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Antibiotic Resistance in Microbes: History, Mechanisms, Therapeutic Approaches, and Strategies for Mitigation

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Abstract

The global emergence of clinically significant antibiotic resistance is increasingly linked to the environment. Antimicrobials, metals, and biocides are just a few of the substances that are released into the environment through paths that are regulated by environmental regulators. Consequently, environmental regulators ought to be heavily involved in developing national and international antimicrobial resistance (AMR) measures. Antimicrobial compounds from pharmaceutical waste, agricultural runoff, and wastewater discharge contribute to the spread of resistance genes in natural ecosystems. However, many AMR action plans lack strategies addressing environmental reservoirs due to limited understanding of AMR pathways and pollutant-microbe interactions. Environmental regulators, such as England's Environment Agency, can help by monitoring pollutants, enforcing antimicrobial discharge regulations, and collaborating with public health and agricultural sectors. Their role should expand beyond pollution control to include research, surveillance, and risk assessment. Strengthening their involvement will enhance AMR action plans, leading to more effective global mitigation strategies. The purpose of this study is to illustrate the issue of AMR in the environment from the viewpoint of an environmental regulator by utilizing the Environment Agency, which is the regulatory body in England, as an example from which global comparisons can be made. There are some suggested thought experiments.

Keywords: Plasmid, Genes, Metals, Biocide, Antimicrobial Resistance, Antibiotics

INTRODUCTION

Microorganisms have been known for decades to acquire resistance to key therapeutic treatments, and this ability is becoming more and more obvious. Although resistance rates among different isolates vary greatly by region, they are on the rise. For instance, by 1998, the percentage of "Staphylococcus aureus" isolates resistant to methicillin had risen from almost zero 10–15 years ago to over 70% in South Korea and Japan, 40% in Belgium, 30% in the UK, and 28% in the US. In a district hospital in the United Kingdom, the expenses incurred in controlling a methicillin-resistant S. aureus epidemic surpassed considerable financial threshold. In 1995, the yearly healthcare cost of treating resistant infections in the United States was anticipated to be over $4 billion; this amount has now been updated to over $7 billion. AMR is a national security issue, especially in the US, as well as a professional and governmental one. It is not only a public health issue [1–2]. The misuse and overuse of antimicrobials significantly accelerate the development of resistance. Contributing factors include:

- Use of low-potency or counterfeit drugs

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resulting from poor manufacturing standards.

- Distribution of antimicrobials by unqualified vendors who lack knowledge of appropriate dosage, indications, and contraindications.

Addressing AMR requires multifaceted strategies and global cooperation. The problem is global in scope, as globalization has increased countries' vulnerability to imported diseases, with infectious diseases spreading faster and further than ever before. During the 1990s, a resistant *Pneumococcus* strain first identified in Spain quickly spread to numerous countries, including Argentina, Brazil, China (Taiwan), South Korea, South Africa, Thailand, and the United States. In alone, no nation can adequately safeguard its citizens against AMR. This study investigates how well national and international organizations can support a coordinated response to antimicrobial resistance. It describes methods to control resistance, assesses the effectiveness of current solutions, looks at possible international organization initiatives, and suggests ways to ensure worldwide coordinated efforts to fight AMR [3].

HISTORY OF ANTIBIOTICS

The use of antibiotics began in the 1920s with Alexander Fleming's discovery of penicillin, marking the start of the "Golden Era" of antibiotic development. Many antibiotic classes that are still in use today were discovered during this time. However, the first reports of antibiotic resistance appeared in the 1930s, not long after sulphonamides were introduced. Antibiotic-resistant bacteria have now emerged at a significantly faster rate due to the overuse and abuse of antibiotics. Resistance occurs through genetic mutations in bacterial chromosomes, which can involve substitutions, deletions, additions, inversions, or duplications of genetic material. Moreover, resistance genes can be transferred between bacteria via lateral gene transfer mechanisms, such as conjugation, transformation, and transduction. The formation of biofilms further complicates the problem by protecting bacteria from antibiotics and immune system responses. There are serious worries regarding the overuse and abuse of antibiotics due to the emergence of resistant strains, such as methicillin-resistant Staphylococcus aureus (MRSA). Antibiotic stewardship initiatives have been created in response to minimize needless prescriptions, promote the prudent use of antibiotics, and impede the emergence of resistance. Antibiotic resistance is a global health concern that the World Health Organization (WHO) has recognized and is working to stop [4–5]. Key efforts focus on:

