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ANTIMICROBIAL RESISTANCE: AN INCREASINGLY GRAVE THREAT TO GLOBAL PUBLIC HEALTH

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ABSTRACT

Antibiotics are one of the most significant discoveries of the 20th century, saving millions of lives from infectious diseases. Antibiotic use and misuse have led to the development of acquired antimicrobial resistance (AMR) in microbes. Human-tohuman contact, both within and outside of healthcare facilities, is the main way that AMR is acquired and spread. Through a variety of drug-resistance mechanisms, AMR is governed by a vast array of interrelated healthcare and agricultural factors. Unrestricted use of antimicrobials in animal feed has significantly contributed to the emergence and spread of AMR. Antimicrobial-resistant bacteria have reached an alarmingly high prevalence worldwide, posing a latent pandemic threat to global public health and needing immediate action. There are few treatment options for illnesses brought on by bacteria that are resistant to antibiotics, which leads to high morbidity and fatality rates and substantial financial costs. The lack of new, innovative antimicrobials to treat infections caused by resistant microorganisms that are lifethreatening contrasts sharply with the demand for them. There is a lack of new antimicrobials available to treat life-threatening illnesses caused by resistant microorganisms, despite high demand. To contain AMR, immediate actions include surveillance and monitoring, reducing the use of over the counter and food-animal antibiotics, providing inexpensive medications, vaccinations, and diagnostics, and enforcing legislation. If coordinated cooperation is not urgently needed within and across numerous national and international agencies, a post antibiotic future may become more likely than a 21st-century catastrophic nightmare. The causes and contributing factors to microbial resistance, as well as important tactics to counteract antimicrobial resistance, are highlighted in this narrative review.

KEYWORDS: antibiotics; antimicrobial resistance; mechanisms of resistance; drivers of resistance; measures to combat resistance.

1. INTRODUCTION

Antibiotics are regarded as the most amazing medical advancement of the 20th century and are the "magic bullets" for combating bacteria. Millions of lives are still saved from bacterial diseases thanks to the development of antibiotics, which has altered the paradigm of treatment. Antibiotics have been a boon to humanity, serving not only therapeutic functions but also as preventive measures in animal husbandry and industry in underdeveloped and emerging countries for decades.[1] Microorganisms have acquired antimicrobial resistance (AMR) because of their growing use and abuse. The ability of bacteria, viruses, fungi, and parasites to survive and proliferate in the presence of medications intended to eradicate them is known as the phenomenon of antimicrobial resistance. In addition to being challenging to cure, infections brought on by organisms resistant to antibiotics always have a higher risk of serious disease or even death. Antimicrobial agents include antibiotics, antifungals, antivirals, disinfectants, and food preservatives, all of which either suppress or kill microorganism development and multiplication. Antibiotics are the most often used antimicrobials, targeting bacterial illnesses and resistance. All species exhibit AMR, an inevitable evolutionary phenomenon, through the development of genetic changes to protect against the deadly selection pressure. Bacteria try to become resistant to antibacterial medications to survive the pressures of environmental selection, making these medications useless.[2] Antibiotic use, particularly in developing countries, increases the risk of bacteria acquiring AMR, leading to greater morbidity and mortality rates.[3-5] The 21st century has seen an unexpected rise in the incidence and prevalence of antibiotic-resistant bacterial illnesses, which pose a silent pandemic danger to global public health and call for immediate interventions.[6] Antibiotic resistance can occur in any country and impact anyone, regardless of age or gender. Currently, AMR poses a significant danger to both global health and food security.[7] Numerous interconnected elements pertaining to agriculture and healthcare have an impact on the development and spread of AMR at the same time. Furthermore, it can be influenced by trade, finance, improper waste management, and medications, making AMR one of the most complex public health issues in the world.[8] The problem of drug-resistance pathogens has reached a serious and concerning level due to the quick global spread of "superbugs," which are germs resistant to the majority of known antimicrobials. The World Health Organization (WHO) has recognized AMR as one of the top three dangers to public health. After cardiovascular disorders, antibiotic-resistant infections are the third most common cause of death.[9] According to a January 2022 study, antimicrobial-resistant infections caused an estimated 1.27 million fatalities in 2019, whereas drug-resistant illnesses contributed to over 5 million deaths. By 2050, this figure is expected to reach 10,000,000 annually, surpassing cancer-related mortality.[10] Methicillin-resistant Staphylococcus aureus (MRSA), a well-known example of the first "superbug," is linked to a high global death toll from antibiotic-resistant illnesses.[11] MDR-TB (multidrug-resistant tuberculosis) affects 3.5% of active TB cases and 18% of previously treated TB cases globally. There is also an increasing worry about XDR-TB (extensively drug-resistant tuberculosis) among MDR-TB cases.[12] Despite being crucial in the fight against bacterial illnesses, antibiotics have been misused and abused for decades at improper doses and durations, which has led to selection pressure and the formation of resistant bacteria. In addition to human health, one of the main causes of AMR's introduction and spread has been the improper use of antibiotics in cattle feed in many developing nations. To reduce the prevalence of drug-resistant microorganisms, more monitoring is required to assess the effects of excessive and uncontrolled antibiotic usage in animal feed.[13] Antibiotic resistance can harm human health, affecting both treatment and prevention. The therapeutic implications include treatment failure and complications, while the preventive implications involve compromising treatment options for immunosuppressive conditions like cancer chemotherapy, advanced surgical procedures like transplantation, and invasive procedures like intubation or catheterization.[14,15] The current investment in the creation of innovative synthetic small molecules and molecules derived from natural products contrasts sharply with the growing need for novel antimicrobials to treat infections that are resistant to antibiotics and can be fatal. Based on their own justifications, pharmaceutical behemoths have given up on the development of new antibiotics and have stopped adding to their substantial stock of antibiotics since the 1980s. In 1987, fluoroquinolone was introduced to the market as part of the final class of broad-spectrum antibiotics discovered in the 1980s. Since then, development has been slow, and there are now very few new antibiotic families under development.[16] Antibiotic use is linked to the development of resistance. Avoiding needless antibiotic use can significantly reduce resistance. Antimicrobials are essential tools for treating and preventing infectious diseases. However, there has been no significant discovery of new compounds in recent decades, making it necessary to preserve the efficacy of existing ones.[17] The foundation, processes, and contributing elements of microbial resistance are highlighted in this narrative review, along with important tactics for preventing antimicrobial resistance.

