**The Silent Threat Unveiled: Microbial Resistance and Our Battle for Survival**

**ABSTRACT**

AMR has become a global health issue, threatening antibiotic and other antimicrobial efficacy. This abstract discusses the complex and diversified effects of antimicrobial resistance (AMR) on public health, agriculture, and the environment. As bacteria, viruses, parasites, and fungi become resistant to antimicrobials, infectious diseases become harder to treat, resulting in longer sickness, higher mortality, and higher healthcare costs.

Misuse of antimicrobials in medicine, animal husbandry, and agriculture worsens AMR. Overprescription, antibiotic abuse, poor cleanliness, and livestock usage of antimicrobials accelerate antibiotic resistance. The globalization of trade and travel allows resistant varieties to spread quickly and demands international cooperation.

These abstracts emphasize the urgent need for a multidisciplinary approach to combat antimicrobial resistance (AMR). Strategies should include better surveillance, infection prevention, and new antimicrobials. In addition, cautious use of current antimicrobial drugs and education for healthcare providers, farmers, and the public are crucial to minimizing antimicrobial resistance.

Keywords: Antibiotics, Anthelminthics, Microbial Resistance, Pharmacology Action, World Health Organization.

**1. INTRODUCTION**

In the microscopic battleground that is our world, a silent war is being waged—one that imperils the very core of our healthcare systems and challenges the efficacy of life-saving treatments. Microbial resistance, the ability of microbes to adapt and thrive in the face of our most potent weapons, has emerged as a formidable adversary, threatening to overturn decades of medical progress**1**. Picture this: a future where common infections become life-threatening, routine surgeries transform into high-stakes gambles, and the antibiotics once hailed as miracle drugs stand powerless against resilient bacteria and viruses. It's a future that looms closer than we dare to imagine. As we traverse this intricate landscape of invisible adversaries, it's imperative to unravel the complexities of microbial resistance. Join us on a journey through the hidden realms of microbiology, where the stakes are high, the challenges immense, and the need for understanding and action has never been more critical**2**.

In the following pages, we'll delve into the origins of this silent menace, explore its far-reaching consequences, and illuminate the paths that lead us toward a future where our weapons against infections remain effective. The battle against microbial resistance is not just a scientific endeavor; it's a call to arms for every individual, every healthcare professional, and every policymaker**2,3,4**.

Welcome to the front lines of a war, we cannot afford to lose. The time to act is now, and the knowledge within these lines may very well hold the key to our survival.

**1.1 Microbial Resistance**, also known as antimicrobial resistance (AMR), refers to the ability of microorganisms, such as bacteria, viruses, parasites, and fungi, to evolve and withstand the effects of antimicrobial agents. These agents include antibiotics, antivirals, antifungals, and antiparasitic drugs. Microbial resistance poses a significant threat to public health and has far-reaching implications for the effectiveness of medical treatments, the control of infectious diseases, and overall healthcare systems**5,6,7**.

**1.2 Significance of Microbial Resistance In Public Health:**

* Treatment Challenges: Microbial resistance reduces the effectiveness of standard treatments for infections. Common illnesses that were once easily treatable may become more challenging to manage, leading to prolonged illness, increased healthcare costs, and a higher risk of complications**6,7**.
* Increased Morbidity and Mortality: Resistant infections can result in higher rates of morbidity and mortality. Patients with infections that do not respond to standard treatments face a greater risk of severe outcomes, including prolonged hospital stays and, in some cases, death**8,9**.
* Impact on Medical Procedures: Procedures such as surgeries, chemotherapy, and organ transplants, which often rely on effective antimicrobial drugs to prevent and treat infections, become riskier when microbial resistance compromises the efficacy of these drugs.
* Spread of Infections: Resistant microbes can spread more easily within communities and healthcare settings. This increased transmission contributes to the persistence and amplification of resistant strains, making it more challenging to contain outbreaks.
* Global Health Security: Microbial resistance is a global health security issue. Resistant strains can cross international borders, challenging efforts to control and manage infectious diseases on a global scale. International collaboration is crucial to address the spread of resistant microbes**10,11**.
* Economic Impact: The economic burden of microbial resistance is substantial. Increased healthcare costs, including prolonged hospital stays and the need for more expensive second-line treatments, contribute to the economic strain on healthcare systems and societies.
* Loss of Medical Advances: The rise of microbial resistance jeopardizes decades of medical advances. In a post-antibiotic era, routine medical procedures and treatments for chronic conditions may become riskier, and the achievements of modern medicine may be compromised.
* One Health Approach: Microbial resistance emphasizes the interconnectedness of human, animal, and environmental health. The One Health approach recognizes the need for a coordinated effort across these domains to address the complex factors contributing to the emergence and spread of resistant microbes.

**1.3 Growing Concern: The Silent Crisis Unfolding**

In the shadows of modern medicine, a quiet yet potent crisis is unfurling—a crisis that threatens to plunge us into a future where once-treatable infections become untamable killers. The growing concern at the heart of this crisis is microbial resistance, an escalating menace that jeopardizes the very foundation of healthcare as we know it**11.12.13**.

* The Alarming Escalation: Over the years, the pace at which microbes are developing resistance to our most potent drugs has accelerated. Antibiotics, once hailed as miracles of modern medicine, are losing their effectiveness against bacterial infections. Viruses, parasites, and fungi are also adapting, rendering antivirals, antiparasitic, and antifungals less reliable. The consequences are dire, with the World Health Organization warning of a looming post-antibiotic era—a scenario where common infections can become lethal, and routine medical procedures turn into high-stakes gambles.
* Threat to Global Health Security: Microbial resistance transcends borders, posing a threat to global health security. Resistant strains travel effortlessly between countries, undermining efforts to control infectious diseases worldwide. The interconnectedness of our world has magnified the impact of this crisis, making it clear that the fight against microbial resistance is a shared responsibility that no nation can afford to overlook**12,13**.

**1.4 The Urgent Need for Awareness and Action:**

* Public Awareness: Many individuals are unaware of the implications of microbial resistance. Public awareness campaigns are crucial to educate people about the risks of overusing antibiotics, the importance of completing prescribed courses, and the potential consequences of a world without effective antimicrobials.
* Healthcare Professional Education: Healthcare professionals play a pivotal role in the fight against microbial resistance. Ongoing education about prudent antibiotic use, infection prevention, and the latest developments in microbial resistance is essential to ensure that they can make informed decisions in their clinical practice**14**.
* Policy and Regulation: Governments and international bodies must enact and enforce policies to regulate the use of antimicrobials in healthcare, agriculture, and other sectors. Restricting the over-the-counter availability of antibiotics, promoting responsible agricultural practices, and incentivizing the development of new antimicrobial agents are critical steps**15**.
* Research and Development: Investment in research and development of new antimicrobial drugs is imperative. The pipeline for novel antibiotics has been stagnant for years, and incentivizing pharmaceutical companies to invest in this area is essential to stay ahead of emerging resistant strains.
* Global Collaboration: Microbial resistance knows no borders. International collaboration is essential to share information, best practices, and resources. Joint efforts can enhance surveillance, coordinate response strategies, and collectively address the root causes of microbial resistance.
* One Health Approach: Adopting a One Health approach that recognizes the interconnectedness of human, animal, and environmental health is paramount. Addressing microbial resistance requires a holistic strategy that considers the factors contributing to its emergence and spread across different domains.

**2. BACKGROUND**

**2.1 History**

The history of antimicrobial resistance (AMR) is a complex and ongoing story that spans over several decades. It involves the emergence and spread of microorganisms (bacteria, viruses, fungi, and parasites) that have developed resistance to the drugs designed to kill or inhibit them, such as antibiotics, antivirals, and antifungals. Here is a brief overview of the key milestones and developments in the history of antimicrobial resistance:

**2.1.1 Discovery of Antibiotics (1920s-1940s)16:**

* Penicillin Discovery: The story of antibiotics began in 1928 when Alexander Fleming, a Scottish bacteriologist, discovered penicillin. Fleming noticed that a mold called Penicillium notatum produced a substance that killed a wide range of bacteria. This serendipitous discovery laid the foundation for the development of modern antibiotics.
* World War II Impact: The development of antibiotics gained momentum during World War II when there was a pressing need for effective treatments for wounded soldiers. Penicillin, the first widely used antibiotic, was produced on a large scale with the help of American pharmaceutical companies like Pfizer and Merck. It played a crucial role in treating bacterial infections in soldiers.
* Streptomycin and Tetracycline: After penicillin, other antibiotics like streptomycin and tetracycline were discovered in the 1940s. Streptomycin was effective against tuberculosis, while tetracycline was used to combat a wide range of bacterial infections.
* Nobel Prizes: Alexander Fleming, Howard Florey, and Ernst Boris Chain were jointly awarded the Nobel Prize in Physiology or Medicine in 1945 for their contributions to the development and production of penicillin. This recognition highlighted the significance of antibiotics in medicine.
* Post-War Antibiotic Boom: The post-World War II era witnessed an antibiotic boom, with the discovery and production of several antibiotics, including chloramphenicol, erythromycin, and gentamicin. These drugs revolutionized medicine by providing effective treatments for bacterial infections.
* Golden Age of Antibiotics: The 1940s and 1950s are often referred to as the "Golden Age of Antibiotics" due to the rapid discovery and widespread use of these life-saving drugs. Antibiotics play a critical role in reducing mortality from bacterial infections and improving overall public health.