- Promoting antibiotic stewardship.
- Developing effective vaccines.
- Discovering new antibiotics.
- Exploring alternative treatments.

Key factors contributing to antibiotic resistance:

- Overprescription and misuse.
- No new antibiotics have been developed.
- Agricultural antibiotic use.
- Genetic adaptation of bacteria.

ANTIMICROBIAL RESISTANCE CONTAINMENT TACTICS: INTERNATIONAL CO-OPERATION

Eradicating antimicrobial resistance (AMR) is neither a realistic nor desirable objective. Achieving eradication would necessitate a significant reduction in antimicrobial use, which could undermine the substantial health benefits these medications provide. Instead, the focus should be on containing resistance by striking a balance between the effective use of antimicrobials to treat infections, reduce morbidity and mortality, and prevent the immediate spread of infections, while also minimizing the emergence and spread of resistance that could lead to future health challenges. Containing resistance is a public good, as its benefits are both non-excludable (available to all) and non-rivalrous (one person's benefit does not reduce another's). Without coordinated efforts, containment will likely fall short, as individuals rely on the contributions of others. This principle holds at both the national and global levels, making AMR containment a global public good [6].

Since transmission can only occur after resistance has emerged, the primary objective is to prevent its emergence. The level at which interventions should be implemented depends on the strategy. Many are best addressed at the national level due to the diversity of local contexts, varying patterns of resistance, and the need for policies tailored to specific regions. However, certain strategies are more efficiently executed through international collective action, as AMR containment transcends borders [7].

Key strategies for containing AMR nationally, regionally, and globally include:

- *Surveillance:* Monitoring AMR trends and tracking antimicrobial use.
- *Research and Development:* Promoting innovation in new antimicrobials and alternative treatments through incentives and collaborative mechanisms.
- *Rational Use:* Ensuring the appropriate and judicious use of existing antimicrobials through education, regulation, and stewardship programs.

These strategies, when coordinated effectively, form a comprehensive approach to addressing AMR, safeguarding public health on both local and global scales.

Surveillance

Since surveillance provide the information required to detect AMR issues, monitor their progression, follow patterns of transmission, and evaluate the efficacy of interventions, it is essential to any approach aimed at managing AMR. Because of several obstacles, including the high initial cost required, especially in developing nations; the fact that the benefits of surveillance transcend national borders, which makes nations hesitant to invest without immediate returns; and the requirement for globally comparable data of sufficient quality, effective surveillance systems necessitate cooperation [8].

Multidrug-resistant tuberculosis (MDRTB) surveillance is one example of a global endeavour; however, surveillance is still very dispersed. Few nations have strong national networks, and many information systems and microbiological labs require improvement. Furthermore, no international laws require uniform data collection, categorization, or reporting. As a result, there is a deficiency in information exchange and a propensity for nations to profit from other nations' data without helping in return. Research from other fields indicates that even legal requirements do not ensure compliance; rather, compliance is contingent upon the availability of enough resources, which are frequently scarce in developing nations or are used to treat urgent health concerns. The cost of setting up surveillance systems varies according to the facilities and infrastructure that a nation already [9].

