Metallo β lactamase (NDM), Oxacillinase (OXA-48), *Klebsiella pneumoniae* carbapenemase (KPC.) This is alarming because

carbapenems are often considered last-line therapy for severe infections.

High burden in hospitals (ICU dominance)

Majority of resistant infections are hospital acquired. Intensive care unit (ICU) settings shows high prevalence of Multi-drug resistant (MDR) and Extensively drug resistant (XDR) organisms. Device associated infections (catheters, ventilators) are major sources of spread.^[15]

Spread of multidrug-resistant (MDR/XDR) strains

There is increasing detection of multidrug resistant (MDR) infections, extensively drug resistant infections (XDR) pathogens and occasional pan-drug resistant isolates. This severely limits treatment options and increases mortality risk.

Strategies to combat AMR

Infection prevention and control and access to antibiotics

Programmes for infection prevention and control are essential to the fight against AMR, especially in low and middle income countries (LMICs). According to a recent analysis, by directly preventing drug-resistant illnesses and lowering antibiotic use, universal access to water, sanitation, hygiene, and immunisations might avert almost 337,000 AMR-associated fatalities every year. Vaccines are effective in preventing AMR both directly and indirectly. By preventing bacterial infections through vaccinations, the requirement of first-line and second line antibiotics is eliminated, which lowers the emergence of drug-resistant isolates and the need for hospitalization. Achieving the 10-20-30 global target by 2030 – a 10% decrease in AMR attributable deaths, a 20% decrease in inappropriate antibiotic use in humans and a 30% decrease in inappropriate antibiotic use in animals – requires improving sustainable and equitable access to effective antibiotics especially in low and middle income countries.^[16]

Antibiotic Stewardship Program (ASP)

Antimicrobial stewardship program is a program to promote rational use of antimicrobials by the prescriber, to minimise their overuse and prevent resistance.

Goals

To collaborate with healthcare professionals to ensure that every patient receives the most appropriate antimicrobial agent at the correct dosage and duration.

To Avoid Overuse, abuse, and misuse of antibiotics in both inpatient and outpatient settings; doctors use antibiotics when they are not required.

In order to reduce the emergence of resistance: Both at the individual patient and population levels, antibiotic use alters susceptibility patterns. Antibiotic-exposed patients are more vulnerable to colonisation or infection by resistant microbes.^[17]

Stewardship Team

Every hospital should make the most of its resources to assemble a productive team within the restrictions of its staff and budget. A collaborative programme involving an infectious disease physician, pharmacist, microbiologist, epidemiologist, and administration would be successful.

Stewardship strategies

Front-end or preprescription approach

Restrictive prescriptive authority is used in the front-end or preprescription approach to stewardship. With the exception of a small number of professionals, several antimicrobials are prohibited and require prior authorisation for usage.

Back-end or postprescription approach

This approach uses prospective review and feedback. Based on the available bacteriological reports and clinical features of the patient, the antibiotic steward advises clinicians to continue, discontinue, modify, or adjust the medication.

Techniques

Formulary restriction

The majority of hospitals have a relatively selective formulary that excludes some of the available antibiotics.

Order sets and treatment algorithms

Encourage the doctor to choose evidence-based antibiotics based on relevant clinical criteria, national guidelines, and local trends of antimicrobial resistance.^[18]

Education

Clinicians are educated about the use of antimicrobials, when reading order sets and treatment algorithms, speaking with an antibiotic steward to get permission to administer a restricted antimicrobial, and performing concurrent review and feedback.

Pharmacodynamic dose optimization

Utilising PK/PD characteristics of an antimicrobial agent to maximise dose effectiveness depending on the organism, infection location, and patient characteristics.

Computer-assisted decision support program

Based on probable illnesses, patient characteristics, local microbiology, and ideal medication dosage, computer-based algorithms direct a practitioner and prescribe an antibiotic treatment.

