A COMPREHENSIVE GUIDE TO ANTIMICROBIAL RESISTANCE AND ITS MECHANISM

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ABSTRACT

Antimicrobial resistance has been ranked as one of the top 10 threats to global public health by the World Health Organization (WHO). Misuse and overuse of antimicrobials are the two primary factors that contribute to the development of bacteria that are resistant to treatment with antibiotics. Inappropriate use of antibiotic therapy could result in pharmaceutical flood that ultimately destroys life itself. More and more frequently infections are being caused by microbes that previously responded well to the treatment of diseases with antimicrobial medications. Antimicrobial resistance gets worse when antibiotics are used misleadingly and when individuals fail to take precautions to prevent and control infections. There are at least 2.8 million cases of illnesses that are resistant to antibiotics every year, as stated by the Centers for Disease Control and Prevention, and as a direct result, more than 35,000 individuals lose their lives. In order to combat antimicrobial resistance at the local national and international levels coordinated initiatives and diverse collaborations are needed. Antibiotics must not be promoted unethically and methods must be put in place to prevent their excessive or inappropriate use. This review identifies different types of antimicrobial resistance and explores mechanistic insights and ways to overcome it.

Keywords: *Antimicrobial resistance, Antibiotics, Prevention, Mechanism*

1. INTRODUCTION

Antimicrobial resistance (also known as AMR) poses a significant danger to people all over the world. Antimicrobial resistance poses a danger to the wellness and development of all people across the world . Urgent action across all sectors is required if we are going to be successful in achieving the Sustainable Development Goals (SDGs). Antimicrobial resistance has been ranked as one of the top 10 threats to global public health by the World Health Organization (WHO). Misuse and overuse of antimicrobials are the two primary factors that contribute to the development of bacteria that are resistant to treatment with antibiotics. Antimicrobial resistance (AMR) happens when pathogens undergo evolutionary changes over time and cease responding to drugs. This makes it more difficult to treat illnesses and increases the risk of disease transmission, serious illness, and death[1]. Our ability to treat common diseases is still in jeopardy as a result of the introduction and spread of drug-resistant organisms that have acquired novel resistance mechanisms, which are creating antimicrobial resistance[2]. This is putting our ability to treat common diseases in jeopardy. The growth of antibiotic resistance is slowed down by using the proper antibiotics to treat infectious diseases. In modern clinical practice, molecular and PCR methods for the identification of pathogens and antibiotic susceptibility testing based on culture are the primary areas of emphasis. (AST)[3], [4].

2. ANTIMICROBIAL RESISTANCE AND INFECTIONS IN PUBLIC

Inappropriate use of antibiotic therapy could result in a pharmaceutical flood that, while temporarily cleansing and healing, ultimately destroys life itself[5]. Since resistance is the evolutionary result of the application of selection