RESEARCH AND DEVELOPMENT ON NEW ANTIMICROBIAL AND OTHER THERAPIES

While knowledge is traditionally considered a public good, the substantial costs associated with research and development (R&D) have led to the use of patents to convert it into a private good. Because they provide exclusivity and enable businesses to make money off their inventions, patents encourage private sector investment. Therefore, it is essential to support private sector research and development to create treatments with reduced rates of antimicrobial resistance (AMR) or substitutes for the antimicrobial treatments that are now in use. However, balancing the need to maintain private sector investment in the discovery of novel antimicrobials with the need for policies to limit antimicrobial use which is crucial for managing resistance – is a significant problem. Many strategies to limit AMR, such as restricting antimicrobial consumption, directly threaten profitability by reducing sales volumes, which are a key driver of returns on investment [10–11]. This conflict can be addressed through compensatory policies, such as:

- Subsidizing price increases to offset reduced sales volumes.
- Granting orphan drug status to certain antimicrobial products.
- Establishing advance purchase agreements to guarantee market demand and incentivize investment.

Alternatively, AMR itself may create market opportunities. As resistance reduces the effectiveness of existing drugs, the demand for new and effective treatments could grow. But despite this promise, there hasn't been much recent investment in the discovery of novel antimicrobials. International variations in drug licensing requirements, patent laws, intellectual property restrictions, and pricing systems make the problem even more complex. Different R&D techniques can be used by businesses, which frequently prioritize items for more affluent markets. Inequitable results may result from this, since effective AMR containment in one nation may unintentionally transfer the burden to others. Reforming global patent laws and harmonizing licensing and regulatory standards. Supporting or directly undertaking R&D for antimicrobials [12–13].

Examples of multinational collaboration on diseases of global concern exist. The World Health Organization (WHO) and the World Bank, for instance, finance the Multilateral Initiative on Malaria, which organizes research on antimalarial drugs. A similar cooperative strategy might be used to address AMR, encouraging creativity and guaranteeing fair access to novel treatments everywhere [14].

DRIVERS TO AMR

A variety of variables, including innate characteristics of the microorganisms and several environmental elements affecting both prescribers and consumers, contribute to antimicrobial resistance. Environmental factors (like overcrowding and population growth, rapid spread through mass travel, poor sanitation, ineffective infection control programs, and widespread agricultural use), drug-related factors (like counterfeit or substandard drugs and over-the-counter availability), patient-related factors (like poor compliance, poverty, lack of education, self-medication, and misconception), and physician-related factors (like inappropriate prescription, inadequate dosing, and lack of updated knowledge and training) are the four main categories of factors that contribute to Advanced Multiplication Risk (AMR) [15, 16]. Some of the recognized AMR driving factors are elaborated below:

Health organizations have warned repeatedly about the dangerously high rates of antibiotic misuse worldwide, which has reached a critical point. Surveys indicate widespread misconceptions about antibiotics, particularly among less-educated populations, who often believe that antibiotics can cure viral illnesses like the common cold or flu. Additionally, antibiotics are frequently prescribed unnecessarily, especially in developing countries where diagnostic facilities are often inadequate. Administering antibiotics without clear clinical indications exemplifies common misuse [17].

The availability of antibiotics as over-the-counter (OTC) drugs for both human and animal use further exacerbates the problem, facilitating the emergence and spread of drug-resistant pathogens. The lack of robust antibiotic policies and standard treatment guidelines in many developing countries compounds the issue. Overprescription by healthcare providers, pharmacy dealers, and veterinarians is rampant, often driven by patient expectations or financial incentives from pharmaceutical companies. Another significant factor is the prevalence of substandard or poor-quality antibiotics in supply chains, particularly in low- and middle-income countries (LMICs), which worsens the antimicrobial resistance (AMR) crisis. Mismanagement of antibiotic courses, such as unnecessarily long durations or inappropriate dosing, also contributes to the problem. According to the Centres for Disease Control and Prevention (CDC), as of 2017, one-third of hospital patients received antibiotic prescriptions without proper diagnostic testing, and these were often continued for excessive durations. In nursing homes, the situation is even direr, with approximately 75% of prescriptions deemed inappropriate due to errors in dosage or duration [18].