2. TIMELINE OF MAJOR ANTIBIOTIC DISCOVERY AND RESISTANCE

In 1910, Paul Ehrlich discovered salvarsan and neosalvarsan, a synthetic prodrug used to treat syphilis caused by Treponema pallidum. This marked the beginning of the modern antibiotic era. Later, bacteriologist Gerhard Domagk found prontosil, a sulfonamide prodrug, which gradually replaced salvarsan. In the 1930s, American microbiologist and biochemist Selman Waksman conducted the first systematic investigation of soil bacteria' potential to produce antibiotic chemicals. He discovered antibiotics in soil from filamentous actinomycetes, including streptomycin, which is commonly used against tuberculosis. He defined antibiotics as "a compound made by a microbe to destroy other microbes". Sir Alexander Fleming, a Scottish physician and microbiologist, developed penicillin from a mold called Penicillium rubens in 1928, marking the beginning of the golden era of antibiotic research, which lasted until the mid-1950s. The period from the 1940s to the 1960s is known as the "Golden Age" of antibiotic discovery, and the majority of antibiotics that are still in use today were discovered during this time. Since then, antibiotic development has gradually declined, along with the growth of drug-resistant bacteria. Bacterial resistance to antibiotics has been known virtually since the beginning of the antibiotic era.[16] The first penicillin-resistant strain of Staphylococcus was identified several years prior to the 1940 launch of penicillin as a medication. Surprisingly, a methicillin-resistant strain of Staphylococcus bacteria was discovered in 1960, just one year after methicillin, the first semisynthetic penicillinaseresistant penicillin, was produced in 1959.[18] Vancomycin, a glycopeptide, was introduced in 1958 to treat infections caused by methicillin-resistant Staphylococci. However, in 1979, resistant strains of coagulase-negative Staphylococci (CoNS) were reported, followed by vancomycin-resistant Enterococcus (VRE) ten years later. Vancomycin's efficacy decreased for S. aureus, leading to the emergence of vancomycinintermediate Staphylococcus aureus (VISA) and vancomycin-resistant Staphylococcus aureus (VRSA) in 1997 and 2002.[19] A β-lactam antibiotic called cephalosporin was discovered in 1945 and used in clinical settings to treat cases of penicillin resistance in 1964. Since then, multiple generations of cephalosporins have been developed, the fifth of which is now on the market. First of all, it was quite effective, particularly against gram-negative bacteria that produce extended beta-lactamases (ESBLs). Up until recently, every cephalosporin generation up to the fourth generation had significantly increased resistance.[20] Tetracycline, developed in 1950, is an effective antibiotic for a variety of illnesses, including gastrointestinal ailments. Tetracycline was found to be ineffective against Shigella strains about a decade after its discovery in 1959. In 1996, the third-generation fluoroquinolone levofloxacin was introduced to the list of medicines, and the same year, reports of levofloxacin-resistant Pneumococcus were made.[21] It is clear from the timeline of antibiotic discovery that the pharmaceutical industry only created new classes of antibiotics for two decades, from 1960 to 1980. After that, the rate of discovery drastically decreased until recently.[17]