**2.1.2 Early Awareness of Resistance (1940s-1950s):**

* Observations of Reduced Efficacy: In the years following the introduction of antibiotics like penicillin, streptomycin, and tetracycline, medical practitioners and researchers began to notice instances where these drugs were less effective than expected in treating bacterial infections.
* Sir Alexander Fleming's Warning: Even before receiving the Nobel Prize for his discovery of penicillin in 1945, Alexander Fleming himself warned about the potential for antibiotic resistance. In his Nobel lecture, he cautioned against the reckless use of penicillin, fearing that excessive exposure might lead to resistance.
* Tetracycline Resistance in the Laboratory: In the early 1950s, scientists in laboratories observed bacteria developing resistance to tetracycline, one of the new antibiotics. This resistance was documented through experiments, demonstrating that bacteria could adapt and become less susceptible to the drug.
* Use of Combination Therapy: To combat resistance, physicians sometimes resorted to combination therapy, using multiple antibiotics simultaneously. This approach aimed to prevent the development of resistance by targeting bacteria with different mechanisms of action.
* Awareness in Veterinary Medicine: Veterinarians also recognized antibiotic resistance in the treatment of animals. The use of antibiotics in agriculture was already raising concerns about the spread of resistance in livestock.
* The Term "Antibiotic Resistance": The term "antibiotic resistance" was coined during this period to describe the phenomenon where bacteria became less susceptible to the effects of antibiotics. This term encompassed various mechanisms through which bacteria could resist the action of these drugs.
* Limited Understanding: While early observations were made, the molecular mechanisms underlying antibiotic resistance were not yet well understood. This limited the ability to develop strategies to combat resistance effectively.

**2.1.3 Overuse and Misuse (1950s-1970s)17:**

* Rapid Increase in Antibiotic Use: In the decades following World War II, antibiotics became widely available and were often seen as a "magic bullet" for treating various infections. This perception led to a rapid increase in their use, both in medical settings and beyond.
* Unrestricted Access: Antibiotics were readily available without a prescription in many places during this time. This allowed individuals to self-medicate, often inappropriately, without consulting a healthcare professional.
* Inadequate Dosage and Duration: Antibiotics were sometimes prescribed or used at inadequate dosages or for insufficient durations. This incomplete treatment allowed surviving bacteria to develop resistance, as they were exposed to suboptimal levels of antibiotics.
* Use in Agriculture: Antibiotics were also heavily used in agriculture to promote animal growth and prevent infections in crowded farming conditions. The use of antibiotics as growth promoters in livestock became common practice, leading to widespread exposure of bacteria to antibiotics.
* Lack of Antibiotic Stewardship: The concept of antibiotic stewardship, which emphasizes responsible antibiotic use, was not widely practiced during this period. Healthcare providers and the public often lack awareness of the importance of completing antibiotic courses as prescribed.
* Broad-Spectrum Antibiotics: Broad-spectrum antibiotics, which can target a wide range of bacteria, were frequently prescribed, even when a narrower-spectrum antibiotic would have been effective. This contributed to the disruption of normal microbial flora, potentially allowing resistant bacteria to thrive.
* Inappropriate Use for Viral Infections: Antibiotics were frequently prescribed for viral infections, such as the common cold or influenza, against which antibiotics are ineffective. This misuse further fueled the development of resistance.
* Self-Medication: Over-the-counter availability of antibiotics led to self-medication, where individuals used antibiotics without a healthcare professional's guidance or diagnosis. This practice often resulted in inappropriate and ineffective treatment.
* Emergence of Resistant Strains: As a consequence of these factors, bacteria were exposed to antibiotics on a massive scale. Some strains acquired resistance genes through mutations or horizontal gene transfer, leading to the emergence of antibiotic-resistant strains.
* Increasing Concerns: As antibiotic resistance began to emerge and spread, concerns within the medical and scientific communities grew. Researchers and healthcare professionals started recognizing the need for more responsible antibiotic use to mitigate the threat of AMR.

The period of overuse and misuse of antibiotics from the 1950s to the 1970s played a pivotal role in the development of antimicrobial resistance. It led to the widespread prevalence of resistant bacteria and set the stage for the global health challenge that AMR represents today. In response to these concerns, efforts to promote responsible antibiotic use and implement antibiotic stewardship programs have become essential components of modern healthcare practices.

**2.1.4 Emergence of Multidrug Resistance (1970s-1980s)18:** Bacteria developed resistance to multiple antibiotics, leading to the emergence of multidrug-resistant strains. Hospitals and healthcare settings became hotspots for resistant infections.

* Widespread Antibiotic Use Continues: The use of antibiotics continued to escalate in both human medicine and agriculture during the 1970s and 1980s. Antibiotics were prescribed for a variety of infections, and their use in agriculture for growth promotion and disease prevention persisted.
* Evolution of Resistant Strains: Bacteria, being highly adaptable, continued to evolve mechanisms to survive the selective pressure imposed by antibiotics. This led to the development of strains resistant to multiple drugs.
* Hospital-Acquired Infections Intensify: Hospitals became hotspots for the emergence of multidrug-resistant bacteria. Patients in healthcare settings were often exposed to multiple courses of antibiotics, creating an environment conducive to the development and spread of resistant strains.
* Proliferation of MDR Gram-Negative Bacteria: Gram-negative bacteria, such as Escherichia coli and Klebsiella pneumonia, were among the bacteria that exhibited multidrug resistance. The development of Extended-Spectrum Beta-Lactamases (ESBLs) became a notable concern, conferring resistance to a broad range of beta-lactam antibiotics.
* Methicillin-Resistant Staphylococcus aureus (MRSA): Methicillin-resistant Staphylococcus aureus (MRSA) gained prominence during this period. MRSA strains were resistant to beta-lactam antibiotics, including methicillin, making them challenging to treat. MRSA infections were not limited to healthcare settings and began to appear in the community as well.
* Vancomycin-Resistant Enterococcus (VRE): Vancomycin-resistant Enterococcus (VRE) emerged, posing challenges in treating infections caused by Enterococci, a group of bacteria commonly found in the gastrointestinal tract.
* Limited Treatment Options: The emergence of multidrug-resistant strains limited treatment options for bacterial infections. Some infections became increasingly difficult to manage, contributing to higher morbidity and mortality rates.
* Transmission of Resistance Genes: Resistance genes responsible for multidrug resistance could be transferred between bacteria through plasmids and other mechanisms. This facilitated the rapid spread of resistance genes among different bacterial species.
* Awareness and Surveillance Increase: The healthcare community became increasingly aware of the magnitude of the problem, leading to improved surveillance systems to monitor the prevalence of multidrug-resistant strains.
* Global Recognition of AMR: The emergence of multidrug resistance contributed to the global recognition of antimicrobial resistance as a serious public health threat. International organizations, including the World Health Organization (WHO), began to address AMR as a priority issue.

 **2.1.5** **Rise of Extended-Spectrum Beta-Lactamases (ESBLs) and Carbapenem Resistance (1990s-2000s)19**

The rise of Extended-Spectrum Beta-Lactamases (ESBLs) and carbapenem resistance during the 1990s and 2000s marked a concerning development in the ongoing evolution of antimicrobial resistance (AMR). This period witnessed the emergence of bacteria with heightened resistance to a broad spectrum of antibiotics, posing significant challenges for clinical management. Here are key points regarding the rise of ESBLs and carbapenem resistance:

* Extended-spectrum beta-lactamases (ESBLs): ESBLs are enzymes produced by certain bacteria that confer resistance to a broad range of beta-lactam antibiotics, including penicillins and cephalosporins. They are particularly effective against extended-spectrum cephalosporins. Bacteria-producing ESBLs are often Gram-negative, such as Escherichia coli and Klebsiella pneumoniae. These enzymes hydrolyze beta-lactam antibiotics, rendering them ineffective.
* Proliferation of ESBL-Producing Bacteria: ESBL-producing bacteria have become increasingly prevalent, especially in healthcare settings. Patients with infections caused by these bacteria faced limited treatment options, as many commonly used antibiotics were no longer effective. The spread of ESBLs was not confined to healthcare facilities; community-acquired infections also became a concern.
* Risk Factors for ESBL Infections: Patients in hospitals, particularly those with prolonged hospital stays and exposure to multiple antibiotics, were at an increased risk of acquiring infections caused by ESBL-producing bacteria. Infections in long-term care facilities, where antibiotic use is often high, contributed to the dissemination of ESBLs.
* Carbapenem Resistance: Carbapenems are a class of antibiotics often considered a last resort for treating serious bacterial infections. The emergence of resistance to carbapenems, known as carbapenem resistance, significantly limited treatment options. Carbapenem resistance is often associated with the production of carbapenemase enzymes, which hydrolyze carbapenem antibiotics. Bacteria within the Enterobacteriaceae family, such as Klebsiella pneumoniae and Escherichia coli, were among the notable contributors to the rise of carbapenem resistance.
* Klebsiella pneumoniae Carbapenemase (KPC): The production of enzymes like Klebsiella pneumoniae carbapenemase (KPC) became a major concern, conferring resistance to carbapenem antibiotics.
* Healthcare-Associated Outbreaks: Carbapenem-resistant strains, often associated with healthcare settings, led to outbreaks in hospitals. These outbreaks posed challenges in infection control and patient management.
* Global Spread of Resistance Genes: The genetic elements conferring ESBL and carbapenem resistance could be transmitted horizontally between bacteria, facilitating the global spread of resistance genes.
* Challenges in Treatment: The emergence of ESBLs and carbapenem resistance further limited treatment options for bacterial infections, complicating the management of serious illnesses.
* Global Surveillance and Action: Increased awareness of the severity of the problem led to the establishment of global surveillance programs to monitor the prevalence and spread of ESBLs and carbapenem-resistant bacteria. International organizations and health agencies developed action plans to address the rise of multidrug resistance, emphasizing the importance of antibiotic stewardship and the development of new antibiotics

