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# Antimicrobial Resistance: The Quiet Menace of Our Time

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## Abstract

In the early days of their introduction, antibiotics were considered miraculous drugs. The fact that most of the populace no longer reveres antibiotics is worrisome and a frustrating indicator of the medical progress that humans have achieved so far. Many of us misuse/overuse these antibiotics, ignoring the potentially catastrophic consequences. Antibiotic misuse is connected to several frightening aftermaths. It may not immediately harm each patient receiving it, but it threatens the entire population in the long run. The excessive use of antibiotics reduces their efficacy by increasing the number of bacteria that have developed resistance against them. The more antibiotics are used, the more severe the prevalence of resistant bacteria is. It is in the broader interests of the community that antibiotics must be responsibly taken only when necessary. Multidrug-resistant pathogens are responsible for serious nosocomial and community-acquired infections, often reaching epidemic proportions. This article examines the mechanism and probable causes of antibiotic resistance and its origin and spread. Also, this paper discusses a comprehensive approach that must be executed on a war footing basis to suppress the menace.

**Keywords:** Drug Resistance; Antibiotics; Bacteria; Health Problems

## Introduction

The persistent emergence of antimicrobial resistance (AMR), which threatens the effective treatment of an ever-expanding range of infections caused by bacteria, parasites, viruses, fungi, and some parasites, is one of the severe public health challenges of the 21st century. Antimicrobial resistance is complex and a pressing concern regarding bacterial infections. The period between 1940 and 1965 was the golden age of antibiotics, during which numerous antimicrobials were discovered and incorporated into modern medicine. The discovery of new antibiotics has revolutionized the branch of contemporary medicine. Very soon, antibiotic-resistant microorganisms emerged partly due to discontinuous, inappropriate, or erratic consumption patterns and excessive or prolonged usage. Antibiotic resistance is growing at an alarming rate and has become one of the world's leading health concerns for a variety of reasons. The real challenge is increased antibiotic resistance in hospitals, communities, and, eventually, the environment. The extraordinary genetic capabilities of microbes have benefited from the excessive use of antibiotics by exploiting every source of resistance genes and every means of horizontal gene transfer. This results in developing multiple resistance mechanisms for every antibiotic introduced into clinical, agricultural, and other settings.

The World Health Organization (WHO) acknowledged it as a significant health threat in response to the substantial increase in the global prevalence of multidrug-resistant strains in 2014 [1]. From the 2016 discovery of the highly resistant mcr-1 gene in the United States to the 2017 death of a woman in Nevada due to a bacterial infection resistant to all 26 antibiotics available in the country, the severity of antibiotic resistance has increased dramatically. According to the 2019 Antibiotic Resistance Threats Report from the Centers for Disease Control and Prevention (CDC, United States), more than 35,000 people die annually in the US due to antibiotic-resistant infections. Several drug-resistant pathogens have emerged and identified over the past two decades. The failure or delay in developing new antimicrobials is a major contributor to this medical crisis and has been decried elsewhere [2]. The Centre for Disease Dynamics, Economics, and Policy (CDDEP) has thoroughly documented the global state of antibiotic policy to comprehend resistance and the need for new antimicrobials [3]. The lack of significant progress in discovering and developing new antibiotics over the past three decades is a primary concern. Numerous pharmaceutical firms are committed to developing drugs with substantial economic value [4]. On the one hand, pathogens are progressively developing resistance to the existing treatments, while on the other hand, limited efforts have been made to discover sufficient new antibiotics. It is imperative to take action to prevent this developing global healthcare crisis. Therefore, finding new antimicrobials effective against a broad spectrum of microorganisms, including drug-resistant pathogens, is paramount.

## Antimicrobial resistance

The introduction of antimicrobials has made remarkable progress in controlling several infections and improved the quality of human life. Antibiotics can now effectively treat many diseases that have previously killed humankind. Certain bacteria, however, have developed resistance to the most common antibiotics in use. They can survive and even proliferate vehemently in the presence of an antibiotic. At least some of the bacteria that cause infections can even develop resistance to all the currently used antibiotics. Bacteria resistant to multiple antibiotics are called multi-resistant organisms (MRO); AMR is a global and complex problem.

Along with other essential reasons, misuse of antibiotics in the medical, veterinary, and agricultural sectors, including the improper prescription of antibiotics, overuse in livestock, and inadequate hospital hygiene practices, all contribute to the rise of AMR. Also, International commerce, trading, and travel hasten the spread. Simultaneously, the development of new antibiotics has lagged, primarily due to a lack of incentives, allowing microorganisms to outpace the speed of development of new drugs. Due to the invention of antibiotics, previously fatal infections could now be successfully treated, and risk-free surgical procedures could be performed, enabling the development of modern medicine [5]. When a microorganism is no longer inhibited by an antibiotic to which it was once sensitive, it is termed "antimicrobial-resistant" or "drug-resistant." This so-called "acquired resistance" is encoded by the resistance genes present in the microbe's genome. Although some resistance genes have evolved over many years due to natural selection by antimicrobials found in the environment, others can arise from spontaneous mutations in the microbial DNA. From drug-resistant to drug-sensitive microorganisms, these genes can propagate antimicrobial resistance. In the late 1940s, i.e., only four years after the widespread use of penicillin had been established, the first drug-resistant bacterium in a clinical setting was identified. Since then, drug-resistant bacteria have developed and increased in prevalence. Many hospital-acquired infections are caused by resistant bacteria, such as vancomycin-resistant enterococci and methicillin-resistant Staphylococcus aureus (MRSA) [6].