3. SUPERBUGS

Superbugs are bacteria and fungi that defy antimicrobial treatments, including multidrug- or pan-drug-resistant strains. In actuality, superbug infections have few or no treatment options. The acronym "ESKAPE" refers to six highly drug-resistant bacteria: Enterobacterales, Staphylococcus aureus, Klebsiella pneumoniae, Acinetobacter baumannii, Pseudomonas aeruginosa, and Enterobacter. It also includes carbapenemresistant enterobacterales (CRE), carbapenem-resistant Klebsiella pneumoniae (CRKP), methicillinresistant Staphylococcus aureus (MRSA), ESBL-producing enterobacterales, and vancomycin-resistant Enterococcus.Multidrug-resistant bacteria have arisen as a result of the long-term and widespread use of antibiotics to treat diseases caused by them. For example, M. tuberculosis has evolved into MDRTB after decades of treatment with tubercular medicines, and it is now a prominent superbug present in both undeveloped and developing countries. Hospital-acquired infections (HAIs) can be caused by both gram-positive (e.g., Staphylococcus epidermidis, Clostridioides difficile, Streptococcus pneumoniae) and gram-negative (e.g., Burkholderia cepacia, Stenotrophomonas maltophilia, Campylobacter jejuni, Citrobacter freundii, Enterobacter spp., Haemophilus influenzae, Proteus mirabilis, Salmonella spp., and Serratia spp.)[22] Infections with superbugs lead to increased morbidity and death due to limited therapeutic options, high treatment costs, and prolonged hospital stays.[23]

4. THE BASIS OF ANTIBIOTIC RESISTANCE

The Basis of Antibiotic Resistance Bacterial resistance is an evolutionary reaction to therapeutic antibiotics. Antibiotics are initially effective against all targeted infections, but over time, bacteria acquire resistance to them. Bacteria evolve resistance to drugs by chromosomal gene mutations or horizontal gene transfer (HGT) with resistance determinants. Antibiotic resistance is caused by mutations in three types of genes: those encoding antibiotic targets, transporters, and regulators that suppress transporter expression (such as antibiotic-modifying enzymes and multidrug efflux pumps) The idea that the antibiotic-resistance gene or genes that are passed on to human pathogenic bacteria by horizontal gene transfer (HGT) originate from commensal or ambient bacteria is intriguingly supported by evidence.[24] Environmental microbes naturally produce several antibiotics, a well-known fact. To protect themselves against the action of selfsynthesized antibiotics, they must also have antibiotic-resistant genes; otherwise, they would have been killed by their own antibiotics.[25] Bacteria with antibiotic resistance may have genes from intrinsic, acquired, or adaptive sources.[26] The term "intrinsic resistance" describes the innate ability of bacteria to exhibit resistance to specific antibiotic classes because they possess their own chromosomal genes without undergoing mutation or acquiring new ones. Intrinsic resistance implies that if these bacteria are utilized to treat infections, they will inevitably develop resistance to specific antibiotics. Regarding the mechanisms underlying drug resistance, intrinsic resistance involves both efflux pumps and decreased permeability. Additionally, it frequently affects the multidrug efflux pumps.[27,28] Acquired resistance occurs when a previously sensitive bacterium gains resistance through chromosomal gene mutation or external genetic material via horizontal gene transfer (HGT). There are three major mechanisms for HGT: transformation, transposition, and conjugation. Resistance is often acquired through plasmid conjugation and can be either transient or permanent.[29,30] Adaptive resistance is a conditional trait that can be either temporary or permanent, contingent on the strength and duration of selection pressure. Bacteria can develop adaptive resistance in humans and livestock when their growth is impacted by subinhibitory antibiotic doses as well as certain environmental cues as growth hormones, nutrition, stress, pH, ion concentrations, etc. Adaptive resistance is often developed temporarily and returns to its initial state when the inciting signals are removed, in contrast to intrinsic and acquired resistance phenotypes. Adaptive resistance evolution is unclear, but factors such as high mutation rates, gene amplification, efflux pumps, biofilm formation, epigenetic inheritance, population structure, and heterogeneity have been proposed as possible explanations.[31,32]

5. SOURCES AND PATHWAYS OF AMR TRANSMISSION

AMR spreads predominantly through human-human interactions, both within and outside healthcare facilities. Humans, animals, water, and the environment have all been identified as reservoirs for antimicrobial resistance genes, which can be spread between and within these reservoirs. In terms of transmission routes, there are substantial differences between bacterial species and resistance elements.[33] Certain hotspot sources, such as wastewater and sludge from urban wastewater treatment facilities and natural fertilizers like pig slurry, cow manure, and fertilizer from chicken farming, greatly aid in the spread of bacteria resistant to antibiotics.[34] The direct pathway of acquiring antimicrobial resistance from animals is by the ingestion of animal feed containing antibiotics, which is then transferred to humans. consumption of these animals constitutes the direct route of acquisition of antimicrobial resistance from animals.[35] consumption of these animals constitutes the direct route of acquisition of antimicrobial resistance from animal's Other prevalent methods of infection include consuming feralcontaminated food or water, as well as direct contact between animals and people.[36]

6. MECHANISM OF DRUG RESISTANCE

Antimicrobials and bacteria coexist in the same ecological niche, and bacteria develop defences against the harmful effects of antibiotic molecules. There are four essential targets in a bacterial cell for antibiotics (e.g., cell wall, cell membrane, protein synthesis, and nucleic acid synthesis). Primary mechanisms for antimicrobial resistance include limiting drug uptake, altering a drug target, inactivating a drug, and increasing active drug efflux (Figure 1).