pressure, it has been observed in all the organisms that we have designated to be the targets of biological battles, from viruses to insects[6]. However, bacterial resistance poses a particular hazard for several reasons: (a) Antibacterial drugs are more commonly abused than antifungal or antiviral ones; those that are rarely self-prescribed, inappropriately used as prophylaxis, or have agricultural applications. (b) In comparison to viruses, fungi, and protozoa, bacteria have genetic traits and capacities that permit a rapid evolution toward resistance. (c) bacteria appear to be much more abundant than viruses, fungi, and protozoa in the human microbiota, which increases the exposure of the former to antibiotics each time they are used clinically, increasing the chances that resistance will emerge and be selected. (d) Bacterial diseases are also more prevalent, at least when it comes to treatment, increasing exposure to antibacterial medications as well, probably except malaria[7]. Thus, even though microbial resistance as a whole poses serious issues for public health, not all resistance can be viewed from the same aspect[8]. The profession of medicine and public health are all at risk from antimicrobial resistance. It complicates efforts to manage infectious diseases, jeopardizes advancements in health outcomes by raising morbidity and mortality, and imposes significant financial burdens on communities[9]. More and more frequently, infections are being caused by microbes that previously responded well to the treatment of these diseases with antimicrobial medications[10]. One of the greatest discoveries of the twentieth century was the antibiotic. The onset of antimicrobial resistance, [11]however, was identified shortly after the discovery of penicillin and coincided with the release of nearly every new medication[12]. With Staphylococcus aureus, a possibly more serious issue is looming[13]. Vancomycin, a commonly used last resort medication, is becoming less effective against strains that are already resistant to methicillin[14]. There are many opportunities for the establishment of vancomycin-resistant strains because in many hospitals, more than 40% of Staph. aureus infections are methicillin-resistant39[15]. At least five strains with intermediate vancomycin resistance have been documented at the start of the twenty-first century in the US and Japan40. For hospitals, other drug-resistant microorganisms are a challenge[16]. The discovery of strains that are solely sensitive to vancomycin as a result of the rise in antimicrobial resistance has already changed the recommended empirical therapy of meningitis in children to include vancomycin. Antimicrobial resistance has not just affected bacteria; it is also a serious public health concern for fungi like Candida, viruses like HIV, and parasites such as malaria[17]. Even though newer antibacterial medications are introduced, their application will put these strains under selective pressure to arise or become resistant[18]. Antimicrobial resistance is probably going to be a big issue in the twenty-first century[19].

2.1 Antimicrobial drug resistance: causes and factors

One cannot generalize about the susceptibility or resistance of bacteria to antibiotics. Resistance levels within related bacterial families can differ significantly. In general, the following list of causes contributes to rising resistance levels: Contributing factors include the prevalence of co-morbidities among hospitalized patients, the use of more invasive devices and catheters, insufficient antimicrobial use for prevention and management of infection, noncompliance with infection-control practices, extended hospital stays, clustering of colonized patients in long-term care facilities, and more frequent and longer stays in the intensive care unit[20]. The following elements contribute to the spread of antibiotic resistance:

- The collection of microorganisms that, in response to some form of selection pressure (antibiotic usage, for example), develop resistance mechanisms on their own or another source.
- The rate at which these resistant organisms are being brought in from the community and used in clinical settings and,
- The rate of spreading from one individual to another.

Controlling the spread of organisms that are resistant to antibiotics in healthcare settings necessitates taking into account each of these aspects[21]. Antibiotic overuse in outpatient settings, as well as its usage in agriculture and animal husbandry, are major contributors to the rise in community-acquired antimicrobial resistance[8], [13]

3. MECHANISM OF ACTION OF ANTIMICROBIAL AGENTS

The modes of action of antimicrobial drugs can be further classified according to the structure of the bacterium or the function that is affected. These include:

- Suppression of cell wall formation.
- Preventing the formation of RNA and DNA
- Suppression of folate metabolism
- Impairment of cellular membrane function

Table-1: Antimicrobial agents with its effect on bacteria

Antimicrobial agent	**Effect on bacteria**	**Mode of action in general**
Carbapenams	Kills bacteria	Inhibition of cell wall synthesis
Polypeptide antibiotics	Kills bacteria	Inhibition of cell wall synthesis
Penicillins	Kills bacteria	Inhibition of cell wall synthesis
Cephalosporins	Kills bacteria	Inhibition of cell wall synthesis
Metronidazole	Kills bacteria	Inhibits DNA synthesis
Quinolones	Kills bacteria	Inhibits DNA synthesis
Rifamycins	Kills bacteria	Inhibitions of RNA transcription
Aminoglycosides	Kills bacteria	Protein synthesis is inhibited
Lincosamides	Kills bacteria	Protein synthesis is inhibited
Tetracyclines	Stops bacterial growth	Protein synthesis is inhibited
Chloramphenicol	Stops bacterial growth	Protein synthesis is inhibited
Macrolides	Stops bacterial growth	Protein synthesis is inhibited
Sulfonamides	Stops bacterial growth	Competitive inhibition

[22]

The two ways that resistance can be described are Natural resistance and Acquired resistance[23].