## Bacteria resistant to antibiotics and resistance mechanisms

Certain bacteria are now resistant to the antibiotics that were once widely used to treat them. Benzylpenicillin, for instance, is now nearly universally ineffective against Staphylococcus aureus (also known as MRSA or "golden staph") and Neisseria gonorrhoeae (the germ that causes gonorrhea). In the past, penicillin was commonly used to treat these infections.

Antibiotic resistance is a serious problem because some bacteria are now resistant to a vast majority of widely available antibiotics. This is a public health concern because these bacteria can cause severe illnesses. Notable Bacterial species in this context include methicillin-resistant, Staphylococcus aureus (MRSA), vancomycin-resistant Enterococcus (VRE), multi-drug-resistant Mycobacterium tuberculosis (MDR-TB), carbapenem-resistant Enterobacteriaceae (CRE).

The remarkable genetic adaptability of bacteria enables them to respond to a wide range of environmental stressors, such as the presence of antibiotic compounds that could threaten their survival. Bacteria that coexist in the same biological niche as species that produce antibiotics have developed antiquated defense mechanisms against the damaging effects of antibiotic molecules, allowing them to thrive there [7]. Understanding the mechanisms by which bacteria develop resistance to antibiotics is essential in solving the problem. Antibiotic-resistant bacteria have a variety of defense mechanisms. An ineffective course of antibiotics results in the risk of incomplete elimination of the colony, thereby permitting the development of resistant bacteria. Incorrect usage of antibiot-

ics may result in the development of resistant bacteria. Several broad categories of drug resistance mechanisms include active efflux pumps, drug inactivation or modification, for instance, involving drug binding sites or targets, changes in cell permeability leading to decreased intracellular drug accumulation, biofilm formation, and many other ways [8,9].

### Efflux pumps

Efflux pumps are transporter proteins that aid in the export and expulsion of harmful substances from the cell. Since they expel various antibiotics to the outside of the cell, bacterial efflux pumps play an essential role in the emergence of drug resistance [10]. Consequently, infections caused by these organisms may be difficult to treat [11]. While some efflux pumps can only transport a single drug, others can transport a variety of substrates. Five primary efflux pump families include the ATP binding cassette (ABC) family, the Major Facilitator Superfamily (MFS), the Resistant Nodulation Cell Division Subfamily (RND), and the Multidrug and Toxic Effects (MATE) family. Protons belonging to the MFS, RND, MATE, and SMR families are propelled by an opposing proton flow. In efflux pumps, either intrinsic or acquired genes can be found. Encoded on the chromosome and activated by environmental cues or regulatory gene mutations, environmental cues or regulatory gene mutations activate the intrinsic efflux mechanism of resistance. [12].

### Drug neutralization

The enzymatic hydrolysis of antibiotics, group transfer, and redox reaction are some mechanisms bacteria employ to render antimicrobials inactive. The production of Beta-lactamases, which hydrolyze the Beta-lactam ring of penicillins, is a classic example of an antibiotic becoming inactive. Bacteria frequently secrete enzymes, rendering antibiotics ineffective before they reach the target microorganisms. The second method of antibiotic inactivation involves transferring a functional group, such as an acyl, ribosyl, phosphoryl, or thiol group, from the antibiotic to an enzyme. Structural alterations that result prevent the modified antibiotic from binding to its target, and the reaction is irreversible [13]. Another way or the third method for inactivating antibiotics is via a redox reaction [14].

### Target alteration

When its target site is altered, the antibiotic molecule loses its ability to bind correctly. Due to the essential biological functions of target sites, microorganisms cannot escape effectively or entirely from the antimicrobial activity. Therefore, by altering the intended targets can render antimicrobial drugs ineffective. The best example of drug target modification is the staphylococcal mechanism of modifying Penicillin Binding Protein (PBP), the target of Beta-lactam antibiotics [15].

### Guard against the intrusion of antimicrobial agents

Most antimicrobial agents must enter the bacterial cells to reach their target sites. Antibiotics typically enter the Gram-negative bacterial cell through the outer membrane via porin channels. Certain bacteria defend themselves by preventing antibiotics from entering their cell walls [16].

### Mutation

A mutation is a spontaneous change in the DNA sequence of a gene that may affect the trait it codes for [9]. One or more of the amino acids it encodes for may change due to a single base pair change, which in turn may affect the pathogen's enzyme or cell structure and alter the targeted antimicrobials' affinity or efficacy. Mutations in prokaryotic genomes are frequently caused by DNA polymerase errors, base alterations caused by external agents, deletions, insertions, and duplications [17].