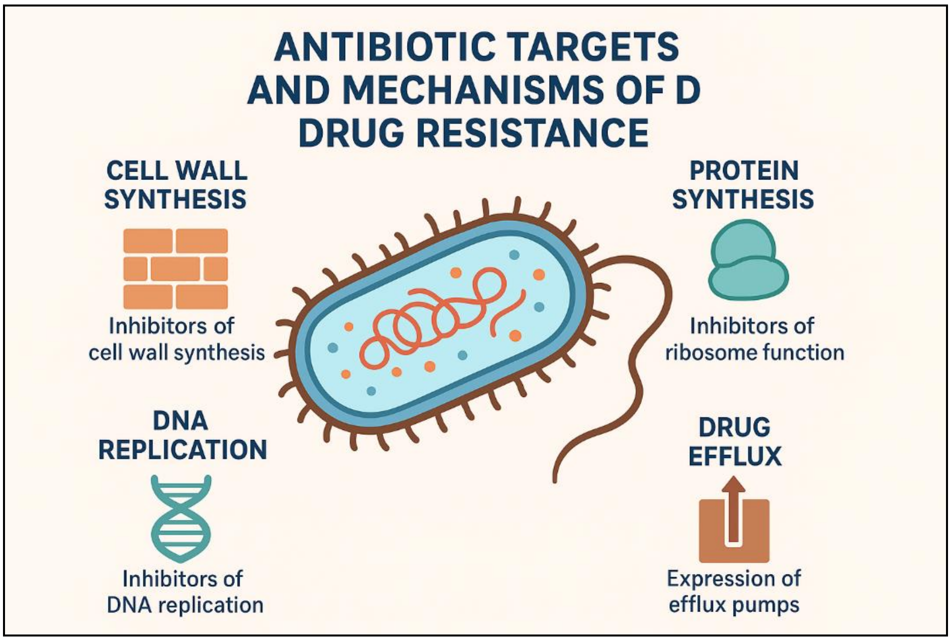

Figure 1: Antibiotic targets and mechanisms of drug resistance (created with BioRender.com (accessed on 12 November 2022)).

In general, for acquired resistance, bacteria use mechanisms such as modification of drug target, drug inactivation, and drug efflux, whereas intrinsic resistance mostly results from restricting uptake, drug inactivation, and drug efflux. Gram-positive and gram-negative bacteria differ in their structural makeup, which causes variance in their drug-resistance mechanisms. Gram-positive bacteria less frequently utilize the method of restricting uptake of a drug because they lack the lipopolysaccharide (LPS) outer membrane and have limited capacity for an efflux mechanism to certain types of drugs.[37,38] Meanwhile, gram-negative bacteria have been shown to use all four main mechanisms of drug resistance.

6.1 Limiting Drug Uptake

Lipopolysaccharide, a highly acylated glycolipid, is a key component of gram-negative bacteria's outer membrane. It acts as a barrier to various substances, including antibiotics. This inherent resistance of gramnegative bacteria reduces permeability to certain drugs, resulting in resistance. Modifications in the permeability of outer-membrane proteins, specifically porin proteins, can result in acquired drug resistance. Porins are the main entrance site for hydrophilic antibiotics such β-lactams, fluoroquinolones, tetracyclines, and chloramphenicol. The quantity and type of porin proteins determine antibiotic entry and bacterial susceptibility.[39] Moreover, changes that affect porin expression or function may lead to acquired antibiotic resistance. When coupled with other coexisting mechanisms, like efflux pumps or the enzymatic breakdown of antibiotics, mutations that impact porin expression result in high levels of resistance.[40] Bacteria such as Enterococcus faecalis, Staphylococcus aureus, Staphylococcus epidermidis, Streptococcus viridian's, E. coli, Klebsiella pneumoniae, Proteus mirabilis, and Pseudomonas aeruginosa exhibit antibiotic resistance through biofilm formation. A biofilm is a collection of microbial cells immersed in selfproduced exopolysaccharide that adhere to abiotic or biotic surfaces. Bacterial tolerance and resistance to antibiotics can occur through various mechanisms, including preventing drug penetration. Additionally, it may prevent antibiotic concentrations from developing up throughout the biofilm.[41,42]

