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Review Article

Global Antimicrobial Resistance: Strategies and Challenges

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ABSTRACT

Antimicrobial resistance (AMR) is a critical health challenge worldwide, that arises when bacteria, viruses, fungi, and parasites become resistant to antimicrobial medications, making diseases more challenging to treat. The enzymatic breakdown of antibiotics, modifications to target locations, elevated efflux pumps, and changes in cell membrane permeability are some of the processes behind AMR. A key factor behind the development and transmission of AMR has been the unregulated use of livestock feed for preventive purposes. Rapid global expansion of antibiotic-resistant bacteria is posing a hidden pandemic risk to public health and demanding immediate action. The misuse and unnecessary overreliance on antibiotics in human medicine is one of the many contributing factors of AMR, veterinary practices, and agriculture, as well as inadequate infection prevention strategies, lack of diagnostic tools, and inadequate sanitation. Preventive measures against AMR involve promoting the rational use of antibiotics through antimicrobial stewardship, improving infection control practices, advancing rapid diagnostic technologies, reducing antibiotic use in food production, and increasing public awareness. Efforts must also focus on global collaboration to monitor resistance trends, enhance regulatory frameworks, and invest in research to develop novel antimicrobial agents and alternative therapies. Addressing AMR requires an interdisciplinary and coordinated approach to safeguard the efficacy of current antimicrobial treatments and reduce the occurrence of resistance.

INTRODUCTION

Antimicrobial resistance (AMR) has serious economic ramifications and is acknowledged as a major worldwide health problem for both people and animals [1]. This can cause infections to remain in the body longer and increase the chance that they will spread to other people. Due to prolonged illness, antimicrobial resistance is also responsible for rising treatment costs and decreasing labor productivity [2]. Examples of antimicrobial chemicals that may be employed against microorganisms to limit their growth potential, stop their multiplication, or even kill them include antibiotics, disinfectants, and food preservatives [3]. Bacterial resistance is considered a major threat in healthcare institutions. With the widespread use of antibiotics, there is a greater chance that bacteria may become resistant to them in more sophisticated ways. Some recently changed strains seem to have reduced the chances that the patients would respond appropriately to the therapies, which has serious repercussions that might lead to clinical problems or morbidity and death [4, 5]. It is estimated that drug-

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resistant illnesses cause 700,000 fatalities globally and 25,000 within the European Union (EU). If nothing is done, this number is predicted to rise to 10 million deaths annually by 2050 [6]. Antimicrobial resistance also contributes to increased treatment costs and decreased worker productivity because of extended sickness. AMR is thought to cost the EU EUR 1.5 billion annually in lost productivity and medical expenses. Drug-resistant diseases are predicted to have a cumulatively detrimental effect on the global economy of USD 100 trillion by 2050 [2, 6]. However, bacteria developed antimicrobial resistance (AMR) as a result of the prolonged, widespread usage of antibiotics. Because of the contradictory degrees of spontaneous genetic development, the emergence of antimicrobial resistance (AMR) is a significant worldwide health problem in the twenty-first century. Therefore, early intervention is required [7]. Antibiotic resistance in bacteria reduces the effectiveness of antibiotic use in healthcare, and there is strong evidence that suggests that the improper use of antibiotics may ultimately encourage the growth and spread of antibiotic-resistant bacteria [8]. Numerous synthetic, semi-synthetic, and natural chemicals have distinct mechanisms that can profoundly impact physiological and metabolic functions. Instances of these substances include β-lactams and glycopeptides, which change how cell walls are made; macrolides and tetracyclines, which prevent proteins from being made; sulfonamides, which stop metabolic processes; and fluoroquinolones, which stop DNA replication and translation [5]. Global occurrence of antimicrobial resistance is investigated [9] (Figure 1).

