

The Antibiotic Era: A Golden Age and Its Challenges

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ABSTRACT: *Antibiotics have revolutionised medicine, helping to reduce infection-related deaths and increase life expectancy globally. They have enabled life-prolonging medical procedures and the foundation for advancements in medicine. This review explores the historical significance of antibiotics in healthcare, underscores the challenges of antibiotic resistance, and emphasises the importance of responsible antibiotic usage. It advocates for developing new antibiotics to combat resistant bacteria and ensure the continued effectiveness of antibiotic therapy in healthcare. A comprehensive search was conducted using academic databases like PubMed, Google Scholar, Web of Science, Science Direct and other search engines. The results were refined using filters, advanced search options, and relevant articles retrieved from the search. Antibiotics target and destroy bacterial cells, and each antibiotic type functions differently. However, the overuse and misuse of antibiotics, along with reduced economic incentives and challenging regulatory requirements, have resulted in antibiotic-resistant bacteria emerging, which is a cause for concern worldwide. The rapid emergence of antibiotic-resistant bacteria endangers the effectiveness of antibiotics that have saved millions of lives and transformed medicine. Antibiotics are essential in medicine, but resistance is a growing concern. New antibiotics need to be developed, and using them wisely is key to maintaining their effectiveness and positive impact on healthcare.*

KEYWORDS: antibiotics, antibiotic resistance, mode of action, antibiotic use, antibiotics misuse

INTRODUCTION

The "antibiotic era" began with Paul Ehrlich and Alexander Fleming. Ehrlich proposed the concept of a "magic bullet" that could target disease-causing microbes while sparing the host. In 1904, Ehrlich, Alfred Bertheim, and Sahachiro Hata synthesised Salvarsan, a drug that cured syphilis-infected rabbits and showed promise in limited human trials. Salvarsan became the most prescribed drug until the 1940s when it was replaced by penicillin [1].

The discovery of penicillin marked the beginning of a golden age in the discovery of natural antibiotic products. This period peaked in the mid-1950s, and antibiotics have since become a standard treatment for bacterial infections. The mid-20th century was known as the "antibiotic era", as these drugs were believed to have the power to eradicate infectious diseases. Antibiotics have played a crucial role in successful invasive surgeries, such as organ transplantation, and have been used in various medical disciplines. However, after several decades of antibiotic use, bacterial infections have become a significant threat [2;3]. The discovery of the first three antimicrobials (Salvarsan, Prontosil, and penicillin) paved the way for new antibiotics to emerge. Several novel antibiotic classes were explored between the 1950s and the 1970s [4].

The rapid emergence of antibiotic-resistant bacteria is a global concern, and it endangers the effectiveness of antibiotics that have saved millions of lives and transformed medicine [5]. The overuse and misuse of antibiotics, as well as the pharmaceutical industry's lack of new drug development due to reduced economic incentives and challenging regulatory requirements, have been blamed for the antibiotic resistance crisis [6].

Significance of antibiotics in healthcare

Antibiotics revolutionised medicine by reducing infections and deaths and increasing life expectancy globally by one to two decades in less than a century. They support life-prolonging medical procedures and form the foundation for ground breaking medical advancements, including cancer chemotherapy, organ transplantation, and intricate surgeries [7]. Antibiotics have been a lifesaver for many patients. They have played a vital role in advanced medicine and surgery and successfully treated and prevented infections in patients undergoing chemotherapy, those with chronic diseases such as diabetes, end-stage renal disease, or rheumatoid arthritis, and those who have undergone complex surgeries like organ transplants, joint replacements, or cardiac surgery [8].

Moreover, antibiotics have also contributed to extending human life expectancy by changing the outcome of bacterial infections. These positive effects of antibiotics have been observed worldwide. In developing countries where sanitation is still poor, antibiotics have helped to reduce the morbidity and mortality caused by food-borne and other infections related to poverty [9].

Mechanism of action

Most antibiotics interfere with the biosynthesis of peptidoglycans, essential to the integrity of the cell wall structure. These antibiotics destroy the integrity of the cell wall, as it is the outermost layer and the main component of the cell wall. The inhibition of cell wall peptidoglycan biosynthesis is preferred because it has no significant negative impact on mammalian host cells, as mammalian cells do not have the peptidoglycan wall structure [10;11]. Some antibiotics interfere with the 30S or 50S subunits of the 70S bacterial ribosome to block bacterial protein synthesis. For example, tetracyclines such as doxycycline prevent the

binding of aminoacyl-tRNA by blocking the A (aminoacyl) site of the 30S ribosome. They can inhibit protein synthesis in 70S and 80S (eukaryotic) ribosomes [12].