**2.1.6** **Global Concern (2000s-Present)19:** The global concern regarding antimicrobial resistance (AMR) has escalated significantly from the 2000s to the present, reflecting the growing recognition of AMR as a major threat to public health, healthcare systems, and global well-being. Several key factors have contributed to this heightened concern:

* Increasing Resistance Rates: Antibiotic resistance rates have continued to rise globally, affecting a wide range of bacterial pathogens. The emergence of resistant strains to multiple classes of antibiotics has become more commonplace.
* Impact on Human Health: Resistant infections pose a severe threat to human health. Treatments for common infections become less effective, leading to prolonged illnesses, increased mortality, and higher healthcare costs.
* Globalization and Travel: Increased global travel and interconnectedness facilitate the spread of resistant bacteria across borders. Resistant strains that emerge in one region can quickly become a global concern.
* One Health Approach: The understanding of AMR as a complex and interconnected issue has led to the adoption of a "One Health" approach. This approach recognizes the interconnectedness of human health, animal health, and the environment in the spread of resistance.
* Overuse in Agriculture: The use of antibiotics in agriculture for promoting animal growth and preventing diseases has raised concerns. Agricultural practices contribute to the development and spread of resistant bacteria, affecting both animals and humans.
* Limited New Antibiotic Development: The pipeline for the development of new antibiotics has remained limited. Pharmaceutical companies face challenges in bringing new drugs to market, leading to a gap in the availability of effective treatments.
* Global Surveillance and Reporting: Increased surveillance efforts and reporting mechanisms have been established globally. Organizations like the World Health Organization (WHO) monitor antibiotic resistance patterns, providing valuable data to guide global strategies.
* High-Profile Reports and Initiatives: High-profile reports, such as the WHO Global Antimicrobial Resistance Surveillance System (GLASS) report, have highlighted the extent of the problem. International initiatives, including the Global Action Plan on AMR, have been launched to coordinate efforts.
* Antibiotic Stewardship Programs: Antibiotic stewardship programs have gained prominence, emphasizing the responsible use of antibiotics in healthcare settings. This includes guidelines for prescribing, educating healthcare professionals, and promoting awareness among the public.
* Public Awareness and Education: Public awareness campaigns have been implemented to educate people about the responsible use of antibiotics. Efforts focus on discouraging self-medication, completing prescribed courses, and understanding the consequences of antibiotic misuse.
* International Collaboration: Countries around the world have recognized the need for international collaboration to address AMR comprehensively. Efforts involve sharing data, coordinating policies, and supporting research to combat resistance.
* Policy and Regulatory Measures: Governments and international bodies are implementing policy and regulatory measures to curb antibiotic misuse. This includes regulations on over-the-counter sales, restrictions on agricultural antibiotic use, and incentives for the development of new antibiotics.

**2.1.7** **Antibiotic Development Challenges:**

The development of new antibiotics faces several challenges, contributing to a notable decline in the number of novel antibiotics reaching the market. These challenges stem from various economic, scientific, and regulatory factors. Here are some key antibiotic development challenges:

* Economic Challenges: Antibiotics are typically short-course therapies, and compared to drugs for chronic conditions, they are less profitable for pharmaceutical companies. The low return on investment has led many companies to prioritize other therapeutic areas.
* Scientific Challenges: Understanding the biology of bacteria and the mechanisms of antibiotic resistance is complex. Developing drugs that effectively target bacterial pathogens while minimizing harm to the host's microbiota is challenging.
* High Development Costs: Conducting rigorous clinical trials to demonstrate the safety and efficacy of new antibiotics is expensive. The high cost of development, coupled with uncertain market returns, makes investors hesitant to fund antibiotic research.
* Regulatory Hurdles: Regulatory agencies have stringent requirements for the approval of new antibiotics to ensure safety and efficacy. Complying with these requirements adds to the time and cost of development.
* Limited Market Size: The market for antibiotics is limited compared to drugs for chronic conditions. As a result, pharmaceutical companies may perceive a smaller market potential, discouraging investment in antibiotic research and development.
* Resistance Concerns: Developers often anticipate that bacteria will eventually develop resistance to any new antibiotic. This understanding may impact the perceived lifespan and profitability of a new drug.
* Lack of Novel Targets: Identifying novel bacterial targets that are essential for survival and have a low risk of resistance is challenging. Many existing antibiotics target similar mechanisms, contributing to cross-resistance.
* Overuse and Misuse Concerns: Developers may be concerned that once a new antibiotic is on the market, it could face overuse or misuse, leading to the rapid development of resistance and reducing its effectiveness over time.
* Clinical Trial Design Issues: Designing clinical trials for antibiotics involves unique challenges, including the need to select appropriate endpoints, demonstrate non-inferiority to existing treatments, and navigate ethical considerations related to placebo-controlled trials.
* Lack of Incentives: The absence of sufficient financial incentives, such as market exclusivity and high reimbursement rates, may discourage companies from investing in antibiotic development.
* Global Access and Affordability: Developers face challenges in finding a balance between making antibiotics accessible and affordable globally while ensuring profitability and recouping development costs.
* Addressing these challenges requires a multi-stakeholder approach involving governments, regulatory agencies, pharmaceutical companies, researchers, and public health organizations. Efforts to incentivize antibiotic development, streamline regulatory processes, and promote responsible antibiotic use are crucial to overcoming these obstacles and ensuring a sustainable pipeline of effective antibiotics for the future

**2.1.8.** **One Health Approach (2010s-Present)20,21:**

The One Health approach, which gained prominence in the 2010s and continues to be a vital framework today, emphasizes the interconnectedness of human health, animal health, and environmental health. This holistic approach recognizes that the health of people, animals, and the environment is interdependent, and it aims to address complex health challenges, including antimicrobial resistance (AMR). Here's an overview of the One Health approach in the context of AMR:

* Interconnectedness of Health Sectors: The One Health approach acknowledges that the health of humans, animals, and the environment is closely linked. Diseases and health threats, including AMR, can originate in any of these sectors and have spillover effects.
* Antibiotic Use in Agriculture: One significant aspect of the One Health approach is its consideration of antibiotic use in agriculture. Antibiotics are commonly used in livestock for disease prevention and growth promotion. This agricultural use contributes to the emergence and spread of antibiotic-resistant bacteria, which can affect both animals and humans.
* Zoonotic Diseases and AMR: Many infectious diseases are zoonotic, meaning they can be transmitted between animals and humans. The transmission of resistant bacteria from animals to humans (and vice versa) is a key concern. The One Health approach addresses the role of animals as reservoirs for resistant strains and the potential for transmission to humans.
* Environmental Reservoirs of Resistance: The environment, including water sources and soil, can serve as reservoirs for antibiotic-resistant genes. The release of antibiotics into the environment, whether from agricultural runoff or human waste, contributes to the selection and dissemination of resistance genes. The One Health approach considers the environmental dimension of AMR.
* Collaborative Efforts: One Health encourages collaboration among various sectors, including human and veterinary medicine, environmental science, agriculture, and public health. This collaborative effort is essential for a comprehensive understanding of AMR and the development of effective strategies to mitigate its impact.
* Surveillance and Monitoring: The One Health approach emphasizes the importance of surveillance and monitoring of antibiotic use and resistance in humans, animals, and the environment. This data is crucial for identifying emerging threats, tracking trends, and designing targeted interventions.
* Antibiotic Stewardship: Antibiotic stewardship programs, which promote the responsible use of antibiotics, are a key component of the One Health approach. These programs aim to optimize the use of antibiotics to treat infections while minimizing the development of resistance.
* Global Health Security: AMR is recognized as a threat to global health security. The One Health approach contributes to global efforts to address this threat by fostering international collaboration, information sharing, and coordinated responses to emerging challenges.
* Research and Innovation: The One Health approach supports research and innovation in areas such as alternative therapies, vaccines, and diagnostic tools. These efforts aim to reduce reliance on antibiotics, develop new treatment options, and combat AMR.

The One Health approach represents a paradigm shift in how we address health challenges, including AMR. By recognizing the interconnected nature of human, animal, and environmental health, this approach provides a comprehensive framework for understanding and combating the complex issue of antimicrobial resistance. Ongoing efforts within the One Health framework are essential for developing sustainable solutions to mitigate the impact of AMR on a global scale.