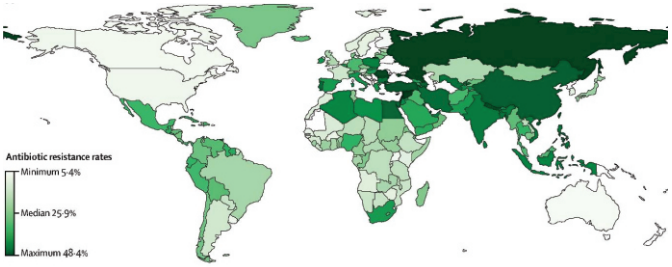

Figure 1: Global Occurrence of Antimicrobial Resistance

Mode of Action of Antibiotics

The vast majority of antimicrobial drugs used to treat bacterial diseases may be categorized according to their main mechanism of action. The four primary mechanisms of antibiotic action include blocking cell wall synthesis, inhibiting protein production, disrupting nucleic acid synthesis, and interfering with metabolic pathways [10]. Beta lactams, which include penicillins, cephalosporins, carbapenems, and monobactams, and glycopeptides, which include teicoplanin and vancomycin, are examples of antimicrobial medications that function by stopping the bacterial cell wall from being produced [10, 11]. By inhibiting the enzymes needed for the development of the peptidoglycan layer, beta-lactam drugs stop the bacterial cell wall from being produced [11]. By binding to the last D-alanine residues of the growing peptidoglycan chain, tecoplanin and vancomycin also prevent the development of cell walls.The cross-linking mechanisms required to form stable cell walls are halted as a result [3]. Macrolides, aminoglycosides, tetracyclines, chloramphenicol, streptogramins, and oxazolidinones are antibacterial agents because they inhibit protein synthesis [10, 11]. Ribosomes in bacterial and eukaryotic cells have different structures. Antibacterial medications target and prevent the growth of certain microbes by using these distinctions. The ribosome's 30S subunit is bound by tetracyclines, aminoglycosides, and macrolides, whereas the 50S subunit is bound by chloramphenicol [3]. Since fluoroquinolones interfere with DNA synthesis and induce deadly double-strand breaks during replication, they have antibacterial qualities [12]. Trimethoprim (TMP) and sulfonamides, however, block the route that produces folic acid, which halts the synthesis of DNA [13, 14]. In a common combination of antibacterial drugs, the sulfonamides sulfamethoxazole (SMX) and the folic acid analogue TMP block two steps in the bacterial folate synthesis enzymatic pathway. One possible fifth, less obvious mode of action is disruption of the structure of the bacterial membrane. Leakage of bacterial compounds out of membranes is assumed to be the mechanism by which polymyxins exert their inhibitory effects. The lipid tail of the cyclic lipopeptide daptomycin seems to pierce the bacterial cell membrane, leading to membrane depolarization and ultimately the bacterium's death [15] (Table 1).

Table 1: Class of Antibiotics Along with Their Mode of Action

Mode of Action	Antibiotics
Inhibitors of Cell Wall Synthesis	Penicillins, cephalosporins, carbapenems, and monobactams are examples of beta-lactam antibiotics
	Glycopeptides: teicoplanin and vancomycin
Inhibition of Protein Synthesis	Linezolid, quinupristin-dalfopristin, clindamycin, macrolides, and chloramphenicol attach to the 50S ribosomal subunit.
	Bind to the 30S ribosomal subunit: Tetracyclines, aminoglycosides
	Mupirocin attaches itself to the isoleucyl-tRNA synthetase in bacteria.
Disruption of Nucleic Acid Synthesis	Fluoroquinolones inhibit the production of DNA
	Rifampin inhibits the production of RNA
Blocking Metabolic Pathways	Sulfonamides and analogues of folic acid
Disordering of Bacterial Membrane Structure	Daptomycin and polymyxins

Mechanisms of Resistance

Antibiotics primarily target four key components in bacterial cells: protein synthesis, nucleic acid synthesis, the cell wall, and the cell membrane. The fundamental mechanisms of antimicrobial resistance include restricted

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drug uptake, modification of drug targets, drug inactivation, and increased active drug efflux. To develop acquired resistance, bacteria often employ strategies such as modifying drug targets, inactivating drugs, and expelling them through efflux mechanisms. In contrast, intrinsic resistance primarily arises from restricted drug uptake, drug inactivation, and active drug efflux [16]. Due to structural variations, gram-positive and gram-negative bacteria exhibit different mechanisms of drug resistance. Gram-positive bacteria, lacking a lipopolysaccharide (LPS) outer membrane and having a reduced capacity for efflux mechanisms against certain drug types, are less likely to rely on this approach to restrict drug absorption [17, 18]. However, studies have revealed that all four main drug resistance pathways are employed by gram-negative bacteria [18].