Several antimicrobial agents interfere with bacterial membrane structures and impair functional impairment by interacting with a lipophilic moiety of the bacterial membrane. Antibacterial agents directed against the cytoplasmic membrane components of bacteria have been reported, and they can act on both Gram-negative and Gram-positive bacteria [13].

Antibiotics can inhibit microorganism replication, transcription, and folate synthesis. Quinolone drugs can interfere with DNA synthesis by inhibiting topoisomerase, an enzyme in DNA replication. For instance, levofloxacin, norfloxacin, and ciprofloxacin are active against Gram-negative and Gram-positive bacteria. Some antibiotics interfere with RNA synthesis by inhibiting RNA polymerases, such as doxorubicin and actinomycin D (dactinomycin). These antibiotics interfere with bacterial and mammalian systems and are commonly used as antineoplastic and antitumor drugs, attacking rapidly growing malignant and normal cells [9; 14].

Mechanisms of Antibiotic Resistance

Antibiotic resistance, the ability of bacteria to resist the effects of antibiotics, is considered a significant threat to global public health. The phenomenon occurs when bacteria develop mechanisms that render antibiotics less effective or ineffective. The rise of antibiotic resistance is a complex issue, influenced by several factors, including but not limited to the overuse and misuse of antibiotics, lack of proper sanitation and hygiene, and the widespread use of antibiotics in livestock and agriculture. Addressing antibiotic resistance requires a multifaceted approach involving global cooperation, improved surveillance, and the development of alternative therapies [15].

Bacteria can differ in their susceptibility or resistance to various antimicrobial agents. To determine susceptibility or resistance, the minimum inhibitory concentration (MIC) of a drug that can halt bacterial growth is measured [15]. Susceptibility is a range of the average MICs for a given drug across the same bacterial species. If the average MIC for a species falls in the resistant part of the range, that species is considered intrinsically resistant to the drug. Bacteria can also acquire resistance genes from related organisms, and the resistance level may vary depending on the species and the genes acquired [15;16].

Antimicrobial resistance mechanisms can be broadly categorised into four main types: (1) limiting the uptake of a drug, (2) modifying the target of a drug, (3) inactivating a drug, and (4) actively pumping out a drug. Intrinsic resistance may use any of the first three mechanisms, while acquired resistance typically involves drug target modification, drug inactivation, and drug efflux [17;18].

There are differences in the mechanisms used by gram-negative bacteria and gram-positive bacteria due to differences in their structures. Gram-negative bacteria use all four main mechanisms, while gram-positive bacteria less commonly use limiting drug uptake as they lack

an LPS outer membrane. Additionally, they do not have the capacity for certain types of drug efflux mechanisms [19].

Limited drug uptake

Drug molecules can enter a cell in three ways: through porins, diffusion through the bilayer, and self-uptake. Bacteria have varying abilities to limit the uptake of antimicrobial agents. The LPS layer in gram-negative bacteria prevents certain types of molecules from entering the cell, making these bacteria naturally resistant to specific groups of large antimicrobial agents [15]. Bacteria without a cell wall, like *Mycoplasma* and related species, are intrinsically resistant to all drugs that target the cell wall, including β -lactams and glycopeptides (Béb ear & Pereyre, 2005). A decrease in the number of porin channels results in reduced entry of β -lactam antibiotics into the cell, leading to resistance to these types of antibiotics [13].

Drug target modification

Antimicrobial agents can target various components of a bacterial cell, and bacteria can modify just as many targets to resist those drugs. Changes in the target site often occur due to spontaneous mutation of a bacterial gene on the chromosome. Since antibiotics interact specifically with the target molecule, even minor alterations in it can have a significant impact on antibiotic binding. Resistance to antimicrobials can result from natural variations or acquired changes in the target sites that prevent drug binding (15; 20).

Examples of drug target modification include alterations in the 30S or 50S subunit of the ribosome, which affects protein synthesis and leads to resistance to macrolides, tetracycline, and chloramphenicol. Chloramphenicol, macrolides, lincosamides, and streptogramin B bind to the 50S ribosomal subunit to suppress protein synthesis, and modification of the 50S subunit will lead to resistance [21].

Gram-positive bacteria may modify their penicillin-binding protein (PBP) to resist antibiotics. Whereas Gram-negative bacteria produce β -lactamases to defend themselves against antibiotics. Some antibiotics, such as vancomycin or teicoplanin, work by inhibiting the cell wall synthesis in Gram-positive bacteria by binding to the D-alanyl-D-alanine residues of peptidoglycan precursors. Resistance to these antibiotics can occur when D-alanyl-alanine is replaced with D-alanyl-lactate, which prevents the antibiotics from cross-linking with them [22;13].

Vancomycin resistance has become a significant problem in enterococci (VRE - vancomycin-resistant enterococci) and *Staphylococcus aureus* (MRSA). This resistance is caused by the acquisition of van genes, which modify the structure of peptidoglycan precursors, leading to a reduced binding ability of vancomycin [23].