6.2. Modification of Targets for Drug

The targets needed for drug binding can be altered by bacteria so that the drug either cannot bind to the altered target or binds to it poorly. The gene or genes encoding the protein that serves as the therapeutic target spontaneously mutate to produce this alteration. For example, fluoroquinolone resistance arises in both gram-positive and gramnegative bacteria when mutations affect the quinolone-resistancedetermining region (QRDR) in the DNA gyrase (topoisomerase II and topoisomerase IV).[43] Methylation is a highly effective approach for modifying targets and increasing resistance. Erm methylases act against macrolides, lacosamide's, and streptogramin B antibiotics in both grampositive and gram-negative bacteria. Methylation of the cur gene has been associated to resistance in several bacteria, such as Proteus vulgaris, Staphylococcus spp., Enterococcus spp., Bacillus spp., and E. coli.[44] Staphylococcus spp. has a reduced affinity for β-lactam antibiotics due to an alternative penicillin-binding protein expressed by Mecca and Mecca genes.[45,46]

6.3. Inactivation of Drug

Drug resistance can result from antibiotic inactivation by certain bacterial species, which can occur in one of two ways: the antibiotic is destroyed, or a chemical group is transferred to the antibiotic. Enterobacter Ales produce β-lactamases, which effectively inactivate β-lactam antibiotics. βlactamases, also known as penicillinases and cephalosporinases, inactivate the β-lactam ring structure by opening it at a precise position, making it useless to engage with the target, penicillin-binding proteins. Several enterobacterial and gram-positive bacteria, including Staphylococcus aureus, Enterococcus faecalis, and Enterococcus faecium, carry βlactamase genes passed down through horizontal gene transfer. Tetracycline is hydrolysed by an enzyme produced by the text gene in some bacteria.[47] Drug inactivation typically involves the transfer of acetyl, phosphoryl, and adenyl groups. Acetylation is the most commonly used method against aminoglycosides, chloramphenicol, streptogramins, and fluoroquinolones, whereas phosphorylation and adenylation are mostly used against aminoglycosides.[38]

6.4. Efflux of Drug

Bacteria can regulate the buildup of antibacterial substances, such as antibiotics, inside bacterial cells by means of an energy-dependent efflux pump found on the cytoplasmic membrane. Efflux pumps allow bacteria to regulate their internal environment by removing toxic substances from the cell, including metabolites, antibiotics, and quorumsensing signal molecules. Tetracycline was forced out of the bacterial cell by the first plasmid-encoded efflux pump in Escherichia coli, which was reported by researchers in 1980. Since then, a wide variety of resistant gram-positive and gram-negative bacteria with various efflux mechanisms have been discovered. Interestingly, most efflux systems use multidrug efflux mechanisms, which are invariably chromosomally encoded to guarantee inherent drug resistance in bacteria.[48] Genes for substrate-specific efflux pumps (e.g., chloramphenicol, tetracyclines, macrolides) are typically found on mobile genetic elements.[38,49] Drug efflux pumps are classified into six families based on their structure and energy source: ATP-binding cassette (ABC), major facilitator superfamily (MFS), multidrug and toxic compound extrusion (MATE), small multidrug resistance (SMR), resistance-nodulation-division (RND), and drug metabolite transporter (DMT). Gram-positive bacteria primarily use efflux pumps from the ABC and MFS families, which are encoded on chromosomal genes or plasmids. Gram-negative bacteria primarily use the RND superfamily, which includes an outer-membrane protein channel, a periplasmic protein, and a cytoplasmic membrane pump.[50]

7. DRIVERS TO AMR

Antimicrobial resistance is caused by a variety of variables, such as innate characteristics of the microorganisms and several environmental elements that affect both consumers and prescribers. Environmental (such as population density and overcrowding, rapid transmission through mass travel, poor sanitation, ineffective infection control program, and widespread agricultural use), drug-related (such as counterfeit or substandard drugs and over-the-counter availability), patient-related (such as poor compliance, poverty, lack of education, selfmedication, and misconception), and physician-related (such as inappropriate prescription, inadequate dosing, and lack of updated knowledge and training) factors are the four main categories of factors that contribute to AMR.[38,51]

Some of the recognized AMR driving factors are elaborated below:

7.1. Misuse and Overuse of Antibiotics

Antibiotic resistance is a natural process, but overuse of antibiotics in humans and animals has exacerbated it. Epidemiological studies have shown a causal association between antibiotic usage and the development of microorganism resistance.[52] Unfortunately, despite repeated warnings from health organizations, antibiotic abuse and overuse persist at a disproportionate rate globally, and the current situation appears to be irreversible.

Surveys show that many people, particularly those without education, have misunderstandings regarding antibiotics, such as their ability to treat common viral infections like colds and flu. Moreover, it has been noticed that antibiotics are a frequently recommended prescription for patient care, particularly observed in many underdeveloped nations where there is lack of effective diagnostic facilities.[53] One excellent illustration of widespread abuse is the administration of antibiotics without a clear indication. The availability of antibiotics as over the counter (OTC) medications for both human and animal usage contributes to the development and spread of drug-resistant bacteria. The absence of antibiotic policies and conventional treatment standards, which are common in underdeveloped nations, also contributes to antibiotic abuse. Furthermore, in many developing and impoverished nations, veterinarians, pharmacy dealers, and healthcare professionals frequently prescribe excessive amounts of antibiotics. Many poor countries have pharmacy merchants and veterinarians. Low-quality antibiotics in the supply chain have exacerbated AMR in many developing nations. Physicians can contribute to antimicrobial resistance by providing unnecessary antibiotic regimens or incorrect dose. Some clinicians, particularly in underdeveloped countries, may administer antibiotics without a proper indication, despite the unethical nature of the practice.[53,54]