Inactivation of Drug

Certain bacterial species can inactivate antibiotics, resulting in drug resistance through two main mechanisms: either by breaking down the antibiotic or by attaching a chemical group to it. This can result in drug resistance. Members of the enterobacterales family generate hydrolyzing enzymes called beta-lactamases, which can render antibiotics that include beta-lactams inactive. Beta-lactamases target penicillin-binding proteins and disrupt their ability to interact with the Beta-lactam ring structure by breaking it at a specific site, ultimately inactivating them as penicillinases and cephalosporinases [16]. It is well known that several gram-positive bacteria, such as *Enterococcus faecalis*, *Staphylococcus aureus*, and *Enterococcus faecium* as well as other members of the Enterobacterales family, have beta-lactamase genes that are passed down by horizontal gene transfer. Additionally, the tet (X) gene in some bacteria produces an enzyme that hydrolyzes tetracycline [19]. The most often transferred chemical groups for pharmaceutical inactivation are adenyl, phosphoryl, and acetyl groups. The most often used technique to combat chloramphenicol is acetylation, fluoroquinolones, aminoglycosides, and streptogramins, whereas adenylation and phosphorylation are reported to be the most commonly used methods against aminoglycosides [18].

Drug Target Modification

The targets required for medication binding can be altered by bacteria, which results in either a poor or nonexistent drug attachment. This modification occurs due to spontaneous mutations in the gene or genes responsible for encoding the therapeutic target protein. In both gram-positive and gram-negative bacteria, fluoroquinolone resistance arises when mutations occur in the quinolone-resistance determining region (QRDR) of DNA gyrase (topoisomerase II and topoisomerase IV) [20]. Another target alteration method that is believed to be a highly successful means of establishing resistance is methylation. Methylation, as seen with erm methylases conferring resistance to lincosamides, macrolides, and streptogramin B antibiotics, occurs in both gram-positive and gram-negative bacteria. Additionally, the CFR gene has been associated with resistance in various bacterial species, including *E. coli, Proteus vulgaris, Staphylococcus, Enterococcus,* and *Bacillus* [21]. The mecA and mecC genes create a unique penicillin-binding protein that causes *Staphylococcus* species to show their affinity for beta-lactam medications has significantly decreased [22, 23].

Limiting Drug Uptake

In gram-negative bacteria, the outer membrane primarily includes lipopolysaccharide, a highly acylated glycolipid that prevents several substances, including antibiotics, from passing through. Moreover, changes in outer membrane protein permeability, particularly porin proteins, can contribute to acquired resistance to drugs. For hydrophilic antibiotics such as chloramphenicol, tetracyclines, fluoroquinolones, and beta-lactams, porins are the main point of entry. Bacterial susceptibility to antibiotics is influenced by the number and type of porin proteins, which also affect how these antibiotics enter the bacterial cell [24]. Furthermore, mutations that affect the function or expression of these porin proteins may lead to acquired resistance to antibiotics. There is an increase in resistance when mutations altering porin expression are coupled with additional mechanisms, such as efflux pumps or enzymatic antibiotic degradation [25]. Biofilm formation is another method in which some bacteria show antibiotic resistance. These include, among others, *Proteus mirabilis, Klebsiella pneumoniae, E. coli, Pseudomonas aeruginosa, Enterococcus faecalis*, *Streptococcus vitridans*, *Staphylococcus aureus,* and *Staphylococcus epidermidis.* A group of microbial cells immersed in their exopolysaccharide and attached to biotic or abiotic surfaces is called a biofilm. Among other ways, it is known to prevent antibiotics from penetrating, giving microorganisms resistance and tolerance to them. Additionally, it may stop antibiotics from developing at bactericidal concentrations across the whole biofilm [26, 27].

Efflux of Drug/ Decreasing Permeability

Efflux pumps are an active transport mechanism that helps bacteria resist aminoglycosides by removing the antibiotic from their cells. However, because of the aminoglycoside polycationic structures, there are only a few functional efflux pumps [28]. The cytoplasmic membrane contains an energy-dependent efflux pump that bacteria use to control the accumulation of antimicrobial agents, including antibiotics, within their cells. Efflux pumps help bacteria keep their internal environment stable by eliminating