The rising global consumption of antibiotics correlates strongly with increasing Gross Domestic Product (GDP), particularly in LMICs. Improved living standards in these regions have led to increased antibiotic consumption, as well as greater demand for animal protein, which contributes to the transmission of AMR through animal sources. Inappropriate prescribing patterns are a major driver of AMR. These include prescribing antibiotics unnecessarily, choosing the wrong type of antibiotic, or administering incorrect doses and durations. Studies show that at least half of hospital patients receive antibiotics without compelling reasons, and proper antimicrobial susceptibility testing is often bypassed, further aggravating resistance. Addressing AMR requires urgent action, including improving public awareness, enforcing strict regulations on antibiotic sales, strengthening diagnostic capabilities, and implementing standardized treatment guidelines worldwide [19–20].

Paucity in Futuristic Antibiotics

Pharmaceutical companies must quickly develop new, innovative medications to address the impending issue of antibiotic resistance. Unfortunately, despite repeated requests from the WHO, there is a lack of progress in the creation of new antibiotics. Surprisingly, the vast majority of the 51 newly created antibiotics are merely reformulated versions of old medications; only 8 of them can be classified as novel medications to treat diseases brought on by bacteria resistant to antibiotics. Consequently, there is conjecture that these novel medications will soon exhibit resistance. According to the current situation, the lack of viable treatment alternatives has gravely threatened the management of urinary tract infections, pneumonia, drug-resistant TB, and other gram-negative diseases. According to pharmaceutical corporations, regulatory limits and economic liability are significant barriers to antibiotic manufacture. As a result, many corporations have significantly cut their expenditure in research and innovation, and, shockingly, 18 big companies have discontinued antibiotic manufacture. In terms of earnings, pharmaceutical corporations have switched their priorities and are now more interested in generating medications for chronic diseases rather than infectious ones [21].

Agricultural Use of Antibiotics

Antibiotic use in livestock husbandry has expanded dramatically in many developing nations, owing to rising demand for animal feed in recent years. This method leads to antimicrobial resistance (AMR) by containing antibiotic residues in animal-derived products, such as meat, liver, kidney, fat, milk, and eggs. Antibiotics are frequently used indiscriminately for a variety of goals, including treating animal ailments, encouraging growth, increasing feed conversion efficiency, and preventing illness. This extensive use is especially prevalent in poorer nations, where the goal is to increase income from livestock husbandry and regulatory restrictions are frequently absent. The unrestricted use of antibiotics has contributed significantly to human AMR [22–23].

EASY TRAVEL ROUTES

The Role of Human Movement in AMR Spread

A growing body of evidence suggests that human migration has a key role in the emergence and global spread of antibiotic-resistant microorganisms. Modern transportation networks enable the mobility of both humans and animals, unwittingly spreading antimicrobial-resistant (AMR) microbes across borders. Travelers frequently return to their home nations colonized or infected with AMR organisms acquired during trips to endemic locations. According to studies, resistant bacteria can remain in the human body for up to 12 months after travel, increasing the likelihood of local transmission when the person returns [24].

Knowledge Gaps and the Importance of Surveillance

Both healthcare professionals (HCWs) and the public frequently lack appropriate understanding regarding effective antibiotic use and the factors underlying antibiotic resistance. Surveillance is critical in identifying the scope of the AMR burden and devising effective intervention methods, such as antimicrobial stewardship programs. However, comprehensive worldwide data on antibiotic usage and AMR prevalence in the healthcare and agriculture sectors is still insufficient. Surveillance data is critical for identifying high-priority locations and driving strategic initiatives to reduce the impact of AMR [25].

MULTISECTORAL COLLABORATION: A KEY TO COMBATING AMR

The fight against AMR requires coordinated efforts across multiple sectors, including healthcare, veterinary medicine, agriculture, finance, trade, education, and international organizations. Multisectoral collaboration must occur both horizontally (across sectors within a country) and vertically (across national, regional, and international levels). For example, multistakeholder forums can drive horizontal coordination, while international alliances address vertical collaboration. Key areas needing immediate attention include reducing the prescription of broad-spectrum antibiotics for minor conditions and closely monitoring the use of antimicrobials in veterinary practices [26].