3.1 Natural resistance:

Natural resistance can be induced or intrinsic. According to certain definitions of intrinsic resistance, it is a characteristic that all members of a bacterial species share, is unaffected by prior antibiotic exposure, and is unconnected to horizontal gene transfer [24]–[26]Common bacterial mechanisms that contribute to intrinsic resistance include naturally existing efflux pumps and decreased outer membrane permeability (most notably induced by lipopolysaccharide, or LPS, in gram-negative bacteria). Several drug efflux pumps are a common contributor to induced resistance. [25], [26].

3.2 Acquired resistance :

Horizontal gene transfer (HGT) refers to the processes through which bacteria acquire genetic material from other organisms, and it includes transformation, transposition, and conjugation. The duration of the purchase is flexible. Resistance genes are often acquired by plasmid-mediated transmission, while bacteriophage-borne transfer is rather rare. The Acinetobacter species are among the naturally competent bacteria that may acquire genetic material from their surroundings. Internal gene transfer via integrins and insertion sequences is a common mechanism for bacterial adaptation to environmental stresses (starvation, UV radiation, toxins, etc). (substitutions, deletions, etc.). Most bacterial mutations are lethal, happening at a rate of around once per 10^6 to 10^9 cell divisions[27], [28]. Most mutations that cause antimicrobial resistance occur in genes for drug targets, drug transporters, regulators of drug transporters, and antibiotic-modifying enzymes[29], [30].

4. GENERAL ANTIMICROBIAL RESISTANCE MECHANISM

Mechanisms of antimicrobial resistance can be categorized into four major groups: (1) reduced uptake of the drug; (2) modifying a drug target; (3) inactivating a drug; and (4) active drug efflux. Drug target modification, inactivation of drug, and efflux of drug are examples of acquired resistance mechanisms while restricting uptake, drug inactivation, and drug efflux are examples of intrinsic resistance mechanisms. The types of methods employed by gram-positive bacteria as opposed to gram-negative bacteria vary due to structural variances, among other factors[31]. Gram-positive bacteria are less likely to use restricting the uptake of medicine because they lack an LPS outer membrane and the ability for some types of drug efflux mechanisms (more on drug efflux pumps later)[32]. All four of these fundamental strategies are utilised by Gram-negative bacteria.[30]

4.1 Resistance to b-Lactam Antibiotics

Antibacterial medications that include a beta-lactam ring are known as b-Lactams, and they include penicillins, cephalosporins, carbapenems, oxazepam, and cephamycins. The b-lactam ring is crucial for the action of these antibiotics, which represses a class of transpeptidases responsible for the last cross-linking processes in peptidoglycan formation in bacteria. These antibiotics' efficiency depends on their capacity to attach to intact penicillin-binding proteins (PBPs) and to penetrate those proteins . The b-lactamases significantly increase the antibiotic resistance of their bacterial hosts by emulsifying the amide bond of the b-lactam ring, which has four members. Antibiotic resistance in bacteria can arise in one of three ways: Gram-negative bacteria can acquire resistance to b-lactam antibiotics in a few different ways: by making b-lactamase enzymes, by using cell wall transpeptidases that are resistant to b-lactams, or by employing efflux pumps [33].

4.2 Tetracycline Resistance

Because of their widespread use in both human and animal medicine and also their less cost, low toxicity, and wide spectrum of activity, tetracyclines are a staple of the healthcare systems of many low-income countries. In the 1940s, tetracyclines were found. By blocking aminoacyl-tRNA from binding to the ribosomal acceptor (A) site, they hinder protein synthesis. According to Roberts (1996), the three mechanisms of antibiotic efflux, ribosome protection, and antibiotic modification are the key ways that these agents become resistant to them. Numerous microorganisms harbor these tetracycline resistance genes [8]. Certain Different strains of bacteria have different levels of innate resistance to tetracyclines because of differences in cell membrane permeability ; this is another reason why innate mechanisms exist. Gram-negative bacteria, for instance, natively resist several antibiotics due to the existence of an outer membrane layer that contains lipopolysaccharide[34].