7.2. Increase in Gross Domestic Product (GDP)

The substantial increase in antibiotic use worldwide is primarily attributed to rising GDP, particularly in many developing nations. The quality of life for individuals in low- and middle-income countries (LMICs) has significantly improved with GDP growth, and this improvement is positively correlated with higher antibiotic use. Klein et al. predict that the use of antibiotics increased by 65% worldwide between 2000 and 2015.[55] Rising GDP has led to increased intake of animal protein in developing countries, contributing to the spread of AMR through animal sources.[56]

7.3. Inappropriate Prescribing Patterns

Antibiotics that are given inappropriately play a major role in fostering AMR.[57] Inappropriate antibiotic. Antibiotic prescribing includes prescribing unnecessary antibiotics, selecting inappropriate medications, and administering incorrect doses or durations.[58] According to one study, 50% of patients received at least one antibiotic during their hospital stay without a valid reason. Prior bacterial isolation and antimicrobial susceptibility testing should ideally guide the introduction of antibiotics; however, a 2017 CDC (Centers for Disease Control and Prevention) report found that approximately one-third of hospital patients received antibiotic prescriptions without proper testing and that these prescriptions were continued for longer periods of time.[59] In nursing homes, around 75% of antibiotic prescriptions are erroneous or inappropriate, including incorrect doses and duration.[60]

7.4. Paucity in Futuristic Antibiotics

Pharmaceutical companies must respond quickly to the impending issue of antibiotic resistance by developing new, innovative antibiotics.[61] Despite the WHO's repeated calls, there has been little progress in developing new antibiotics. Surprisingly, only 8 of the 51 newly produced antibiotics may be classified as unique medications for treating illnesses caused by antibiotic-resistant bacteria; the vast majority are just reformulations of existing drugs. As a result, it is expected that these new medications will develop resistance soon. Limited treatment choices have made it difficult to manage drug-resistant tuberculosis, urinary tract infections, pneumonia, and other gram-negative diseases. Due to a lack of new medications, individuals of advanced age are more vulnerable to potentially fatal illnesses.[62]

7.5. Agricultural Use of Antibiotics

Antibiotics are increasingly being used in livestock husbandry in developing countries to meet rising demand for animal feed. As a result, it contributes to AMR by including antibiotic residues in animal-derived products (e.g., muscles, kidney, liver, fat, milk, and eggs). Antibiotics are used for many goals, such as treating animal infections, promoting growth, improving feed conversion efficiency, and preventing diseases.[63] This method, which has been a key contributor to human AMR, is more common in underdeveloped nations in order to increase revenue from food animal farms and because there are fewer regulations in place.[64] Approximately 70% of medically essential antibiotics are sold for animal usage in the US.[65]

7.6. Easy Travel Routes

There is mounting evidence that human mobility has a significant role in the emergence and global dissemination of microorganisms resistant to antibiotics. Easy and contemporary travel routes that are available to people, animals, and goods all play a major role in the global spread of AMR.[66] Travelers often unwittingly bring back antimicrobial-resistant organisms from the nations they visit. Antimicrobial resistant bacteria can remain in the body for up to 12 months following travel to endemic AMR regions, increasing the potential of transmission to vulnerable populations.[67]

7.7. Knowledge Gap

There is strong evidence that the public and healthcare professionals (HCWs) lack enough information regarding the proper use of antibiotics and the causes underlying antibiotic resistance.[68] Surveillance is necessary to evaluate the AMR burden and develop intervention options, such as antimicrobial stewardship. Unfortunately, accurate statistical data on the usage of antibiotics and the state of AMR in both the healthcare and agriculture sectors have yet to be gathered globally.[69] Critical information is provided by surveillance data, which also aids in pinpointing areas that require strategic actions to optimize results. The current information gap must be filled before effective intervention strategies can be started through collaboration from various stakeholders (such as international agencies, the human and veterinary care sectors, the agriculture and animal production businesses, and consumers).

8. CLINICAL IMPLICATIONS OF AMR

There are many clinical implications of AMR, and following are some of the major concerns[70]:

- Antimicrobial resistance makes it difficult to treat bacterial, fungal, and viral infections effectively.
- The emergence and spread of new resistant mechanisms endanger the spectrum of treatment for many common ailments, including urinary tract infections, upper respiratory tract infections, typhoid, and influenza, resulting in treatment failure, severe impairment, or even death.
- Without new medications, AMR will pose a severe threat to the effectiveness of cancer chemotherapy, transplant surgery, and even basic dental procedures.
- AMR infections necessitate long-term treatment, leading to increased healthcare expenditures and the need for costly alternative medications.