Core Strategies to Combat AMR

Addressing AMR demands a comprehensive approach that incorporates rational antibiotic use, education, and systemic improvements. Key strategies include:

- *Rational Prescribing and Usage:* Encourage judicious antibiotic prescriptions for humans and animals and limit prophylactic antibiotic use.
- *Hospital Hygiene:* Implement robust infection control measures and antimicrobial stewardship programs.
- *Advanced Diagnostics:* Develop and deploy rapid diagnostic tools to enable targeted antibiotic therapy based on precise microbial profiling.
- *Surveillance and Research:* Strengthen AMR monitoring systems to generate actionable data.

Global Strategic Action Plans

The World Health Assembly has identified five major pillars for combating antimicrobial resistance (AMR) on a global scale:

- *Raise Awareness:* Increase healthcare providers' and the public's understanding of AMR.
- *Strengthening Surveillance and Research:* Create effective methods for tracking AMR trends and identifying risk factors.
- *Improving Hygiene and Infection Control:* To avoid infections, enforce proper hygiene and sanitation standards.
- *Optimizing Antimicrobial Use:* Encourage the judicious use of antibiotics in human and animal health.
- *Encouraging Innovation:* Increase investment in the development of novel medications, vaccines, and diagnostic tools to keep up with growing resistance.
- Mitigating it needs coordination across many sectors and stakeholders, supported by effective policies and education [27].

International Measures

The following international steps can be taken:

- Enhancing collaboration among international agencies, governments, nonprofit organizations, and professional groupings.
- Building global surveillance networks for antimicrobial usage and AMR.
- Developing laboratory capacity to detect and report pathogens with AMR, which have global health implications.
- Improving international tracking systems for rapid detection and mitigation of new infections.

- International surveillance to prevent counterfeit antimicrobials worldwide.
- Investing in research, medicine development, and vaccinations [28].

National Strategies

The following national steps can be taken

- Implementing an "antibiotic policy" for responsible use in healthcare and agriculture settings.
- Integrating public health and veterinary sectors can enhance national surveillance, monitoring, and evaluation activities.
- Creating novel point-of-care diagnostic tests to identify pathogens and track resistance.
- Investing in research for novel antibiotics and vaccines, both basic and applied.
- Enhancing worldwide coordination to combat AMR.

Using an essential medicine list to promote antimicrobial stewardship in hospital settings (Figure 1) [29].