4.3 Chloramphenicol Resistance

The peptidyl transferase stage of protein synthesis is blocked by chloramphenicol by binding to its 50S ribosomal subunit. Chloramphenicol resistance is typically brought on by a chloramphenicol acetyltransferase that renders the antibiotic inactive. Both gram-negative and gram-positive bacteria possess the cat gene family, and its products are diverse enzymes with little sequence similarities [35]. Resistance in gram-negative bacteria can be caused by several mechanisms, including a reduction in the permeability of the outer membrane or active efflux [8]

4.4 Aminoglycoside Resistance

The aminoglycoside class of antibiotics is notable for its antibacterial activity across a wide range of bacteria and its structural hallmark, an aminocyclitol ring linked to amino sugars. Common antibiotics include streptomycin, kanamycin, gentamicin, tobramicin, and amikacin. Diseases caused by both gram-positive and gram-negative bacteria are commonly treated with them. Several bacteria have evolved resistance to aminoglycosides including gentamicin, tobramycin, amikacin, and streptomycin, and even more than 50 aminoglycoside-modifying enzymes have been discovered[36]. Most of these genes are only found in gram-negative bacteria. Several processes contribute to bacterial resistance to aminoglycoside antibiotics, including the development of a permeability barrier, alteration of the target site, and enzymatic inactivation of the drug. Based on the nature of the change they undergo, these enzymes fall into one of three categories. Aminoglycoside phosphotransferases (AGP), aminoglycoside acetyltransferases (AAC), and aminoglycoside adenyltransferases (ANT) (APH) Antimicrobial resistance mechanisms, Handbook of Clinical Microbiology[37]Aminoglycosides that have had their amino groups transferred

by AAC enzymes or their hydroxyl groups transferred by ANT or APH enzymes do not halt protein synthesis [8]. Aminoglycoside-modifying enzymes have been described in addition to efflux systems and rRNA mutations[38]

4.5 Quinoline resistance

Antimicrobials called quinolones are synthetic and often utilized in clinical practice. With increased clinical use, resistance developed and spread widely among some bacterial infections. Two types of mutations and the acquisition of genes that give resistance are examples of resistance-inducing mechanisms. Mutations that reduce drug binding to the enzyme-DNA complex are common in DNA topoisomerase IV (TpoIV) and DNA gyrase (GyrA and ParE, respectively). Other resistance mutations occur in the regulatory genes that control the production of membrane-bound native efflux pumps in bacteria (s). There is a wide range of substrate specificities for these pumps, including quinolones, other antimicrobials, disinfectants, and dyes. Both types of mutations can accumulate under intense selective pressure, producing very hardy offspring. Low-level resistance can be conferred via plasmid-obtained resistance genes, facilitating the selection of mutated high-level resistance[39]. Plasmid-encoded resistance can be attributed to a variety of mechanisms, including mobile efflux pumps, a single mutant aminoglycoside-modifying enzyme that alters particular quinolones, and Qnr proteins that protect the target enzymes from quinolone action. These methods are frequently found in plasmids, which can also transfer multidrug resistance, including quinolone resistance, and additional antimicrobial resistance result, there is a wide variety of bacterial quinolone-resistance weapons[40].