Antibiotic inactivation

Three main enzymes inactivate antibiotics: β -lactamases, aminoglycoside-modifying enzymes, and chloramphenicol acetyltransferases [24]. There are two main ways bacteria inactivate

drugs: by actual drug degradation or by transfer of a chemical group to the drug. Drug inactivation by transfer of a chemical group to the drug most commonly uses the transfer of acetyl, phosphoryl, and adenylyl groups and a large number of transferases have been identified. Acetylation is the most diverse mechanism against aminoglycosides, chloramphenicol, streptogramins, and fluoroquinolones. Phosphorylation and adenylation are known to be used primarily against aminoglycosides [15;25].

Drug efflux

Bacteria have various types of efflux pumps, which are classified into five main families based on their structure and energy source. These families include ATP-binding cassette (ABC), multidrug and toxic compound extrusion (MATE), small multidrug resistance (SMR), major facilitator superfamily (MFS), and resistance-nodulation-cell division (RND) [26]. Bacteria have developed advanced resistance mechanisms, such as efficient drug efflux pumps that can handle many substrates, including antibacterials and non-antibacterials. This type of resistance can have clinical implications, making antibacterial therapy ineffective. Additionally, it provides a baseline resistance that promotes the emergence of further resistance mechanisms, such as drug inactivation or modification of drug targets [27].

Genes in the bacterial chromosome encode these pumps and function primarily to eliminate toxic substances from the bacterial cell. While some efflux pumps are expressed constitutively, others are induced or overexpressed under specific environmental stimuli or in a suitable substrate. Most efflux pump families are single-component pumps transporting substrates across the cytoplasmic membrane. Many of these are multidrug efflux pumps, which can transport various compounds. The type of available carbon source influences the resistance capability of these pumps [26; 28].

The overuse and misuse of antibiotics

Excessive consumption of antibiotics mainly leads to the development of antibiotic resistance. The issue of antibiotic resistance is becoming more severe due to the misuse and overuse of medication, as well as insufficient infection prevention and management. This problem is growing globally, and to reduce its impact, it is crucial to take appropriate measures at all levels of society. Prescribing medication is an essential part of medical practice. Infections are a common problem, and antibiotics are frequently prescribed [29].

Antibiotic resistance is exacerbated by the excessive use of antibiotics in agriculture, food and feed production, incorrect prescriptions, and misuse by patients. Individuals often misuse antibiotics through self-prescription or by not adhering to the doctor's instructions. This includes changing the prescribed dosage, shortening or extending the treatment period, or failing to take the antibiotics at the specified time [30].

According to sixty-one studies, the most commonly sold antibiotics without a prescription are amoxicillin (86.9%), azithromycin (39.3%), ciprofloxacin (39.3%), and amoxicillin-clavulanic acid (39.3%). Out of 65 articles referencing diseases/symptoms, this practice was primarily associated with respiratory system problems (100.0%), diarrhoea (40.0%), and urinary tract infections (30.8%) [31].

Dispensing antibiotics without a prescription is common in many countries and can contribute to the global development of resistance. The prevalence of antibiotic misuse exceeds 75% in low- and middle-income countries worldwide, where prescriptions are not always required [29].

The presence of family or friends working in a health-related field is associated with the indiscriminate use of antibiotics. Another study found a similar result, showing that individuals with a family member employed in a health-related field were likelier to use non-prescribed and keep leftover antibiotics [32].

A meta-analysis of 85 studies from 42 countries found that individuals misuse antibiotics regardless of their education level [33]. A survey was conducted among medical students in Mali, which revealed poor knowledge and extensive misuse of antibiotics [34]. Overusing antibiotics for uncomplicated respiratory infections and using cephalosporins, macrolides, and injection antibiotics in primary care are major clinical practice problems in rural areas of Guizhou [35].

The role of inappropriate prescribing practices by healthcare professionals

Inappropriate prescribing occurs when medications are either prescribed in excess or not. In low- and middle-income countries where the patient-to-physician ratio is low, pharmacies are a primary source of healthcare services with multiple pharmacy worker (non-pharmacist) level factors that may lead to the inappropriate dispensing of antibiotics. However, due to the significant variation in the training of pharmacy workers, inappropriate dispensing of antibiotics is a common problem. This can ultimately lead to poor therapeutic outcomes and an increased risk of antibiotic resistance [36].

Accessing primary care is becoming increasingly complex, partly because many physicians are leaving the field. For this reason, a recent study compared potentially inappropriate prescribing practices between primary care physicians (PCPs) and nursing practitioners. The study focused on adults aged 65 and older and found that NPs and PCPs had almost identical rates of potentially inappropriate prescribing [37].