**2.1.9.** **Research and Innovation (2010s-Present)20,21**

In the 2010s and continuing into the present, research and innovation in the field of antimicrobial resistance (AMR) have been crucial in developing new strategies, treatments, and interventions to address the growing challenges posed by resistant pathogens. Here are key aspects of research and innovation in the context of AMR during this period:

* New Antibiotics and Therapies: The development of novel antibiotics has been a focus of research. Scientists have explored new classes of antibiotics or modified existing ones to enhance their effectiveness. This includes research into drugs that target resistant bacteria, especially those that have become resistant to multiple existing antibiotics.
* Alternative Therapies: Researchers have investigated alternative treatment approaches to antibiotics. This includes the exploration of bacteriophage therapy, which involves using viruses that infect and kill bacteria. Other alternatives include antimicrobial peptides and probiotics, which can help modulate the microbial balance in the body.
* Combination Therapies: Research has explored the effectiveness of combining multiple antibiotics or therapies to overcome resistance. Combining drugs with different mechanisms of action can enhance their efficacy and reduce the likelihood of the development of resistance.
* Precision Medicine for Infectious Diseases: Advances in precision medicine have allowed for more targeted and personalized treatment approaches. Understanding the genetic makeup of both the host and the infecting pathogen enables the development of treatments tailored to the specific characteristics of the infection.
* Vaccines Against Resistant Pathogens: Research has focused on developing vaccines to prevent infections caused by resistant bacteria. Vaccination not only reduces the incidence of infections but also helps minimize the need for antibiotics, thus lowering the selective pressure for resistance.
* Diagnostic Innovations: Rapid and accurate diagnostics play a crucial role in the appropriate use of antibiotics. Advances in diagnostic technologies, including point-of-care tests and molecular diagnostics, enable healthcare providers to identify the causative agents of infections quickly and determine their susceptibility to antibiotics.
* Antimicrobial Stewardship Programs: Research has been conducted to evaluate the impact and effectiveness of antimicrobial stewardship programs. These programs aim to optimize the use of antibiotics in healthcare settings, ensuring that they are used appropriately, and helping to prevent the development and spread of resistance.
* Surveillance and Epidemiology: Ongoing research involves the surveillance of resistance patterns and the epidemiology of resistant strains. This information is crucial for understanding the dynamics of resistance, identifying emerging threats, and designing targeted interventions.
* Global Collaborations and Initiatives: International collaborations and initiatives have been established to foster research and innovation on a global scale. Organizations, governments, and researchers work together to share data, resources, and expertise in the fight against AMR.
* Public Awareness and Education: Research has explored effective ways to raise public awareness and educate healthcare professionals about the responsible use of antibiotics. Communication strategies and educational campaigns aim to reduce unnecessary antibiotic prescriptions and promote awareness of the consequences of AMR.

Research and innovation in the field of antimicrobial resistance have been dynamic and diverse in the 2010s and beyond. The multifaceted nature of this challenge requires ongoing efforts to develop new tools, therapies, and strategies to effectively combat resistant pathogens and ensure the continued efficacy of antimicrobial treatments.

**2.2.10** **Global Action (2020s-Present)20,21:** In the 2020s and continuing into the present, global action against antimicrobial resistance (AMR) has gained momentum as a critical component of public health and international collaboration. Efforts have been made at various levels, involving governments, international organizations, healthcare professionals, researchers, and the public. Here are key aspects of global action against AMR in the current decade:

* Global Strategies and Policies: International organizations, including the World Health Organization (WHO), the Food and Agriculture Organization (FAO), and the World Organization for Animal Health (OIE), have continued to develop and implement global strategies and policies to address AMR. These frameworks guide surveillance, prevention, and control measures.
* National Action Plans: Many countries have developed and implemented national action plans to tackle AMR. These plans outline specific measures and interventions at the national level, involving healthcare systems, agriculture, and other relevant sectors.
* Surveillance Systems: Enhanced global surveillance systems for monitoring antimicrobial use and resistance have been established. These systems help track trends, identify emerging threats, and guide interventions to address specific challenges in different regions.
* Collaboration Across Sectors: The One Health approach, emphasizing collaboration between human health, animal health, and environmental sectors, continues to be a central theme in global efforts against AMR. Collaborative initiatives bring together professionals from diverse fields to address the interconnected nature of resistance.
* Regulatory Measures: Regulatory agencies in many countries have implemented measures to control the use of antibiotics in human medicine, veterinary medicine, and agriculture. These measures include restrictions on over-the-counter antibiotic sales and the implementation of prescription-only policies.
* Research and Development Incentives: Efforts to incentivize research and development of new antibiotics and alternative therapies have been explored. Mechanisms such as public-private partnerships, grants, and regulatory incentives aim to stimulate innovation in the development of antimicrobial agents.
* International Partnerships: Countries and organizations collaborate through international partnerships to share knowledge, resources, and best practices. These partnerships facilitate a coordinated global response to AMR, addressing challenges that extend beyond national borders.
* Awareness Campaigns: Public awareness campaigns and educational initiatives seek to inform the general public, healthcare professionals, and policymakers about the importance of responsible antibiotic use. These campaigns aim to reduce unnecessary antibiotic prescriptions and raise awareness of the consequences of AMR.
* Access to Essential Medicines: Ensuring access to essential medicines, including antibiotics, while promoting responsible use is a key consideration in global action against AMR. Efforts focus on striking a balance between providing necessary treatments and preventing misuse.
* Global Health Security Agenda: AMR is recognized as a threat to global health security, and efforts are aligned with broader global health security agendas. Preparedness for infectious disease threats, including those involving resistant pathogens, is integrated into these agendas.
* Pandemic Response and AMR: The COVID-19 pandemic has underscored the importance of addressing AMR, especially in the context of secondary bacterial infections. The pandemic has highlighted the need for resilient health systems and strategies that consider both viral and bacterial threats.

The 2020s have seen increased global awareness and action against AMR, with concerted efforts to implement strategies, foster collaboration, and address the multifaceted challenges posed by resistant pathogens. Continued commitment to these efforts is essential to mitigate the impact of AMR on a global scale and ensure the effectiveness of antimicrobial treatments in the years to come.

Microbes develop resistance to drugs through a natural process of evolution driven by selective pressure. This phenomenon is a result of the microbes' ability to adapt to their environment, including exposure to antimicrobial drugs. Here's an overview of how and why microbes develop resistance to drugs:

**2.2 How Microbes Develop Resistance24,25**

* Genetic Variation: Microbial populations naturally have genetic variation. Within a population of microbes, some individuals may have genetic mutations or variations that provide them with a survival advantage when exposed to drugs**33**.
* Selective Pressure: When antimicrobial drugs are introduced, they exert selective pressure on the microbial population. The drugs may kill or inhibit the growth of susceptible microbes, leaving behind those with genetic traits that confer resistance**34**.
* Survival of Resistant Strains: Resistant microbes survive and reproduce, passing on their resistance traits to the next generation. Over time, the proportion of resistant microbes in the population increases by 35.36.
* Horizontal Gene Transfer: Microbes can also acquire resistance genes through horizontal gene transfer. This is the transfer of genetic material (often carried on plasmids) between different microbes, allowing the rapid spread of resistance traits within a population.



 **Fig-1:**

 (Timeline of discovery of major antibiotics and antibiotic resistance)

**2.3 Why Microbes Develop Resistance**

* Natural Selection: Microbial resistance is a classic example of natural selection. The use of antimicrobial drugs creates an environment where only the resistant microbes survive and reproduce, leading to a population with an increasing proportion of resistant individuals.
* Overuse and Misuse of Antimicrobials: Overuse and misuse of antimicrobial drugs contribute significantly to the development of resistance. When antibiotics are used unnecessarily or inappropriately (e.g., not completing a prescribed course), it creates conditions for the survival of resistant strains.
* Incomplete Treatment Courses: Not completing a prescribed course of antibiotics allows some microbes to survive exposure to the drug. These surviving microbes may be the ones with resistance traits, leading to the development of a more resilient population.
* Inadequate Dosing: Inadequate dosing of antimicrobials, whether due to underprescribing or patient non-compliance, can also contribute to the incomplete elimination of microbes and the selection of resistant strains.
* Use in Agriculture: The use of antimicrobials in agriculture for growth promotion and disease prevention in livestock contributes to the overall selective pressure on microbes. Resistant strains that develop in animals can be transmitted to humans through food consumption or environmental exposure.
* Hospital Environments: In healthcare settings, overreliance on broad-spectrum antibiotics and inadequate infection control practices can promote the survival and spread of resistant microbes within hospitals.

**2.4 The Silent Crisis Unfolding: Microbial Resistance in Numbers**

In the microscopic battleground of microbes versus medicine, the statistics paint a chilling picture of a crisis steadily intensifying. The scope and scale of microbial resistance demand our attention and action, for the numbers tell a story of a world on the brink.