### Biofilm development

Biofilms are complex microbial communities composed of bacteria and fungi. The protective matrix was synthesized and secreted by the microorganisms that firmly attach to a living or nonliving surface. A biofilm is a thick, slimy, carbohydrate- and protein-based barrier that contains bacteria. The biofilm barrier shields the microbes from danger. Due to the high cell density in biofilms, the absolute number of resistant mutants that can be selected under antimicrobial pressure increases [18].

### Principal factors causing antimicrobial resistance

Frequently contributing to antibiotic resistance are:

- **Antibiotic quality:** The consumption of expired or counterfeit antibiotics can promote drug resistance. In addition, it may also result from quality compliance and lack of proper monitoring.
- Excessive use of antibiotics; antibiotic resistance results from using antibiotics when they are neither necessary nor advantageous. Viral infections, for instance, are the leading cause of pharyngitis, and antibiotics lack efficacy in this scenario. The majority of bacterial ear infections resolve and abate without medications.

- **Misuse of antibiotics:** Bacteria seize every opportunity to proliferate; missing a specific dose of medication for a day (or for several days), discontinuing the therapy too soon, or using the wrong antibiotics (such as taking someone else's medication), bacteria begin to multiply. They may change as their numbers increase (mutate). A drug certainly loses its effectiveness against mutated microorganisms.
- **Agricultural use:** Moreover, bacteria in animals can develop antibiotic resistance. Animal farming accounts for 80% of antibiotic usage in the United States.
- **Spontaneous resistance:** Bacteria occasionally undergo spontaneous mutations or alterations to their genetic makeup. Antibiotics do not recognize this newly modified bacterium, preventing them from effectively targeting the pathogens; perhaps some modifications may help the bacteria resist the effects of medications.
- **Transmitted resistance:** A communicable, drug-resistant bacterial infection can be transmitted from one individual to another, catalyzing the spread of antibiotic-resistant infections.
- **Inadequate surveillance and susceptibility testing:** Unknown susceptibility patterns of bacteria can lead to empiricism and drug resistance. In addition, a lack of skilled workers and infrastructure can also add to the problems, thereby worsening it.
- Environmental factors such as a large population, overcrowding, and poor sanitary conditions can exacerbate the problem.

### Consequences of antimicrobial resistance

- Chronic difficulties brought on by ineffective treatment
- High mortality (Disability, subpar results) and morbidity
- Bad Effects of alternative medicine that is not desirable (potentially less effective, possibly more toxic)
- Recurrence of the infection following therapy
- Increasing transmission of germs resistant to antibiotics and associated community- and hospital-acquired illnesses.
- Frequent use of antibiotics
- Higher consumption of clinically effective antibiotics resulting in their nonavailability
- Longer and more complicated stays in the hospital
- Excessive medical expenses

### Methods for decreasing antimicrobial resistance

Similar to other pathogens, antibiotic-resistant bacteria are also highly contagious. Consequently, they can spread in our environment and from one individual, animal, or a specific food item to another. The interdependencies among the various sectors indicate that measures to combat antibiotic resistance must be formulated from a broader perspective. In agriculture, animal health, and healthcare settings, the prudent use of antibiotics is essential for preventing the development of resistance and extending the shelf life of effective antibiotics. Antibiotic resistance and the dearth of newly introduced medications have led to a gradual decline in the effective treatment of bacterial diseases. Reducing prescriptions is one of the most effective methods for decreasing the selection pressure, as it is now evident that the constant usage of antibiotics may accelerate the development of resistant bacteria [19].

## Conclusion

Antibiotics are indispensable for treating infectious diseases, and their value and significance cannot be underestimated. They should never be considered unwanted. In addition to treating infectious diseases, antibiotics are crucial in the success of complex surgical procedures, such as organ and prosthetic transplants.

Despite the best efforts taken to restrict the constant use of antibiotics, the scenario concerning their resistance is disappointing. The widespread occurrence of resistance mechanisms brings tremendous clinical and financial burden on the health care systems across the globe; no simple or easy solutions are available to solve this problem. Even when it is possible to save lives, firm decisions based on commitment and enforcement are rarely made. Fortunately, not all bacterial diseases are always resistant, and many of them can be empirically treated with antimicrobials given to the general public. With so many unknown factors, the best that can be hoped for is that all doctors and medical staff must take more stringent measures concerning infection control and antibiotic use. This, in turn, can ensure that the patients receive adequate care. This must be accompanied by combined efforts to prevent the release of unused antibiotics into the environment via wastewater systems. To prevent the spread of resistance and prolong the efficacy of potent antibiotics, it is essential that antibiotics are used responsibly in healthcare settings, animal farms, and agriculture sectors, and the search for new antimicrobial drugs must continue potentially and indefinitely.

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