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harmful compounds from within the cell, such as metabolites, antibiotics, and quorum-sensing signalling molecules. In the 1980s, scientists found that the first plasmid-encoded efflux pump in *Escherichia coli* was responsible for eliminating tetracycline from the bacterial cell. Since then, several resistant bacteria, both gram-positive and gram-negative, with various efflux pathways have been discovered. It is noteworthy that the majority of efflux systems rely on chromosomally encoded multidrug efflux mechanisms to guarantee intrinsic drug resistance in bacteria [29, 30]. Instead, genes on mobile genetic elements are more likely to be linked to efflux pumps that are unique to a given substrate, including those for tetracyclines, macrolides, and chloramphenicol [18]. The structure and energy source determines which of the six different drug efflux pumps are present. The ATP-binding cassette (ABC), resistance nodulation–division (RND), drug metabolite transporter (DMT), major facilitator (MFS), small multidrug resistance (SMR), and toxic compound extrusion (MATE) are among its super-families. Typically, a periplasmic protein, an outer membrane protein channel, and a cytoplasmic membrane pump comprise the RND superfamily, which includes the most clinically significant efflux systems in gram-negative bacteria [19]. Gram-positive bacteria, on the other hand, have most of their efflux pumps encoded by chromosomal genes or carried on plasmids, and they are members of the ABC and MFS families.

Causes of Antimicrobial Resistance

Various mechanisms contribute to antimicrobial resistance, including intrinsic traits of the microorganisms and a wide range of environmental variables affecting both prescribers and consumers. Antimicrobial resistance (AMR) factors can be broadly classified into subsections; environmental aspects (overcrowding, rapid transmission through mass travel, inadequate sanitation, ineffective infection control programs, and extensive agricultural use); drug-related issues (including counterfeit, substandard, and easily accessible over-the-counter medications); patient-related factors (such as non-adherence to treatment, poverty, lack of education, self-medication, and misconceptions); and physician-related contributors (which may involve any combination of these elements), medical and veterinary misuse (self-medication, overuse in agriculture) and economic and social factors (poverty, lack of education). Although there are many causes of antimicrobial resistance, the following are the most prominent ones.

Misuse or Unnecessary Use of Antibiotics

Antibiotic resistance occurs naturally, but its advancement has been significantly accelerated by the overuse of medications in both humans and animals. According to epidemiological studies, antibiotic use and the rise in bacterial resistance are causally related [31]. Despite repeated warnings from health groups, antibiotic misuse and abuse continue at a disproportionate rate worldwide, suggesting that the current situation is irreparable. Research has indicated that individuals worldwide, especially those from less educated backgrounds, hold misunderstandings and incorrect ideas regarding antibiotics. One such myth is that most viral diseases, such as the flu and the common cold, can be cured with medications. Additionally, antibiotics are commonly recommended as part of patient care; this is particularly true in many impoverished countries with limited diagnostic resources [32]. One such example of misuse is the administration of antibiotics without a clear indication. The accessibility of antibiotics as over-the-counter (OTC) drugs for both animals and humans contributes to the emergence and transmission of drug-resistant infections. Antibiotic abuse is also exacerbated by the absence of standard treatment guidelines and antibiotic policies, which are prevalent in developing countries, and by the over-prescription of antibiotics by veterinarians, pharmacy owners, and health professionals in many developing and underdeveloped countries [16]. The supply chain's use of subpar or low-quality medicines has made the antimicrobial resistance (AMR) problem worse in many developing nations. Antibacterial resistance may also result from giving antibiotics at the incorrect dosage or from providing long courses of treatment. Even though it is unethical, many doctors, particularly in developing nations, prescribe antibiotics without a prescription to meet patient expectations and occasionally receive financial incentives from pharmaceutical companies [33, 32] One more thing that contributes to resistance is drug self-medication [34, 35]. The illegal drug trade, particularly in nations like South and Central America, Asia, Europe, and Africa, lends support to this [7, 36]. Ineffective control measures would lead to drug addiction and easy access to less expensive medications [37].

Inappropriate Prescribing Patterns

Inappropriate administration of antibiotics has a major impact on the development of AMR [38]. Examples of "inappropriate antibiotic prescribing" include prescribing antibiotics when they are not needed, choosing the wrong medications, or administering antibiotics at the wrong dose and for the wrong amount of time [39]. A survey found that 50% of patients were prescribed antibiotics at least once while in the hospital without a valid reason. Approximately one-third of hospitalized patients were prescribed antibiotics without the required testing, and these prescriptions were kept on file for a longer period [40]. Antibiotic introduction should preferably be guided by previous bacterial isolation and antimicrobial sensitivity testing. In assisted living facilities, where around 75% of

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antibiotic prescriptions are written erroneously, with wrong dosages and time limits, the situation is even worse [41].