* Global Antibiotic Consumption: According to the World Health Organization (WHO), global antibiotic consumption rose by 65% between 2000 and 2015. This surge reflects not only an increased demand for treatment but also the potential for heightened selective pressure leading to resistance.
* Antibiotic Resistance and Mortality: A study published in The Lancet estimates that by 2050, antibiotic resistance could cause 10 million deaths annually, surpassing current numbers for cancer-related deaths.
* Multidrug-Resistant Tuberculosis (MDR-TB): Tuberculosis, a disease once controllable with antibiotics, now faces the challenge of multidrug resistance. Approximately 3.5% of new TB cases and 18% of previously treated cases are estimated to be multidrug-resistant globally.
* Hospital-Acquired Infections: The Centers for Disease Control and Prevention (CDC) reports that in the United States alone, about 2.8 million antibiotic-resistant infections occur each year, leading to over 35,000 deaths. Hospital-acquired infections contribute significantly to these alarming numbers.
* Agricultural Antibiotic Use: Antibiotic use in agriculture is substantial. The Food and Agriculture Organization (FAO) estimates that approximately 73% of global antibiotic use is in the agricultural sector, contributing to the rise of resistant strains that can affect both animals and humans.
* Limited New Antibiotics: Despite the growing threat of microbial resistance, the development of new antibiotics remains sluggish. Only a handful of new antibiotics have been approved in recent years, highlighting the urgent need for increased research and innovation.
* Economic Impact: A report commissioned by the UK government estimates that by 2050, the global economic impact of antimicrobial resistance could result in a cumulative loss of $100 trillion, posing a severe strain on healthcare systems and economies.
* Global Surveillance Challenges: Surveillance of antimicrobial resistance remains a challenge. The WHO Global Antimicrobial Surveillance System (GLASS) reveals significant gaps in data availability, hindering our ability to fully comprehend the global landscape of microbial resistance.

**2.5 Facing the Numbers: A Call to Urgent Action**

As we confront these statistics, it becomes evident that microbial resistance is not just a theoretical concern; it's an imminent threat demanding our immediate attention. The figures underscore the urgent need for a comprehensive, coordinated effort—from individual responsibility in antibiotic use to global collaborations in research and policy. It is a call to action that must resonate in laboratories, hospitals, and homes alike, for the numbers speak of a future we can still shape, provided we act decisively now.

* The statistics on microbial resistance serve as a stark wake-up call, ringing loud and clear in the corridors of healthcare, research, and policy. Behind each figure lies the potential for a future where our most formidable medical tools crumble in the face of microscopic adversaries. It's a call to arms, a rallying cry for urgent action that resonates across borders and disciplines.
* Individual Responsibility: Completing Antibiotic Courses: Individuals must adhere to prescribed antibiotic courses diligently, avoiding premature discontinuation even if symptoms alleviate. Incomplete courses contribute to the survival of resilient strains.
* Responsible Antibiotic Use: The indiscriminate use of antibiotics, whether obtained over the counter or through self-prescription, must be curbed. Public awareness campaigns are vital to educate communities on the consequences of misuse.
* Healthcare Practices: Infection Control Protocols: Hospitals and healthcare facilities must prioritize stringent infection control measures. Robust protocols can mitigate the spread of resistant strains within healthcare settings, safeguarding both patients and healthcare workers.
* Prudent Antibiotic Prescribing: Healthcare professionals play a pivotal role in combating resistance. Prudent antibiotic prescribing, informed by diagnostic tests and a thorough understanding of microbial resistance patterns, is paramount.
* Research and Innovation: Investment in New Antibiotics: Governments, pharmaceutical companies, and research institutions must collaborate to incentivize the development of new antibiotics. The current pipeline's inadequacy underscores the urgent need for increased research and innovation.
* Alternative Therapies: Exploring alternative therapies, such as bacteriophage therapy and immunotherapies, can diversify our arsenal against microbial infections, reducing the selective pressure on traditional antibiotics.
* Policy and Regulation: Global Collaboration: International cooperation is indispensable. Countries must unite to enact and enforce regulations that govern the use of antimicrobials in healthcare, agriculture, and other sectors, ensuring a cohesive global response.
* Antibiotic Stewardship Programs: Implementing antibiotic stewardship programs in healthcare settings can optimize antibiotic use, promoting the right drug, at the right dose, and for the right duration.
* Public Awareness and Education: Empowering Communities: Robust public awareness campaigns must convey the gravity of microbial resistance. Empowered communities can become advocates for responsible antibiotic use, influencing societal norms.
* Educating Future Generations: Integrating education on microbial resistance into school curricula fosters a generation with a deep understanding of the importance of preserving the efficacy of antimicrobials.
* International Collaboration: Data Sharing and Surveillance: Strengthening global surveillance efforts is imperative. Countries should share data on antimicrobial resistance patterns to enhance our collective understanding and response to this global threat.
* Capacity Building in Developing Nations: Support for developing nations is crucial in building capacity for surveillance, research, and the implementation of antimicrobial stewardship programs.

**3. TYPES OF MICROBIAL RESISTANCE**

Microbial resistance manifests in various forms, and understanding these types is crucial in devising effective strategies to combat the growing threat. Here are the main types of microbial resistance:

* Antibiotic Resistance**24**: Bacteria adapt and develop mechanisms to withstand the effects of antibiotics, rendering these drugs less effective or entirely ineffective. Include the production of enzymes that inactivate antibiotics, alterations in the target sites of antibiotics, and the efflux of antibiotics from bacterial cells.
* Antiviral Resistance**25**: Viruses can develop resistance to antiviral drugs, limiting the effectiveness of treatment against viral infections. May involve mutations in the viral genome that affect drug binding or the inhibition of the drug's target enzyme.
* Antifungal Resistance: Fungi, including yeasts and molds, can develop resistance to antifungal medications, making the treatment of fungal infections more challenging. Include changes in the structure of fungal cell membranes or cell walls, as well as the overexpression of efflux pumps that remove antifungal drugs from fungal cells.
* Antiparasitic Resistance: Parasites, such as protozoa and helminths, can develop resistance to drugs used to treat parasitic infections. Involve genetic changes in the parasites that affect drug targets or the ability of the parasites to pump out or metabolize the drugs.
* Multi-Drug Resistance (MDR): Microbes become resistant to multiple drugs, often belonging to different classes, making the treatment of infections increasingly challenging. Bacteria, especially in healthcare settings where the use of broad-spectrum antibiotics is prevalent.
* Cross-Resistance: Resistance to one drug confers resistance to another drug with a similar mechanism of action. Cross-resistance between different classes of antibiotics, where resistance to one class may result in reduced efficacy of another class.
* Intrinsic vs. Acquired Resistance**24,25**
* Intrinsic Resistance: Naturally present in some microbes due to inherent characteristics that make them less susceptible to certain drugs**27,28**.
* Acquired Resistance: Develops over time through genetic changes, often in response to exposure to antimicrobial drugs**29,30**.
* Biofilm-Mediated Resistance: Microbes within biofilms (aggregations of microorganisms on surfaces) can exhibit increased resistance to antimicrobial agents compared to their planktonic counterparts. Biofilm structure and the production of protective extracellular substances contribute to reduced drug penetration.
* Heteroresistance: Within a population of microbes, some individuals exhibit resistance while others remain susceptible to the same drug. Heteroresistance can complicate treatment, as the presence of resistant subpopulations may lead to treatment failure.

***Microbes employ various mechanisms37,38*** to become resistant to antimicrobial drugs, enabling them to survive and thrive in the presence of these agents. Understanding these mechanisms is crucial for developing strategies to counteract microbial resistance. Here are some common mechanisms by which microbes develop resistance:

* Mutation of Target Sites**43**: Microbes can undergo genetic mutations that alter the structure of their cellular targets, such as enzymes or proteins, which are essential for the action of antimicrobial drugs. Bacteria may undergo mutations in the target site of antibiotics, preventing the drugs from binding effectively and inhibiting microbial functions.
* Enzymatic Inactivation**37,44,48**: Microbes can produce enzymes that modify or degrade antimicrobial drugs, rendering them inactive. Beta-lactamase produced by some bacteria can break down beta-lactam antibiotics, such as penicillin before they can exert their antibacterial effects.
* Efflux Pumps**40,48**: Microbes can develop efflux pumps that actively pump out antimicrobial drugs, reducing their intracellular concentration and efficacy. Bacterial cells may have efflux pumps that expel antibiotics, preventing the drugs from reaching concentrations sufficient to inhibit microbial growth.
* Changes in Cell Permeability**45**: Microbes may alter the permeability of their cell membranes or walls to reduce the entry of antimicrobial drugs. Some bacteria can modify the composition of their outer membrane to limit the penetration of antibiotics.
* Biofilm Formation**41**: Microbes within biofilms, structured communities of microorganisms, can exhibit increased resistance to antimicrobial agents compared to their planktonic counterparts. Biofilm matrix and structure create physical barriers that impede the penetration of drugs, making it challenging to eradicate microbial populations.
* Genetic Transfer and Horizontal Gene Transfer: Microbes can acquire resistance genes through horizontal gene transfer, exchanging genetic material with other microbes. Plasmids carrying resistance genes can be transferred between bacteria, contributing to the rapid spread of resistance.
* Antibiotic Modification: Microbes may modify the chemical structure of antimicrobial drugs, reducing their effectiveness. Some bacteria produce enzymes that modify the structure of antibiotics, preventing the drugs from interacting with their target sites.
* Heteroresistance: Within a population of microbes, some individuals may exhibit resistance while others remain susceptible to the same drug. Heteroresistance can complicate treatment, as the presence of resistant subpopulations may lead to treatment failure.
* Stress Response and Persister Cells: Microbes can enter a dormant state (persister cells) during stress conditions, becoming less susceptible to antimicrobial drugs. Persister cells can survive antibiotic treatment and later resume active growth, contributing to recurrent infections.
* Adaptive Responses: Microbes can activate specific pathways in response to stress, inducing changes that enhance their survival in the presence of antimicrobial agents. Bacteria may upregulate stress response genes, leading to increased tolerance to antibiotics**31,32**.