9. HOW TO COMBAT AMR

Antimicrobial resistance is a severe issue that impacts not just humans but also plants, animals, and the environment. Like humans, animals can occasionally harbour MDR bacteria, which can be spread by intimate contact or ingestion of animal products. The issue of AMR's constant growth cannot be solved by a single government agency or private group in any nation. The healthcare, pharmaceutical, agricultural, financial, trade, educational, and nongovernmental organizations at the national and international levels are just a few of the sectors that must coordinate and work together to limit and control antimicrobial resistance (AMR). There are two types of multisectoral collaboration: vertical and horizontal.[71] Physicians should stop administering broad-spectrum antibiotics for minor diseases. Veterinarians should likewise closely supervise their use of antimicrobials on animals. To address AMR, strategies include rational antibiotic prescription, limited use of prophylactic antimicrobials, patient education, adherence to antibiotic medication, and proper hospital hygiene through antimicrobial stewardship.[72] Additionally, it's critical to develop and make available quicker diagnostic technologies as well as precise antimicrobial profiling for targeted antibiotic therapy.

The World Health Assembly approved five strategic action plans to address AMR, including the following steps: Efforts to combat antimicrobial resistance include increasing awareness and understanding, conducting surveillance and research, implementing effective sanitation and hygiene measures, optimizing antimicrobial use in human and animal health, and encouraging sustainable investment in new medicines, diagnostic tools, and vaccines.[73] Below are highlights of some significant national and worldwide initiatives to combat AMR and depicted in Figure (2).

9.1. International Measures

The following are international measures that can be taken:

- Improving collaboration among international agencies, governments, nongovernmental organizations, and professional groupings.
- Establishing worldwide surveillance networks for AMR and antibiotic use.
- Increasing laboratory capability for detecting and reporting pathogens with AMR that have global health implications.
- Putting in place and enhancing global monitoring systems to enable prompt detection and control of new infections.
- International surveillance to combat counterfeit antimicrobials around the world.
- Spending money on vaccines, research, and the development of new drugs.

9.2. National Strategies

The following are national measures that can be taken:

- Putting in place an "Antibiotic policy" for the prudent use of antibiotics in medical and agricultural contexts.
- National surveillance, monitoring, and evaluation activities will be strengthened through the merging of the public health and veterinary sectors.
- Creating cutting-edge point-of-care diagnostic technologies to identify pathogens and track resistance
- Investing in basic and applied research for new antibiotics and vaccines.
- Enhancing global cooperation and developing capabilities to fight AMR.

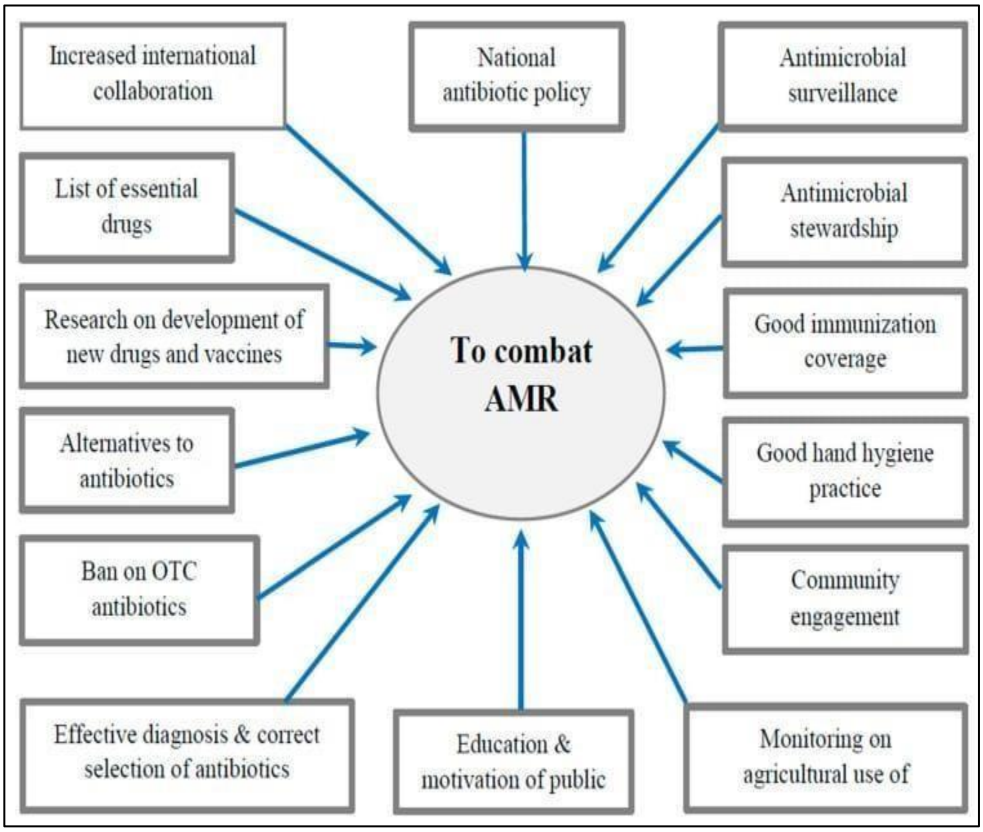

Figure 2: Major interventions to combat AMR.