Misconceptions and misinformation regarding the use of antibiotics have led to inappropriate practices among different categories of healthcare providers for both humans and animals in Bangladesh. Healthcare providers, especially those in rural areas with little or no training, showed a low understanding of antibiotic action and resistance [38].

In many African countries, a significant number of people still buy antibiotics without a prescription, and some community pharmacies in these countries dispense antibiotics without a prescription. Various factors drive this trend, including the high cost of medicines and healthcare services, physician costs, and travel expenses to healthcare facilities. Additionally, long waiting times to see a healthcare professional may result in loss of earnings, making community pharmacists a more convenient option for many people [7].

The impact of antibiotic resistance on the treatment of common infections.

The problem of antibiotic resistance has become a primary concern for public health, posing significant challenges to the prevention and treatment of persistent diseases. The cost of antibiotics can be grouped into three levels: patient level, healthcare level, and economic level [39;40].

The impact of this resistance on mortality rates and healthcare costs is difficult to estimate. However, resistant bacteria doubles the likelihood of developing a severe health problem compared to non-resistant bacteria and triples the chances of death. The availability of effective antibiotic drugs is crucial in many areas of modern medicine, including cancer treatment, organ transplantation, hip replacement surgery, intensive care for pre-term newborns, and various other medical procedures [41].

Infections caused by bacterial strains resistant to multiple drugs often affect patients undergoing medical procedures. This is a significant factor that leads to increased morbidity and mortality rates. The problem of resistance also poses a serious challenge to global efforts to combat infectious diseases such as tuberculosis, human immunodeficiency virus (HIV), and malaria. In particular, the number of HIV cases that are resistant to medication is increasing, especially in Sub-Saharan Africa, where 60% of patients with HIV have developed resistance to HIV medicine [40].

Potential for increased mortality and morbidity.

The world faces an antibiotics pipeline and access crisis. There is an inadequate research and development pipeline in the face of rising levels of resistance and an urgent need for additional measures to ensure equitable access to new and existing vaccines, diagnostics and medicines. Antibiotic resistance is increasing globally, making it harder to treat bacterial infections. The 2022 Global Antimicrobial Resistance and Use Surveillance System (GLASS) report shows alarming resistance rates in prevalent bacterial pathogens. *E. coli* and *Staphylococcus aureus* have 42% and 35% resistant rates, respectively. *Klebsiella pneumoniae* also has high resistance levels against critical antibiotics, increasing the use of last-resort drugs like carbapenems, which are now ineffective. By 2035, a twofold surge in resistance to last-resort antibiotics is projected, underscoring the need for robust antimicrobial stewardship practices and enhanced surveillance coverage worldwide [42].

Global Spread of Antibiotic Resistance

The antimicrobial resistance (AMR) issue is becoming increasingly alarming and requires urgent attention from world leaders and policymakers. The threat posed by AMR is just as concerning as the impact of COVID-19. Therefore, there is a need to implement standardised reporting of AMR infections, improve diagnostics, and invest in the development of vaccines, antimicrobial agents, and reporting systems on a global scale, as suggested by Walsh et al [43]. To tackle antibiotic resistance, a comprehensive policy that prioritises human, animal, and environmental well-being is required. This policy should focus on surveillance systems, stewardship programs, education, research, preventive measures, and public awareness.

Robust surveillance systems are essential to monitoring antibiotic-resistant bacteria. Stewardship programs, continuous education, and research can promote responsible antibiotic use and aid in developing new therapies and diagnostic tests. Preventive measures, such as safe food handling, hand hygiene, and personal protective equipment, are crucial. Public education campaigns can also help reduce unnecessary antibiotic use [44].

CONCLUSION

Antimicrobial resistance is a significant concern that demands the immediate attention of the global community. It affects all countries, irrespective of their income level, and its spread knows no boundaries. If left unchecked, antimicrobial resistance will affect everyone, regardless of nationality or country's development level. It will pose a serious threat to healthcare, making standard procedures like cancer chemotherapy or caesarean sections much more dangerous than they are today. The pharmaceutical industry needs to focus on developing new antibiotics to tackle this issue. We must use antibiotics judiciously and responsibly to ensure their effectiveness in the future and continue to reap their benefits in healthcare.

List of abbreviations

ABC	ATP-binding cassette
AMR	Antimicrobial resistance
COVID-19	Coronavirus disease
DNA	Deoxyribonucleic acid
GLASS	Global antimicrobial resistance and use surveillance system
HIV	Human immunodeficiency virus
PCP	Primary Care Physicians
MATE	Multidrug and toxic compound extrusion
SMR	Small multidrug resistance
MFS	Major facilitator superfamily
RND	Resistance-nodulation-cell division

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Availability of data and material

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Competing interests

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EL conceptualised the topic for review. ELL and SR wrote the article.

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