 **Fig-2**

 (Antibiotic targets and mechanisms of drug resistance)

**4. FACTORS CONTRIBUTING TO MICROBIAL RESISTANCE**

Microbial resistance is a complex and multifaceted issue influenced by various factors. Understanding these contributing factors is essential for devising effective strategies to mitigate the emergence and spread of resistant microbes. Here are key factors that contribute to microbial resistance**38.50,51**:

* Overuse and Misuse of Antimicrobials**52**: Excessive and inappropriate use of antimicrobial drugs in human and animal healthcare. Overuse and misuse create a selective pressure that Favors the survival of resistant strains**53,54**.
* Inadequate Dosage and Treatment Duration**57**: Not completing prescribed courses of antimicrobial treatment or using inadequate dosages. Incomplete treatment allows surviving microbes with resistance traits to proliferate**58**.
* Self-Medication and Over-the-Counter Availability**59.60**: Self-prescription and over-the-counter availability of antimicrobial drugs without a prescription. Unregulated access contributes to inappropriate use and the development of resistance.
* Use in Agriculture and Animal Husbandry**63**: Widespread use of antimicrobials in agriculture for growth promotion and disease prevention in animals. Agricultural use contributes to the emergence of resistant strains that can affect humans through food consumption and environmental exposure 64,65.
* Globalization and Travel**66**: Increased global travel facilitates the spread of resistant microbes across borders. Resistant strains can be introduced to new regions, making containment and control challenging**67**.
* Lack of Access to Clean Water and Sanitation**61**: Poor sanitation and lack of access to clean water can lead to the spread of infections, increasing the demand for antimicrobial treatment. Higher infection rates contribute to increased antimicrobial use and selective pressure.
* Lack of Surveillance and Monitoring**62**: Inadequate systems for monitoring antimicrobial use and resistance. Insufficient data hinders the understanding of resistance patterns and the development of targeted interventions.
* Poor Infection Prevention and Control Practices**68**: Inadequate hygiene measures in healthcare settings contribute to the spread of infections. Increased infection rates lead to higher antimicrobial use, fostering the development of resistance.
* Global Antibiotic Supply Chain Issues**69**: Disruptions or deficiencies in the global supply chain for antibiotics. Shortages or limited availability may lead to inappropriate use or the use of suboptimal alternatives.
* Lack of New Drug Development: Limited investment and incentives for the development of new antimicrobial drugs. The stagnant pipeline for new drugs leaves healthcare providers with fewer options to combat emerging resistant strains.
* Inappropriate Use in Veterinary Medicine: The use of antimicrobials in veterinary medicine for growth promotion or disease prevention without proper oversight. Similar to agriculture, veterinary use contributes to the development of resistant strains that may affect humans.
* Environmental Factors: The release of antimicrobial residues into the environment. Environmental exposure can contribute to the selection and persistence of resistant microbes

**5. CONSEQUENCES OF MICROBIAL RESISTANCE**

The consequences of microbial resistance are profound and extend across various domains, impacting individuals, communities, healthcare systems, and global public health. Here are the key consequences of microbial resistance**70**:

* Limited Treatment Options: Microbial resistance reduces the effectiveness of existing antimicrobial drugs, limiting the available treatment options for bacterial, viral, fungal, and parasitic infections.
* Increased Morbidity and Mortality: Resistant infections are associated with higher rates of morbidity and mortality. Common and once-treatable infections become more challenging to manage, leading to severe health outcomes.
* Prolonged Illness and Suffering: Patients with resistant infections often experience prolonged illness, suffering, and a reduced quality of life due to the limited efficacy of available treatments.
* Complications in Medical Procedures: Surgeries, chemotherapy, and organ transplants become riskier as the risk of infections increases, and the effectiveness of prophylactic and therapeutic antimicrobial measures diminishes.
* Economic Burden: The economic burden of treating resistant infections is substantial. Increased healthcare costs, longer hospital stays, and the need for more expensive second-line treatments contribute to economic strain on individuals and healthcare systems.
* Reduced Effectiveness of Healthcare Interventions: The efficacy of various healthcare interventions, including cancer treatments, is compromised when microbial resistance limits the effectiveness of supporting antimicrobial therapies.
* Spread of Infections: Resistant microbes can spread more easily within communities and healthcare settings, leading to increased transmission of infections. This contributes to the persistence and amplification of resistant strains.
* Global Health Security Threat: Microbial resistance poses a threat to global health security. Resistant strains can cross international borders, challenging efforts to control and manage infectious diseases on a global scale.
* Loss of Medical Advances: The rise of microbial resistance jeopardizes decades of medical advances. Routine medical procedures, such as cesarean sections and joint replacements, become riskier without effective antimicrobial support.
* Compromised One Health: The interconnectedness of human, animal, and environmental health is disrupted. Microbial resistance affects not only human health but also agricultural practices, veterinary medicine, and ecosystems.
* Impaired Control of Epidemics and Pandemics: Microbial resistance can impede the control of infectious disease outbreaks, making it more challenging to contain and manage epidemics and pandemics.
* Undermined Trust in Healthcare: The inability to effectively treat infections erodes trust in healthcare systems. Patients may face disillusionment with medical interventions, leading to a decline in healthcare-seeking behavior.
* Social and Equity Issues: Vulnerable populations may bear a disproportionate burden of resistant infections, exacerbating existing social and health inequalities.
* Antibiotic-Resistant Tuberculosis: The rise of multidrug-resistant tuberculosis (MDR-TB) poses a severe threat to tuberculosis control efforts, with longer and more complex treatment regimens and higher mortality rates.
* Challenges in HIV Treatment: Antiretroviral therapy for HIV may face challenges as resistant strains emerge, making it more difficult to control the virus and manage the HIV epidemic

 **6.** **GLOBAL INITIATIVES AND EFFORTS**

Addressing microbial resistance requires a coordinated and global effort, and several initiatives and efforts have been established to tackle this pressing issue. These initiatives aim to promote responsible antimicrobial use, enhance surveillance, support research and development of new drugs, and foster collaboration among nations. Here are some notable global initiatives and efforts**71**:

* World Health Organization (WHO) Global Action Plan on Antimicrobial Resistance (AMR): To ensure effective action across multiple sectors and promote the development of new antimicrobial drugs. Advocates for improved awareness, surveillance, infection prevention and control, optimal use of antimicrobials, and research to fill gaps in knowledge.
* Global Antimicrobial Resistance Surveillance System (GLASS): To improve the understanding of antimicrobial resistance by collecting, analyzing, and sharing data on a global scale. Facilitates the standardization of surveillance methods and data reporting to enhance the comparability of resistance data across countries.
* The Global AMR R&D Hub: To accelerate research and development (R&D) of new antimicrobial treatments. Promotes collaboration among countries, research organizations, and industry to address gaps in R&D and facilitate the development of new antimicrobial drugs.
* The Global Antibiotic Research and Development Partnership (GARDP): WHO and the Drugs for Neglected Diseases Initiative (DNDi) is to develop new antibiotic treatments and ensure their sustainable access for all. Focuses on developing treatments for bacterial infections that pose a threat to global public health, with an emphasis on affordability and accessibility.
* CARB-X (Combating Antibiotic Resistant Bacteria Biopharmaceutical Accelerator): To accelerate the development of innovative antibacterial products. Provides funding, expertise, and resources to support the early development of new antibiotics, vaccines, and diagnostics.
* Global Research on Antimicrobial Resistance (GRAM): To provide a comprehensive analysis of the funding landscape for research on antimicrobial resistance. Offers insights into the funding priorities and gaps in research, guiding future investments to address critical needs.
* Re-Act - Action on Antibiotic Resistance: To advocate for the development and implementation of national and international strategies to combat antimicrobial resistance. Engages in policy advocacy, research, and capacity-building activities to promote responsible use of antibiotics and strengthen healthcare systems.
* The Fleming Fund: to support low- and middle-income countries in strengthening their capacity to collect and use data on antimicrobial resistance. Focuses on surveillance, laboratory capacity building, and the development of national action plans.
* European Antibiotic Awareness Day (EAAD) & European Centre for Disease Prevention and Control (ECDC): To raise awareness about the threat of antibiotic resistance and promote prudent use of antibiotics. Conducts campaigns and educational activities across Europe to engage healthcare professionals, policymakers, and the public.
* Preserving Antibiotics for Medical Treatment Act (PAMTA): Initiated by: the U.S. Congress To incentivize the development of new antibiotics and address the economic challenges associated with antibiotic development. Proposes market-based reforms to support the sustainable development of new antibiotics.