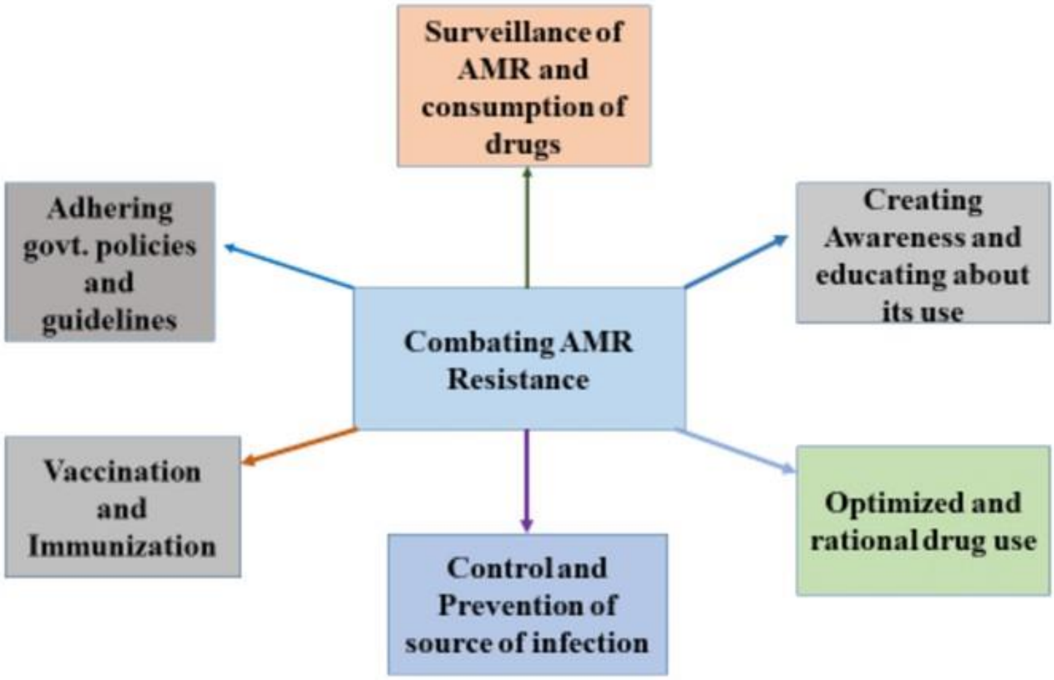

Figure 1. Major interventions to combat AMR.

RATIONAL USE OF ANTIBIOTICS

According to the WHO, "rational use of medicine" means giving patients the right antibiotics and other therapies that are appropriate for their clinical needs, in the right dosages, for the right amount of time, and for the least amount of money. It is only by prudent antibiotic administration that pathogen selection, drug toxicity, and resistance development can be prevented and the best results for infection treatment can be achieved. The main goal of antibiotic stewardship programs (ASPs) in healthcare settings is to guarantee that antibiotics are used appropriately [30].

Ban on Over-the-Counter (OTC) Antibiotics

OTC sales and distribution of oral and injectable antibiotics, which are still popular in many undeveloped and developing nations, should be subject to strict regulatory controls. Only prescriptions from qualified medical professionals should be used to prescribe antibiotics. It is highly recommended that current antibiotic policies be reevaluated considering local and regional AMR surveillance data, as well as that patients and pharmacy drug dispensers participate in ongoing antibiotic and AMR awareness efforts [31].

Infection Prevention and Control (IPC)

The practical, evidence-based approach of infection prevention and control (IPC) is essential for safeguarding patients and healthcare personnel against preventable diseases, such as those caused by bacteria that are resistant to drugs. To lower AMR in healthcare settings, this is an essential step. Using IPC to combat AMR requires the contributions of doctors, nurses, pharmacists, and other healthcare professionals. To stop the spread of infections, nurses and other medical professionals should also receive training on antimicrobial resistance (AMR) and aseptic techniques [32, 33].

To address IPC in healthcare facilities, consider establishing an "infection prevention and control committee".

- Maintains proper hand hygiene.
- Successfully diagnosed and treated infections.
- Use antimicrobials responsibly.
- Continuously monitor antibiotic use and resistance.
- Creating a quality antibacterial supply chain.
- Adhere to good microbiological laboratory practices.

Antimicrobial Stewardship Program (ASP)

A concerted initiative known as "antimicrobial stewardship" aims to minimize microbial resistance and enhance patient outcomes by educating and convincing prescribers to use antimicrobial medications appropriately. Ensuring that medical professionals administer the best antimicrobial for each patient at the right dosage and time is the primary goal of antimicrobial stewardship. The second goal is to prevent antibiotic overuse, abuse, and misuse. The ultimate objective is to minimize resistance development [34, 35].

Use of Antibiotics in Animals

The WHO specifically called for stricter laws pertaining to the use of medications with medical significance in animals to combat antimicrobial resistance. Additionally, for the purpose of promoting growth and preventing sickness, it argues for the widespread reduction and total prohibition of antibiotic use. It is possible to prevent disease by using antibiotics if infection has been verified in other animals within the same flock, herd, or fish group. As substitutes, better vaccination practices, changes to animal husbandry methods, probiotics or nutritional supplements in feed, and improved hygiene are all advised [36].