4.6 Lincosamide , Streptogramin and Macrolide Resistance

Antibiotics with the MLS structure are novel compounds that block protein synthesis in bacteria. Gram-negative bacilli naturally resist MLSB (including streptogramin B) antibiotics due to a limited permeability of their outer membrane to these hydrophobic compounds[8]. Methylation of rRNA (target modification), active efflux, and enzymatic inactivation are the main mechanisms connected to resistance to macrolides, lincosamides, and streptogramin B (MLSB) antibiotics. Currently, 92 genes have been identified that contribute to resistance to MLSB antibiotics. The most common genes, erm, which code for rRNA methylases, cause the target alteration of these antibacterial medicines. Around 42 different erm genes have been identified, and bacteria carrying them display cross-resistance to all of these antimicrobial medicines[13], [41].

4.7 Drug resistance to TB

Infections like tuberculosis can be avoided, treated, and even cured. The predicted number of tuberculosis cases and deaths in 2020, however, was 9.9 million and 1.5 million, respectively. Tuberculosis is second only to COVID-19 in terms of mortality due to a single infectious pathogen[42]. Rifampicin, an essential first-line treatment for tuberculosis, was resistant in nearly 500,000 people who contracted the disease in 2019. Rifampicin resistance may be evident at the time of the disease's onset or may develop as a result of insufficient therapy as the illness progresses[43] Rifampicin-resistant TB is responsible for about 25% of antimicrobial resistance-related deaths worldwide. [44], [45]

Similar to how drug-susceptible TB spreads, drug-resistant TB (DR TB) does as well. One individual can infect another with TB by breathing infected air. When a person with lung or throat TB coughs, sneezes, talks, or even sings, the germs are discharged into the air and can infect others. These germs could infect surrounding individuals through inhalation. In those who do not take their TB medications consistently, drug-resistant TB is more prevalent. Avoid utilizing all of their TB medications. become ill with TB disease once more after receiving prior treatment origins from regions where drug-resistant TB is widespread have interacted with a patient with a drug-resistant form of TB.

4.7.1 Types of Drug-Resistant TB

MDR TB occurs when tuberculosis germs are immune to several anti-TB drugs, including the two most successful ones: isoniazid and rifampin. The first stage of tuberculosis drug resistance is called pre-XDR TB. The pre-extensively drug-resistant type of tuberculosis (pre-XDR TB) is caused by bacteria that have become resistant to isoniazid, rifampin, and a fluoroquinolone OR by bacteria that have become resistant to isoniazid, rifampin, and a second-line injectable drug (amikacin, capreomycin, and kanamycin). Extremely drug-resistant tuberculosis (XDR TB) is a subset of MDR-TB caused by tuberculosis bacteria that are resistant to multiple drugs, including first- and

second-line injectable antibiotics amikacin and capreomycin, as well as third- and fourth-line oral antibiotics isoniazid and rifampin, and fluoroquinolones.

Table-2: Types of drug-resistant TB

Types of resistance	**Resistance drug**
Multidrug-Resistant TB (MDR TB)	at least isoniazid and rifampin
Drug-Resistant Tuberculosis in its Early Stages (pre-XDR TB)	either by bacteria that are resistant to isoniazid, rifampin, and a fluoroquinolone OR by bacteria that are resistant to isoniazid, rifampin, and a second-line injectable antibiotic (amikacin, capreomycin, and kanamycin).
Large-scale drug-resistance in tuberculosis (XDR TB)	Resistant to isoniazid and rifampin, plus any fluoroquinolone and at least one of the three second-line injectables (amikacin, capreomycin, or kanamycin).

Source: [46]