 **7.** **CURRENT RESEARCH AND INNOVATIONS**

As of my last knowledge update in January 2022, ongoing research and innovations in the field of microbial resistance continue to be crucial for developing new strategies, treatments, and technologies. Keep in mind that the information might have evolved since then. Here are some general areas of current research and innovations in the field:

* Development of Novel Antibiotics: Researchers are exploring new classes of antibiotics and modifying existing ones to enhance efficacy and overcome resistance mechanisms. Efforts focus on discovering compounds with unique modes of action.
* Bacteriophage Therapy: Phage therapy involves using bacteriophages (viruses that infect bacteria) to target and kill bacterial infections. Researchers are investigating the potential of phage therapy as an alternative or complementary approach to antibiotics.
* Antibiotic Stewardship Programs: Research is ongoing to optimize antibiotic use through stewardship programs. These programs aim to improve prescribing practices, reduce unnecessary use, and ensure the appropriate use of antibiotics.
* Antimicrobial Peptides: Antimicrobial peptides are naturally occurring molecules with antimicrobial properties. Research is exploring the development of synthetic peptides as potential alternatives to traditional antibiotics.
* Precision Medicine for Infectious Diseases: Advances in genomics and personalized medicine are being applied to infectious diseases. Understanding the genetic makeup of both microbes and individuals can help tailor treatment strategies for better outcomes.
* CRISPR-Cas Technology for Antimicrobial Resistance: CRISPR-Cas technology is being investigated for its potential in combating antimicrobial resistance. Researchers are exploring its application in modifying bacterial genomes to make them more susceptible to existing antibiotics.
* Innovative Diagnostic Technologies: Rapid and accurate diagnostic tools are essential for identifying infections and determining their antibiotic susceptibility. Ongoing research focuses on developing point-of-care diagnostics to guide targeted treatment decisions.
* Combination Therapies: Researchers are exploring the use of combination therapies, where multiple drugs are administered simultaneously or sequentially, to enhance efficacy and prevent the development of resistance.
* Vaccines to Prevent Infections: Vaccines play a crucial role in preventing infections and reducing the need for antimicrobial treatments. Research is ongoing to develop vaccines against a wide range of bacterial, viral, and parasitic pathogens.
* One Health Approaches: The One Health concept, recognizing the interconnectedness of human, animal, and environmental health, is guiding research efforts. Understanding the factors contributing to microbial resistance in various ecosystems is essential for developing comprehensive strategies.
* Public Health Interventions: Public health campaigns and interventions aim to raise awareness about responsible antibiotic use, proper hygiene practices, and the consequences of microbial resistance. Education is a key component in changing behaviors and reducing the spread of resistance.
* Global Surveillance Networks: Strengthening global surveillance networks, such as the Global Antimicrobial Resistance Surveillance System (GLASS), is crucial for monitoring resistance patterns, tracking emerging threats, and informing public health strategies.
* Community Engagement and Behavioural Research: Understanding the behaviors and perceptions of communities regarding antibiotic use is vital. Behavioral research informs the development of targeted interventions to promote responsible antimicrobial practices.
* Environmental Approaches: Researchers are investigating the environmental aspects of antimicrobial resistance, including the presence of antimicrobial residues in water systems. Strategies for mitigating environmental contributions to resistance are under exploration.

**8**. **PREVENTIVE MEASURES**

Preventing and mitigating microbial resistance requires a multifaceted approach that involves individuals, healthcare professionals, policymakers, and the broader community. Here are key preventive measures to address microbial resistance**71,72**:

* Promoting Responsible Antibiotic Use**71**: Increase public awareness about the appropriate use of antibiotics, emphasizing the importance of completing prescribed courses and not self-medicating. Healthcare professionals should prescribe antibiotics judiciously, based on accurate diagnoses and bacterial cultures when necessary.
* Antibiotic Stewardship Programs**76,77**: Healthcare Settings: Implement and strengthen antibiotic stewardship programs in healthcare facilities to optimize the use of antibiotics, minimize unnecessary prescriptions, and prevent the development of resistance.
* Enhancing Infection Prevention and Control**75**: Promote proper hand hygiene practices in healthcare settings, communities, and households to prevent the spread of infections. Ensure the appropriate use of PPE to reduce the risk of healthcare-associated infections and limit the need for antimicrobial treatments.
* Vaccination Programs: Routine Immunization: Support and enhance routine vaccination programs to prevent infections and reduce the need for antimicrobial treatments.
* One Health Approach: Interdisciplinary Collaboration: Adopt a One Health approach that involves collaboration between human and animal health sectors, as well as environmental agencies, to address the interconnected nature of microbial resistance.
* Global Surveillance and Data Sharing: Data Collection: Strengthen global surveillance systems to monitor antimicrobial use and resistance patterns. Encourage countries to collect and share data to improve their understanding of the global landscape.
* Research and Development Incentives**78**: Provide financial incentives and support for research and development of new antibiotics, antivirals, antifungals, and other antimicrobial agents. Consider innovative models, such as market entry rewards, to incentivize the development of new antimicrobial drugs.
* Public Awareness Campaigns: Education Programs: Conduct public awareness campaigns to educate individuals about the consequences of microbial resistance, emphasizing the role of everyone in preventing its escalation.
* Point-of-Care Diagnostics: Invest in the development and deployment of rapid and accurate point-of-care diagnostic tools to enable healthcare professionals to prescribe targeted treatments.
* Regulation and Enforcement 74: Regulate the sale of antibiotics to prevent over-the-counter availability without a prescription. Implement and enforce regulations on the use of antibiotics in agriculture to minimize the development of resistance in animal populations.
* Environmental Management: Improve wastewater treatment processes to reduce the release of antimicrobial residues into the environment. Monitor environmental factors contributing to microbial resistance and implement measures to mitigate their impact.
* Community Engagement: Engage communities in antimicrobial resistance prevention efforts, fostering a sense of responsibility and participation in promoting prudent antimicrobial use.
* International Collaboration**72**: Encourage international collaboration and policy alignment to address the global nature of microbial resistance. Support capacity building in low- and middle-income countries to enhance surveillance, research, and implementation of preventive measures.
* Research on Alternatives**78,80,81,82,83,84,85,86,87**: Promote research on non-antibiotic alternatives, such as bacteriophage therapy, probiotics, and immune-based therapies.
* Legislation and Regulation 73.75: Develop and implement national action plans on antimicrobial resistance, encompassing a range of preventive measures. Strengthen legislation and regulatory frameworks to ensure adherence to guidelines on antimicrobial use.

**9. CHALLENGES AND FUTURE OUTLOOK**

The challenges associated with microbial resistance are complex and multifaceted, spanning across healthcare, agriculture, the environment, and global governance. As we look to the future, several challenges and considerations need to be addressed to effectively combat microbial resistance:

**9.1 Challenges:**

* Limited Pipeline of New Antibiotics**85,86**: There is a limited pipeline of new antibiotics entering the market, and the development of novel antimicrobials is often economically challenging for pharmaceutical companies. The lack of new antibiotics diminishes our ability to address emerging resistant strains.
* Global Disparities in Access and Surveillance: There are significant disparities in access to healthcare and surveillance capabilities between high-income and low-income countries. Global efforts must address these inequalities to ensure a coordinated and effective response to microbial resistance.
* Agricultural Practices and Veterinary Use: The use of antibiotics in agriculture and veterinary medicine for growth promotion and disease prevention contributes to the development of resistant strains. Sustainable and responsible practices in agriculture and veterinary medicine need to be implemented and enforced globally.
* Overuse and Misuse in Healthcare**87**: Overuse and misuse of antibiotics in healthcare settings continue to be a challenge, driven by factors such as inappropriate prescribing and patient demand. Antibiotic stewardship programs and educational initiatives are essential to address these practices.
* Environmental Contamination: Antimicrobial residues in wastewater contribute to environmental contamination, fostering the persistence and spread of resistant microbes. Improved wastewater treatment and environmental management are necessary to reduce the environmental impact.
* Lack of Rapid Diagnostics: The lack of widely available, rapid diagnostic tools hinders the timely identification of infections and determination of antibiotic susceptibility. Investment in the development and deployment of point-of-care diagnostics is crucial for targeted treatment.
* Patient and Public Awareness: There is often a lack of awareness among patients and the public regarding the consequences of microbial resistance and the importance of responsible antibiotic use. Public awareness campaigns are needed to empower individuals to play an active role in preventing resistance.
* Economic Models for Antibiotic Development: Traditional economic models for antibiotic development are not conducive to sustained investment by pharmaceutical companies. Innovative models, such as market entry rewards, need to be explored to incentivize the development of new antibiotics.

**9.2 Future Outlook:**

* Multidisciplinary Approaches**88,89**: Future strategies should embrace multidisciplinary approaches, involving healthcare, agriculture, environmental science, and policy, to address the complex nature of microbial resistance.
* Technological Innovations: Advances in technology, such as artificial intelligence and genomics, hold promise for accelerating the discovery of new antimicrobials and improving diagnostics.
* One Health Integration**90 91**: Integration of One Health principles into global health policies is critical for a holistic approach that considers the interconnectedness of human, animal, and environmental health.
* Global Governance and Collaboration: Strengthened global governance and collaboration are essential to harmonize policies, share data, and implement coordinated efforts across borders.
* Sustainable Agricultural Practices: Encouraging and enforcing sustainable and responsible agricultural practices will contribute to reducing the selective pressure that drives microbial resistance.
* Incentivizing Research and Development: Continued exploration of innovative incentives and funding mechanisms is crucial to attract investment in research and development for new antimicrobials.
* Community Engagement and Education: Continued community engagement and education efforts will be essential to foster a culture of responsible antibiotic use and infection prevention.
* Resilient Health Systems: Building resilient and adaptive health systems will be crucial for responding effectively to infectious diseases and microbial resistance.
* Policy Advocacy: Advocacy for policy changes at national and international levels will play a pivotal role in addressing systemic challenges and implementing preventive measures.
* Surveillance and Data Sharing: Strengthening global surveillance networks and promoting transparent data sharing will enhance our understanding of microbial resistance patterns and trends

**10.** **CONCLUSION**

To summarize, the increasing menace of microbial resistance poses a substantial obstacle to worldwide public health. The widespread and unselective utilization of antimicrobials in various fields including healthcare and agriculture has resulted in the formation of resistant strains, hence reducing the efficacy of current treatments. The ramifications of microbial resistance have extensive implications, affecting individuals, communities, and healthcare systems globally **[57,58].**

Tackling microbial resistance necessitates a thorough and cooperative strategy. The World Health Organization's Global Action Plan on Antimicrobial Resistance, global surveillance systems like GLASS, and research groups such as GARDP and CARB-X are essential elements in the ongoing fight against resistance **[73,75,76,78]**

To effectively tackle the intricate issue of microbial resistance, it is crucial to allocate resources toward research and development, encourage technical advancements, and enhance global governance. Public awareness and education are essential elements of a comprehensive approach, enabling citizens to actively participate in the responsible utilization of antimicrobials.