9.3. Antimicrobial Stewardship Program (ASP)

Antimicrobial stewardship is a coordinated program that educates and persuades prescribers on the proper selection, dosage, and duration of antimicrobial medicines in order to improve patient outcomes and prevent germ resistance and dissemination. The initial goal of antimicrobial stewardship is to ensure that healthcare practitioners provide the most suitable antibiotic at the optimal dose and duration for each patient. The second purpose is to avoid overuse, misuse, and abuse of antimicrobials. The third goal is to maintain resistance development at a minimum in order to accomplish the main objectives of antimicrobial stewardship, there are two main overlapping strategies: (1) utilizing antibiotics to improve healthcare outcomes, and (2) using antibiotics to guarantee long-term access for everyone who requires them. The "Core Elements" of antimicrobial stewardship in accomplishing these objectives were published by the CDC in 2014. These guidelines apply to all hospitals, regardless of size, and provide particular recommendations for small and critical-access hospitals in their execution.[74,75]

9.4. Use of Antibiotics in Animals

The WHO recommended stronger regulations for using medically relevant antibiotics in animals to prevent antimicrobial resistance. It focuses on reducing and restricting antibiotic use for growth promotion and disease prevention. If other animals in the flock, herd, or fish population have been infected, antibiotics can be given to prevent disease. Alternative strategies include improving hygiene, adding probiotics or nutritional supplements to feed, increasing vaccination rates, and changing animal husbandry techniques.[76]

9.5. Development of New Drugs and Vaccines

Strategy that encompasses the development of both vaccines and novel antibiotics is crucial because of the difficulties in creating new, effective medications and the speed at which resistance to each new class of antibiotic is developing. Increased funding is needed for operational research and the development of novel antibiotics through industry and academic collaboration at the national and international levels in order to tackle AMR. Vaccines have long been used as preventative measures against infectious diseases and are seen as a crucial weapon in the fight against antimicrobial resistance (AMR) by reducing the demand for antimicrobial medications.[75]

9.6. Introduction of Checkpoints

Prevalent in some countries, particularly in underdeveloped and low-income countries areas where medications can be purchased without a doctor's prescription. Physicians should not be influenced by patients' desires when prescribing antibiotics, as this is irresponsible behaviours. To prevent the spread of AMR, it's important to implement strict controls and checkpoints.

Implementing proper legislation can help decrease illegal medicine sales, particularly for antibiotics.[58,60] *9.6. Community Engagement* waste disposal, home and animal hygiene, and health-seeking behaviours. Furthermore, it's possible that every group has its own vocabulary and viewpoints on drug resistance and the usage of antibiotics. Therefore, a community-based strategy to changing antimicrobial usage behaviour may protect current and future therapeutic options and provide improved communitylevel AMR prevention tactics. It calls for additional study on getting individuals to share their knowledge and experiences to turn these concepts into solutions to address the AMR issue.[79]

CONCLUSIONS

Antimicrobial resistance in bacteria is a constantly evolving phenomena that can be caused by either new chromosomal mutations or the acquisition of drugresistant genes through horizontal gene transfer. AMR's gradual rise over the past 20 years has significantly reduced treatment choices and prompted serious concerns for global public health. It is currently regarded as the greatest health threat of the twenty-first century. Worldwide, MDR bacteria are commonly found in a wide range of common illnesses, including TB, pulmonary, urinary, and sexually transmitted infections. The discovery and supply of new antibiotics have slowed since the 1980s, falling behind the rapid rise of AMR. The rise of multidrug-resistant bacteria and limited discovery of novel antimicrobials pose a threat to the success of antimicrobial therapy. Without worldwide action to combat AMR, a post-antibiotic period in the 21st century may become a reality rather than a distant nightmare.

Antimicrobial resistance is a global concern for human and animal health, with multiple mechanisms contributing to its spread. Antimicrobial-resistant infections are more difficult to treat, resulting in treatment failure and consequences, as well as significant financial implications for individuals and communities. Proper antibiotic administration, including optimal dosage and duration, is crucial for reducing the selective pressure that leads to the development of resistance organisms. Implementing strict infection prevention and control strategies in healthcare facilities is crucial for preventing the development of multidrug resistant bacteria.[57,58]

Combating AMR requires a more concerted and coordinated worldwide effort from all international official and nongovernmental organizations, as well as significant political momentum. Policymakers, researchers, public health practitioners, pharmaceutical corporations, hospital administrators, agricultural sector executives, and members of the public must all work together to achieve this goal. The alliance aims to reduce the health and economic burdens associated with AMR by slowing down current trends.[77-81]

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