4.8 Drug resistance to Malaria

One of the greatest threats to humankind over the ages has continuously been malaria. This parasitic disease is still widespread over the world at the start of the twenty-first century and is responsible for major morbidity and mortality[47]. A possible 600 million instances, with far over 2 million fatalities from human malaria are caused each year by Plasmodium falciparum, one of the four most deadly species. Despite widespread belief that the other three species (P. vivax, P. ovale, and P. malariae) are harmless, they nonetheless contribute significantly to yearly morbidity rates; P. vivax alone is responsible for an expected 400 million instances[48].The impact of malaria is most obvious in sub-Saharan Africa, where it causes more than 90% of all malaria-related deaths worldwide [44], [49], primarily in young children under the age of five[50]. Resistance to antimalarial medications is developed and spread as a result of numerous reasons. The many antimalarial medications can be effective against a variety of parasites that cause malaria[51]. Although antimalarial drugs are not mutagenic, it is presumed that resistance-inducing gene alterations occur naturally regardless of pharmaceutical influence [52]. These genetic occurrences include gene mutations or copy number changes in genes that code for the drug's parasite target or are connected to it, as well as changes to proteins that regulate drug concentrations inside parasites [8].

Evidence suggests that some types of vectors may aid in the spread of drug-resistant parasites. Anopheles Stephens and Anopheles dirus, two crucial malarial vectors in Southeast Asia, seem to be more vulnerable to parasites that are drug-resistant than those that are drug-sensitive [53]. Despite fairly comparable pharmacological pressure and human populations settings, pockets of chloroquine sensitivity may still exist around the globe, which could partially explain this [54]. The discovery that resistance to chloroquine arose from many places whose common denominator was the long-term use of this medicine for either prophylaxis or therapy highlights circumstantial evidence for its special involvement in the development of resistance [55]. If two drugs are chemically closely related, developing resistance to one may make it easier to acquire resistance to the other. Cross-resistance has been extensively discussed, especially concerning the 4-aminoquinoline family of medications chloroquine and amodiaquine [56]. Similarly, the emergence of mefloquine resistance may also result in the emergence of quinine or halofantrine resistance. The potential drug combination chlorproguanil-dapsone (LapDap) may already be at risk because of its structural resemblance to other antifolates. To solve this issue, antimalarials with novel mechanisms of action must be created. A parasite can become resistant to a malaria drug with a single-point mutation. However, more complex genomic changes involving sequential mutations might be required for some medications.[8]

Table-3: Parasitic Antimalarial drug resistance

Organism	**Drug-resistant to**	**Gene involved**
P.falciparum	Chloroquine	Pfcrt,Pfmdr 1
	Mefloquine	Pfmdr 1

	Sulfadoxine	dhps
	Pyrimethamine	dhfr
	Atovaquone	cyb
P.vivax	Pyrimethamine	dhfr
	Chloroquine	unknown

4.9 Antifungal resistance

Mycoses, diseases associated with fungi, affect more than one billion people annually, although their contribution to the global disease burden is largely underappreciated [57]. According to reports, 1.7 million mortality from fungi infections occurred in 2020 [58]. Given the rising increase in fungus infections, medical professionals face a great challenge when selecting anti-fungal treatments[59]. This increase is closely related to the growth in immunocompromised individuals brought on by modifications in clinical settings, including the use of strong immunosuppressant medications and extensive chemotherapy [60]. A serious problem for global public health is resistance to traditional antifungal medications [61]. Some fungi are unaffected by antifungals[62]. They already have a variety of antibiotic resistance built in. This is referred to as inherent or intrinsic resistance[63]. Fungal pathogens can become resistant to common treatments for a variety of causes, which is referred to as acquired resistance. The availability of therapeutic options is significantly constrained by the development of antifungal resistance. Additionally, studies have indicated that when a fungal disease becomes resistant to one class of antifungals, the other options may also be less effective[64]. Several types of fungi have become immune to common antifungal drugs, although some have evolved resistance. They are aspergillus and several Candida species[65]. The new species Candida auris is highly infectious in healthcare settings and resistant to antifungal drugs[66]All antifungal classes have three basic mechanisms that microorganisms exploit to counteract the fungicidal or fungistatic effects of the drugs: (i) lowering the drug's concentration inside the fungus cell; (ii) lowering its the ability to bond with its intended target; and (iii) modifying metabolic processes to counteract the drug's side effects. Since 2017, two species of Candida—Candida auris and Candida glabrata—have become more resistant to several antifungal medications[65]. The only two first-line nanotherapeutic medications for invasive candidiasis that have been reported to be effective against these two species are fluconazole and antifungal medications of the echinocandin class [67]. Amphotericin B (a polyene), which is only effective against a small percentage (3–10%) of C. aureus isolates from patients, is not effective against these isolates [68]. These C. aureus isolates fall under the XDR (extreme drug resistance) category because they are resistant to at least one agent from each of the three drug classes [67]. Aspergillus species causing invasive, chronic, and allergic aspergillosis can also show multidrug resistance, which is defined as an isolate that is resistant to at least one agent in two different families of antifungal drugs. [60]. Many A. fumigates isolates can show pan-azole resistance and are triazole-resistant. Itraconazole and isavuconazole are two oral azole medications that A. niger is resistant to. Amphotericin B can't kill A. terreus and A. nidulans [68]. Therefore, identification and analysis of resistant Aspergillus species are essential for the proper management of aspergillosis patients[69].