Use of Antibiotics in Animals

Because of several factors, including the recent growth in demand for animal protein, the usage of antibacterial medication in the livestock industry has expanded dramatically in the majority of developing countries. Antibiotic residues that can be found in animal-derived products, including muscle, liver, kidney, fat, eggs, and milk, are also contributing to the problem of antimicrobial resistance (AMR). Antibiotics can be used to prevent disease, prepare animal feed to promote growth, cure animal illnesses, and increase feed conversion efficiency, among other uses [42]. This strategy is more common in developing nations and has contributed significantly to the rise of AMR in humans due to a lack of government oversight and the need to increase revenue from food animal farms [43]. About 70% of the antibiotics that are sold in the United States for medicinal purposes are meant for use in animals [44]. There are significant issues when antibiotics given for human use are either closely related to or identical to those used in animal medicine in terms of their kinds, functions, and modes of action.

Easy Traveling Routes

There is compelling evidence that human migration has a major impact on the emergence and global dissemination of antibiotic-resistant bacteria. Convenient, contemporary transportation routes that are available to people, animals, and goods also have a big impact on AMR's global spread [45]. Travelers are likely to unintentionally bring antimicrobial-resistant organisms back to their home countries from their travel destinations. Research has shown that travelling to regions with high AMR prevalence can result in the presence of antibiotic-resistant bacteria in the human body can persist for up to 12 months, increasing the risk of spreading to vulnerable individuals [46].

Lack of Information

There is compelling evidence that the public and healthcare workers (HCWs) lack knowledge of the processes underlying antibiotic resistance and the proper use of antibiotics [47]. Surveillance is required to assess the extent of the antimicrobial resistance (AMR) issue and to create intervention plans such as antimicrobial stewardship. Regretfully, precise statistical information about the frequency of AMR and antibiotic use in the global agriculture and healthcare industries has not yet been obtained [47]. Surveillance data helps identify areas that should be the focus of strategic initiatives to achieve the greatest results and provides crucial information. Before implementing effective intervention strategies, several stakeholders must work together to close the existing knowledge gap (e.g., agriculture and animal production companies, consumers, international organizations, and the human and veterinary care sectors).

Strategies for Prevention of Antimicrobial Resistance (AMR)

To combat the growing threat of antimicrobial resistance (AMR), a multifaceted approach is essential. First, antibiotic stewardship programs must be implemented to promote the rational use of antibiotics, ensuring they are prescribed only when necessary and in the correct dosage and duration. Second, infection prevention and control (IPC) measures, such as improved hygiene, vaccination, and hospital sanitation, can reduce the spread of resistant pathogens. Third, public awareness campaigns are essential to educate communities about the dangers of misuse and overuse of antibiotics. Additionally, investing in research and development for new antibiotics, vaccines, and alternative therapies is vital to stay ahead of resistant strains. Public awareness campaigns and global collaboration among healthcare providers, veterinarians, policymakers, and farmers ensure a collective effort in combating AMR, preserving the effectiveness of life-saving drugs for future generations [47, 48]. Further details regarding AMR prevention is provided below.

Infection Control and Prevention

Preventing infectious illnesses is the best course of action since it stops the growth and spread of resistant bacteria and the need for medication. Monitoring prescription trends designing and enforcing effective infection prevention measures procedures, and teaching healthcare facilities like primary care clinics on how to use antibiotics appropriately are all ways to prevent antimicrobial-resistant infections. Antibiotic resistance can be prevented by tracking changes in resistance patterns, which requires identifying and tracking the main sources of antibiotic-resistant characteristics [48]. Monitoring and measuring food-borne illnesses, looking into outbreaks, teaching people how to handle food safely, identifying high-risk individuals, and encouraging hand-washing practices can all help to drastically slow the spread of infections. An efficient way to monitor patients and contacts who are at risk is through contact tracing. This guarantees that those who are vulnerable are appropriately recognized and given the required treatments.

Preventing Misuse of Antibiotics

The use of efficient evidence-based disease diagnosis and treatment techniques should be one component of improving antibiotic prescribing practices. Healthcare providers might be held responsible for improving patient safety by implementing such tactics. In addition, it is imperative to enact evidence-based policies to discourage the unnecessary prescription of antibiotics and guarantee the efficient execution of suggested policies. Physicians

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should be observed and their prescription practices should be regularly reviewed. To ensure optimal prescription optimization, patients and clinicians should instead receive educational support. The Get Smart initiative is one such successful tactic of center for Disease Control and Prevention. This program takes action to educate legislators, patients, and healthcare professionals about the severity and consequences of antibiotic misuse. It also supports state-based initiatives in this regard [47-49].