DEVELOPMENT OF NEW DRUGS AND VACCINES

An emphasis on research into an integrated strategy that encompasses the generation of both vaccines and novel antibiotics is crucial due to the complexity of producing new, effective drugs and the quick development of resistance to each new class of antibiotic. Coordination between academia and industry at the national and international levels, as well as greater investment in operational research and the development of novel antimicrobials, are crucial to addressing AMR. Vaccines are considered a key tactic in lowering the demand for antimicrobial drugs and so preventing antimicrobial resistance (AMR). They have long been used as preventative treatments to avoid infectious diseases. Furthermore, unlike antibiotics, they are not held responsible for the development of resistance. Thus, discovery and utilization of vaccinations against antimicrobial-resistant bacterial diseases, particularly [37, 38].

Introduction of Checkpoints

Some countries continue to have a high prevalence of illegal antibiotic sales and self-medication, particularly in developing and low-income nations where anybody can purchase medications from pharmacies without a licensed physician's prescription. It is completely inappropriate for doctors to occasionally base their antibiotic prescription decisions on their patients' preferences. Strict controls and checkpoints ought to be implemented to stop these harmful behaviours that accelerate the spread of AMR. To reduce the illegal sale of medications, particularly antibiotics, adequate legislation and its execution may be a suitable first step. Additional checkpoints could include delayed antibiotic prescribing, which is an effective therapy in which the patient is given explicit instructions on when to begin taking an antibiotic and the prescription is not filled until symptoms emerge [39, 40].

Community Engagement

Many individuals believe that the emergence and spread of AMR is a biological process that is connected to many of the community's daily activities, including food production, waste disposal, home and animal hygiene, and health-seeking behaviors. Furthermore, it is probable that any group may have its own language and perspective about drug resistance and the usage of antibiotics. Accordingly, a community-based strategy to changing antimicrobial use behaviour may protect current and future therapeutic options and provide more effective community-level AMR prevention tactics. To turn these concepts into applications that will help address the AMR issue, further research is needed to engage individuals in exploring their knowledge and experiences [41].

Alternatives to Antibiotics

Every effort is being made by researchers to identify natural resources that could serve as antibiotic substitutes. According to recent research on chemicals produced from plants, including polyphenolics, alkaloids, and other plant extracts, plants are thought to be unexplored sources of potential antimicrobial agents. Polyphenolics, alkaloids, and flavonoids are among the phytochemical substances whose antibacterial properties have not yet been studied. Translating and transferring some of these valuable discoveries from labs to hospital practices is another major difficulty [42].

CONCLUSIONS

A rising worldwide concern that jeopardizes contemporary medicine, agriculture, and public health is antibiotic resistance in microorganisms. Antibiotic abuse and overuse during the past century have sped up the emergence of resistant strains, making many traditional therapies useless. Through a variety of processes, such as the enzymatic breakdown of medications, target site alteration, efflux pumps, and biofilm development, microbes acquire resistance. Researchers are looking into cutting-edge therapeutic strategies like bacteriophage therapy, CRISPR-based gene editing, antimicrobial peptides, and repurposed medications to address this issue. Additionally, maintaining the effectiveness of already available antibiotics depends on mitigating techniques such antibiotic stewardship, enhanced diagnostics, public awareness campaigns, and international policy initiatives. To maintain sustainable antibiotic use, create novel treatment options, and slow the emergence of resistance, a concerted, multidisciplinary effort is required.

A coordinated, multidisciplinary effort is necessary to slow the spread of resistance, develop innovative treatment alternatives, and ensure sustainable antibiotic use. Addressing this issue now is imperative to prevent a post-antibiotic era where even minor infections could become life-threatening. Through scientific advancements and responsible healthcare practices, we can work towards controlling antibiotic resistance and safeguarding future generations.

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Conflict of Interest

The authors declare that there are no conflicts of interest.

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