4.10 Antiviral resistance

Those who use antivirals for long durations to treat chronic viral infections like HIV, genital herpes, hepatitis B, or hepatitis C are more prone to acquire resistance to these drugs[70]. Those whose immune systems have been compromised due to autoimmune illnesses, organ transplants, or cancer therapies like chemotherapy are also at an increased risk of developing antiviral resistance[71]. Antiviral medications help lower viral loads, but the virus is still there. If antiviral treatment is not taken as prescribed, the virus may return. Over time, the virus's genetic composition might shift (change). As a virus evolves, antiviral drugs become ineffective because they cannot recognise the new virus strain[72] . When a virus evolves resistance to therapy, it can spread unchecked regardless of how aggressively it is combatted[73]. There are occasions when a virus suddenly stops responding to treatments that were successful in the past. This effect is referred to as spontaneous resistance[74], [75].

When a person contracts HIV, the virus starts to grow inside their body. HIV may morph into several strains as it develops. Certain HIV mutations can lead to drug-resistant HIV when anti-HIV drugs are used. Antiretroviral drugs that were formerly efficient in controlling the virus in humans have become useless because of the development of drug resistance. HIV therapy may fail if drug resistance is present. Drug-resistant HIV can be passed from patient to patient. (called transmitted resistance)[76].

AIDS, hepatitis B and C, herpes, influenza, and other human viral infections have all been associated with antiviral drug resistance to date. Similarly, exposing animal reservoirs to environmental waters that contain antiviral medications could hasten the development of antiviral drug resistance. For instance, numerous studies have raised concerns about the possibility of anti-influenza drug resistance in the population of waterfowl, which are regarded as the virus's natural reservoirs. Ducks and other waterfowl may consume anti-influenza medications and metabolites in ambient waterways during an influenza epidemic. Oseltamivir carboxylate, the active metabolite of oseltamivir (Tamiflu), was detected in river water at concentrations as high as 864.8 ng/L6 during the previous pandemic of novel influenza in Japan. This is significantly higher than the concentration that inhibits 50% of in vitro growth (IC50) of influenza-A virus (97210 ng/L). In a pandemic with the widespread use of antiviral medications, this shows that contaminated natural waterways could start antiviral selective pressure in animal reservoirs. In the same way that COVID-19 may acquire drug resistance in its animal reservoirs by interaction with contaminated surface waters, SARS-CoV-2 can do the same thing in its reservoirs (which include bats and pangolins)10(Kumar et al., 2020).