Antimicrobial Stewardship Program (ASP)

Antimicrobial stewardship involves a systematic and collaborative approach that efforts to stop the spread of microbial resistance by educating and convincing prescribers to use antimicrobial agents according to the right choice, dosage, and duration for better patient outcomes. Ensuring that healthcare professionals prescribe the best antibiotic at the right dose and duration for each patient is the primary objective of antimicrobial stewardship. The second objective is to stop antibiotics from being overused, abused, and misused. Limiting the development of resistance is the third objective. The two main overlapping strategies for accomplishing antimicrobial stewardship's main objectives are: Antibiotics can be used in two ways: (1) to enhance healthcare results; and (2) to provide long-term access for everyone who needs them. The Centers for Disease Control and Prevention (CDC) released the "Core Elements" of antimicrobial stewardship in 2014 to achieve these goals. All hospitals, regardless of size, can follow these principles, which include specific advice to support small and critical-access hospitals in their execution [50, 51].

Promotion of Education and Innovation

Stakeholder awareness can be raised by implementing creative educational programs that enhance and implement successful public health strategies. The mechanism, causes, effects on health, and hazards of antibiotic resistance should also be emphasized in educational programs. However, fact sheets, posters, or videos should be used to promote effective communication among the stakeholders. To prevent resistance, the importance of early recognition must be emphasized [47]. Therefore, information modules in this regard need to be provided to clinicians, health organizations, and health providers. Furthermore, since early intervention depends on the identification of novel resistant strains of microbes, it is imperative to support the development of cutting-edge technologies, laboratories, research projects, and instruments. Public-private partnerships can be introduced to facilitate the development of novel antimicrobial drugs. The legal obstacles that pharmaceutical companies face when conducting research and developing new medications may be addressed by introducing changes to the enforcement. It may be possible to support pharmaceutical companies by taking steps like streamlining regulatory approval or allocating additional funds for research [52, 53].

Establishing Checkpoints

To stop the unauthorized sale of antibiotics and the practice of self-medication, certain checkpoints should be established. The reason for this is that medications are sold in pharmacies without a prescription from a doctor. It is necessary to introduce legislation to restrict this unauthorized sale [54, 55]. Furthermore, a variety of factors, including the patient's wishes and presentation, affect the decision to prescribe antibiotics. Prescriptions should therefore be based on information rather than the preferences of the patient. It is effective for doctors to prescribe antibiotics at first consultations, but to postpone the patient's drug intake until the development of clinical symptoms. Information submitted to this network by surveillance organizations and institutions enables the surveillance and targeting of microorganisms that cause diseases linked to healthcare. Thus, it is critical to ensure the efficient execution of this network in healthcare environments such as nursing homes and hospitals. Clinicians must acknowledge the significance of conducting essential tests to identify resistant bacterial strains and resistance patterns that may have a substantial impact on patient outcomes [48].

CONCLUSIONS

Antimicrobial resistance (AMR), a significant global health issue that makes treating infections more challenging, poses a danger to the efficacy of medications. Bacterial genetic alterations or the Resistance genes acquired from other bacteria, typically via horizontal gene transfer, are the causes of AMR. These techniques allow bacteria to alter drug targets, neutralize antibiotics, or increase drug efflux, rendering treatment ineffective. AMR has several contributing components. Among the main causes are the overuse and abuse of antibiotics in veterinary and human medicine, insufficient infection control, inadequate personal cleanliness, and the use of antibiotics in agriculture to promote growth. Additionally, the problem has been made worse by the absence of new antibiotic research. To prevent AMR, coordinated preventative measures are required. Antibiotic usage in food production should be decreased, infection prevention and control (IPC) regulations should be strengthened, antimicrobial stewardship programs should be implemented to encourage the responsible use of antibiotics, and sanitation and hygiene should be improved.

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Authors Contribution

Conceptualization: AS, FURS, FH, TM, MAS, AURS
Methodology: SAL
Formal analysis: QUK, MMR
Writing review and editing: SAL, QUK, MMR, AS, FURS, FH, TM, MAS, AURS
All authors have read and agreed to the published version of the manuscript.

Conflicts of Interest

All the authors declare no conflict of interest.

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