Antibiotic cycling

The scheduled removal and substitution of particular antimicrobials or antimicrobial classes in a given patient care unit is known as antibiotic cycling. The idea is that resistance can be prevented by routinely eliminating particular kinds of antibiotics.^[19]

Increasing AMR surveillance and diagnostics

With 127 member jurisdictions, the Global Antimicrobial Resistance and use surveillance system was established by WHO in 2015 as the first international cooperative effort to standardise AMR monitoring through data collection, analysis, interpretation and exchange.^[20] AMR surveillance data can guide empirical antimicrobial protocols, reduce inappropriate prescribing, preserve last-resort antibiotics for specific drug-resistant infections and help choose the most effective (narrow-spectrum antibiotics). Reducing antibiotic abuse or misuse requires prompt and correct diagnosis of the ailment. Uncertainty in the diagnosis of viral or self-limiting disease can result in the needless prescription of antibiotics. Over the past ten years, high-throughput molecular diagnostics such as whole genome sequencing, surveillance, and quick point of care microbial testing or detection.

New non-antibiotic antimicrobial therapies

Antibodies

Human monoclonal antibodies have recently shown promise in treating COVID-19, but they have primarily been utilised to treat autoimmune diseases and cancer. A long acting human monoclonal antibody Nirsevimab has been approved recently in many countries for prevention of respiratory syncytial virus (RSV) infection in infants.

Antibody-antibiotic conjugate

Antibody-antibiotic conjugates are advanced medications made up of strong antibiotics covalently bound to monoclonal antibodies.^[21] The purpose of antibody-antibiotic conjugates is to deliver antibiotics directly to the site of infection by selectively binding to particular antigens.

Antimicrobial peptides

A subset of natural host defence peptides, antimicrobial and antibiofilm peptides are tiny, cationic, amphiphilic molecules

that typically contain less than 50 amino acids.^[22] Antibacterial peptides have demonstrated significant promise as a potential treatment for AMR due to their strong and quick broad-spectrum antibacterial activity, with little chance of causing AMR. Daptomycin is an approved antimicrobial peptide for treating gram positive infections like methicillin resistant staphylococcus aureus (MRSA) infections and Vancomycin resistant enterococci (VRE).

Bacteriophages

Bacteriophages, often known as phages, are extremely common viruses in the biosphere that infect bacteria.^[23] The introduction of antibiotics obscured any possible medicinal value of phages, even though they were discovered as early as 1915. Phages have attracted attention again as an antibiotic substitute due to the increase of AMR.

Gene therapy

The CRISPR immune system is one of the many strategies bacteria employ to fight off phages.^[24] The CRISPR-Cas systems act like genetic scissors, cut specific resistance genes in bacteria, can kill bacteria or remove resistant plasmid. Also, an effective approach for gene therapy is to repair the underlying host abnormalities (such as cystic fibrosis) that predispose to clinically resistant infections.

The various new non-antibiotic antimicrobial therapies are shown in Figure 3.

Figure 3 is a schematic representation of novel non-antibiotic antimicrobial strategies developed to combat antimicrobial resistance (AMR). The figure illustrates bacteriophage therapy, antimicrobial peptides, monoclonal antibodies, antimicrobial photodynamic therapy, CRISPR-Cas based antimicrobial approaches, immunotherapy, antivirulence therapy and nanoparticle based therapies.^[25] [Figure created with the assistance of ChatGPT(Open AI)].

Potential role of artificial intelligence (AI) in tackling AMR

Artificial intelligence is becoming a potent tool for combating infectious diseases and addressing AMR, ranging from antibiotic susceptibility testing, AMR surveillance, antimicrobial stewardship, and diagnosis to antimicrobial drug discovery or development, due to development in Artificial intelligence (AI) driven technologies, increased computational power and resources, and the availability of big data (including electronic health record and omics data).^[26]

Early detection and diagnosis

Artificial intelligence analyzes lab data, imaging and clinical records, helps rapidly identify resistant infections, supports faster antibiotic susceptibility prediction.

Predicting resistance patterns

Machine learning models predict which bacteria may become resistant, helps in empirical antibiotic selection and useful in hospital surveillance systems.

Antibiotic stewardship support

AI systems guide doctors in choosing correct antibiotics, dose and duration, reduces misuse of antibiotics and overprescription.