5. ANTIMICROBIAL RESISTANCE PREVENTION AND CONTROL

Misleading or excessive use of antibiotics, as well as a lack of infection prevention and control measures, contribute to the spread of antibiotic resistance. Measures can be undertaken at every level of society to mitigate impacts and halt the spreading of resistance. The following are some things people may do to prevent or lessen the spread of antibiotic resistance: Antibiotics should only be taken if your doctor says to. If your doctor says you don't need antibiotics, don't request them. Never share or use antibiotics that have been left over. Policymakers can halt and delay the spread of antibiotic resistance by ensuring a robust national action plan to deal with the issue. Increase the monitoring of infections that are resistant to antibiotics. Antibiotic resistance may be prevented and managed by healthcare practitioners by: washing their hands and sanitizing their equipment, Antibiotics will only be prescribed and administered when absolutely necessary, in accordance with standard practice. Infections that are resistant to antibiotics must be reported to monitoring groups.

5.1 Antibiotic stewardship

Each year, there are a minimum of least 2.8 million antibiotic-resistant illnesses, and over 35,000 deaths occur as a direct result of these infections, as reported by the Centers for Disease Control and Prevention. Well over 3 million infections and 48,000 fatalities are accounted for when Clostridioides difficile (a bacteria that can cause lethal diarrhoea and is connected with antibiotic usage) is factored in. Antibiotic stewardship programmes are essential to promoting effective antibiotic prescribing practises and lowering antibiotic resistance, both of which are crucial to optimising antibiotic usage and ensuring patient safety. Thus, The Joint Commission revised Standard MM.09.01.01 to reflect changes in federal rules and modern suggestions from scientific and professional groups [78], [79].

Antibiotic stewardship programs are essential in fighting the rising tide of antibiotic-resistant infections because they encourage responsible use of antibiotics. [78], [80]. Antibiotic stewardship programmes aim to improve how antibiotics are prescribed. Antibiotic usage measurement in hospitals is an important initial step in finding areas for optimising antibiotic prescribing and gauging the success of antibiotic stewardship initiatives. The National Healthcare Safety Network's Antimicrobial Usage Option encourages hospitals to electronically submit antibiotic use statistics so that they may compare their rates to those of other facilities throughout the country.[78], [80], [81] Strategies such as preauthorization for specific antibiotics and prospective review and feedback are effective interventions to improve antibiotic use. These strategies can be adapted to the level of expertise of the antibiotic stewardship program team and the complexity of the organization[78], [80]–[82] Also, improving prescribing

procedures by offering recommendations for antibiotic selection and length of therapy, evidence-based criteria for the diagnosis and treatment of the hospital's most prevalent reasons for antibiotic usage may be developed and implemented.[78], [80], [81], [83] There is no impact on practise from the implementation of evidence-based guidelines unless organisations track how well doctors are following the rules and give feedback. [83], [84]. Hospital administration and doctors may learn more about the effectiveness of their antibiotic stewardship initiatives by analysing the data collected from these initiatives.[78], [80]The antibiotic stewardship programme may use one of the following approaches to antibiotic prescription optimization: Preauthorization for the use of certain antibiotics, followed by an in-house evaluation and endorsement; Antibiotic stewardship programme member prospectively reviews antibiotic prescribing procedures, such as how to handle positive blood culture results, and provides comments. [79].

6. CONCLUSION

Antibiotic resistance (ABR) has become a major public health issue in the 21st-century Modern medicine, animal health, and food security are all under threat from a global public health crisis. Our ability to treat typical infections is being challenged by new global resistance mechanisms. Animal and agricultural antibacterial use increases microbial selective pressure. ABR's impact is difficult to assess in some locations because increased surveillance involves personnel, equipment, and financial resources that are not always available. However, ABR has a global economic and patient impact. Most doctors know about antimicrobial resistance but often fail to recognize it in their hospitals and give medicines improperly. To combat AMR at the local, national, and worldwide levels, coordinated initiatives and diverse collaborations are needed. To better govern the use and sale of antibiotics for both humans and animals, strong political commitment can play a crucial role in the formulation of legislation, implementation, and ongoing educational updates. Antibiotics must not be promoted unethically, and methods must be put in place to prevent their excessive or inappropriate use.

7. CONFLICT OF INTEREST:

The authors declare no conflict of interest.

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