Drug discovery and development

AI identifies new antimicrobial compounds, screens millions of molecules quickly and helps design drugs active against MDR/XDR bacteria.

Genomic analysis of bacteria

AI analyzes bacterial genome to detect resistant genes (e.g New-Delhi metallo- β lactamase gene (NDM), Extended



Figure 3: New non-antibiotic antimicrobial therapies

spectrum β lactamases (ESBL genes) and tracks spread of resistance in populations.

Infection outbreak prediction

AI models monitor hospital and community data and predicts outbreaks of resistant infections early.

Discussion

In the 21st century, antimicrobial resistance has become one of the biggest challenges to worldwide public health. The effectiveness of traditional treatment plans has been undermined by the rising incidence of resistant microorganisms, which has led to longer hospital stays, higher medical costs, treatment failures and increased mortality rates. The present study highlights the growing burden of antimicrobial resistance among clinically important pathogens, the present situation in India and the world, mechanism of drug resistance and antimicrobial stewardship program being implemented for rational use of antibiotics and preventing the drug resistance. Our study reflects the widespread and escalating nature of AMR reported globally. Numerous national and international surveillance studies have reported similar trends, showing rising resistance in both gram-positive as well as gram-negative organisms.^[27] Our study shows there is a progressive decline in susceptibility to commonly prescribed antibiotics which is consistent with the findings of the previous studies.

The current state of antimicrobial resistance (AMR) is especially concerning in low and middle income countries, where factors like indiscriminate antibiotic use, over the counter antimicrobial availability, inadequate infection control measures, poor sanitation, and limited diagnostic facilities contribute significantly to the development of resistance. According to recent estimates, antimicrobial resistance is a major obstacle to achieving sustainable healthcare goals and is thought to be a contributing factor in millions of deaths each year.^[28]

The mechanisms responsible for antimicrobial resistance are diverse and complex. In the present study, the resistance patterns observed may be explained by several well-established mechanisms, including enzymatic degradation of antibiotics through β -lactamase production, modification of antimicrobial target sites, reduced membrane permeability, activation of efflux pumps, and biofilm production. Horizontal gene transfer through conjugation, transformation, and transduction plays a critical role in the dissemination of resistance determinants among bacterial populations. These mechanisms have been extensively described in previous studies and are considered key drivers of multidrug resistance worldwide.^[29]

Selective pressure imposed on by improper usage of antibiotics has a significant impact on the development and spread of resistance. The emergence of resistant strains is accelerated by empirical prescribing without microbiological validation, insufficient treatment regimens, needless use of

broad spectrum antibiotics, and widespread antimicrobial use in livestock and agriculture.^[30]

Antimicrobial Stewardship Programs (ASPs) is a notable strategy which must be implemented for combating AMR. Though evidence-based prescribing, optimisation of antibiotic selection, dose modification, de-escalation of therapy, and ongoing monitoring of antimicrobial consumption, ASPs encourage the prudent use of antibiotics. Numerous studies have shown that stewardship actions minimise the growth of resistant organisms, enhance clinical outcomes, lower healthcare costs, and reduce unnecessary antibiotic use. Our study emphasize the need for strengthening ASP implementation at institutional and national levels to curb the further spread of resistance. The current study emphasizes the significance of routine antimicrobial resistance surveillance, the creation of local antibiograms, stringent infection prevention and control procedures, and efficient antimicrobial stewardship. When combined these strategies can reduce the establishment and spread of resistant bacteria while maintaining the efficacy of currently available antibiotics.^[31] Further studies ought to emphasise on developing new treatment approaches, enhancing quick diagnostic methods, and assessing how stewardship actions affect resistance patterns over the long run.

Conclusion

The findings of this study are consistent with growing body of evidence demonstrating that antimicrobial resistance is an escalating public health emergency that threatens the effective treatment of infectious diseases. The concerning prevalence of resistance among clinically significant pathogens highlights the diminishing efficacy of commonly used antimicrobial agents. Maintaining the efficacy of current antimicrobials and reducing the likelihood of antimicrobial resistance in the future depend on strengthening infection prevention strategies, encourage prudent prescription practices, and cultivating multidisciplinary collaboration.

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