To overcome these problems, it is crucial to have a collective and synchronized endeavor. Collaboration among governments, healthcare professionals, researchers, industry, and the public is vital to safeguard the effectiveness of current medicines, create innovative remedies, and guarantee a viable future for worldwide healthcare. The repercussions of not taking action are serious, but through ongoing dedication and ingenuity, we may endeavor to surmount the menace of microbial resistance and ensure a healthy environment for future generations.

 **11. REFERENCE**

1. Williams-Nguyen J., Sallach J.B., Bartelt-Hunt S., Boxall A.B., Durso L.M., McLain J.E., Singer R.S., Snow D.D., Zilles J.L. Antibiotics and Antibiotic Resistance in Agroecosystems: State of the Science. J. Environ. Qual. 2016;45:394–406. doi: 10.2134/jeq2015.07.0336. [PubMed] [CrossRef] [Google Scholar]

2. CDC How Antimicrobial Resistance Happens. [(accessed on 2 June 2023)]; Available online: https://www.cdc.gov/drugresistance/about/how-resistance-happens.html

3. Tenover F.C. Mechanisms of antimicrobial resistance in bacteria. Am. J. Med. 2006;119:S3–S10; discussion S62–S70. doi: 10.1016/j.amjmed.2006.03.011. [PubMed] [CrossRef] [Google Scholar]

4. Zhou G., Shi Q.S., Huang X.M., Xie X.B. The Three Bacterial Lines of Defense against Antimicrobial Agents. Int. J. Mol. Sci. 2015;16:21711–21733. doi: 10.3390/ijms160921711. [PMC free article] [PubMed] [CrossRef] [Google Scholar]

5. Khameneh B., Diab R., Ghazvini K., Fazly Bazzaz B.S. Breakthroughs in bacterial resistance mechanisms and the potential ways to combat them. Microb. Pathog. 2016;95:32–42. doi: 10.1016/j.micpath.2016.02.009. [PubMed] [CrossRef] [Google Scholar]

6. Read A.F., Woods R.J. Antibiotic resistance management. Evol. Med. Public Health. 2014;2014:147. doi: 10.1093/emph/eou024. [PMC free article] [PubMed] [CrossRef] [Google Scholar]

7. George A. Antimicrobial resistance, trade, food safety and security. One Health. 2018;5:6–8. doi: 10.1016/j.onehlt.2017.11.004. [PMC free article] [PubMed] [CrossRef] [Google Scholar]

8. Samreen, Ahmad I., Malak H.A., Abulreesh H.H. Environmental antimicrobial resistance, and its drivers: A potential threat to public health. J. Glob. Antimicrob. Resist. 2021;27:101–111. doi: 10.1016/j.jgar.2021.08.001. [PubMed] [CrossRef] [Google Scholar]

9. ARC Global burden of bacterial antimicrobial resistance in 2019: A systematic analysis. Lancet. 2022;399:629–655. doi: 10.1016/S0140-6736(21)02724-0. [PMC free article] [PubMed] [CrossRef] [Google Scholar]

10. O’Neill J. Antimicrobial resistance: Tackling a crisis for the health and wealth of nations (The Review on Antimicrobial Resistance, London, 2016, United Kingdom) Rev. Antimicrob. Resist. 2014 [Google Scholar]

11. WHO Antimicrobial Resistance. [(accessed on 2 November 2022)]. Available online: https://www.who.int/news-room/fact-sheets/detail/antimicrobial-resistance

12. WHO Multidrug-Resistant Tuberculosis (MDR-TB) [(accessed on 4 June 2023)]. Available online: https://www.who.int/docs/default-source/documents/tuberculosis/multidrug-resistant-tuberculosis-mdr-tb.pdf

13. Ghimpețeanu O.M., Pogurschi E.N., Popa D.C., Dragomir N., Drăgotoiu T., Mihai O.D., Petcu C.D. Antibiotic Use in Livestock and Residues in Food-A Public Health Threat: A Review. Foods. 2022;11:1430. doi: 10.3390/foods11101430. [PMC free article] [PubMed] [CrossRef] [Google Scholar]

14. Founou R.C., Founou L.L., Essack S.Y. Clinical and economic impact of antibiotic resistance in developing countries: A systematic review and meta-analysis. PLoS ONE. 2017;12:e0189621. doi: 10.1371/journal.pone.0189621. [PMC free article] [PubMed] [CrossRef] [Google Scholar]

15. Levy S.B., Marshall B. Antibacterial resistance worldwide: Causes, challenges, and responses. Nat. Med. 2004;10:S122–S129. doi: 10.1038/nm1145. [PubMed] [CrossRef] [Google Scholar]

16. Hutchings M.I., Truman A.W., Wilkinson B. Antibiotics: Past, present and future. Curr. Opin. Microbiol. 2019;51:72–80. doi: 10.1016/j.mib.2019.10.008. [PubMed] [CrossRef] [Google Scholar]

17. Iskandar K., Murugaiyan J., Hammoudi Halat D., Hage S.E., Chibabhai V., Adukkadukkam S., Roques C., Molinier L., Salameh P., Van Dongen M. Antibiotic Discovery and Resistance: The Chase and the Race. Antibiotics. 2022;11:182. doi: 10.3390/antibiotics11020182. [PMC free article] [PubMed] [CrossRef] [Google Scholar]

18. Uddin T.M., Chakraborty A.J., Khusro A., Zidan B.R.M., Mitra S., Emran T.B., Dhama K., Ripon M.K.H., Gajdács M., Sahibzada M.U.K., et al. Antibiotic resistance in microbes: History, mechanisms, therapeutic strategies, and prospects. J. Infect. Public Health. 2021;14:1750–1766. doi: 10.1016/j.jiph.2021.10.020. [PubMed] [CrossRef] [Google Scholar]

19. Parmar A., Lakshminarayanan R., Iyer A., Mayandi V., Leng Goh E.T., Lloyd D.G., Chalasani M.L.S., Verma N.K., Prior S.H., Beuerman R.W., et al. Design and Syntheses of Highly Potent Teixobactin Analogues against Staphylococcus aureus, Methicillin-Resistant Staphylococcus aureus (MRSA), and Vancomycin-Resistant Enterococci (VRE) in Vitro and in Vivo. J. Med. Chem. 2018;61:2009–2017. doi: 10.1021/acs.jmedchem.7b01634. [PubMed] [CrossRef] [Google Scholar]

20. Zaman S.B., Hussain M.A., Nye R., Mehta V., Mamun K.T., Hossain N. A Review on Antibiotic Resistance: Alarm Bells are Ringing. Cureus. 2017;9:e1403. doi: 10.7759/cureus.1403. [PMC free article] [PubMed] [CrossRef] [Google Scholar]

21. Suay-García B., Pérez-Gracia M.T. Present and Future of Carbapenem-resistant Enterobacteriaceae (CRE) Infections. Antibiotics. 2019;8:122. doi: 10.3390/antibiotics8030122. [PMC free article] [PubMed] [CrossRef] [Google Scholar]

22. Kaur N., Prasad R., Varma A. Prevalence and antibiotic susceptibility pattern of methicillin-resistant staphylococcus aureus in tertiary care hospitals. Biotechnol. J. Int. 2014;4:228–235. doi: 10.9734/BBJ/2014/4245. [CrossRef] [Google Scholar]

23. Parmanik A., Das S., Kar B., Bose A., Dwivedi G.R., Pandey M.M. Current Treatment Strategies Against Multidrug-Resistant Bacteria: A Review. Curr. Microbiol. 2022;79:388. doi: 10.1007/s00284-022-03061-7. [PMC free article] [PubMed] [CrossRef] [Google Scholar]

24. Davies J., Davies D. Origins and evolution of antibiotic resistance. Microbiol. Mol. Biol. Rev. MMBR. 2010;74:417–433. doi: 10.1128/MMBR.00016-10. [PMC free article] [PubMed] [CrossRef] [Google Scholar]

25. Koch N., Islam N.F., Sonowal S., Prasad R., Sarma H. Environmental antibiotics and resistance genes as emerging contaminants: Methods of detection and bioremediation. Curr. Res. Microb. Sci. 2021;2:100027. doi: 10.1016/j.crmicr.2021.100027. [PMC free article] [PubMed] [CrossRef] [Google Scholar]

26. Lee J.H. Perspectives towards antibiotic resistance: From molecules to population. J. Microbiol. 2019;57:181–184. doi: 10.1007/s12275-019-0718-8. [PubMed] [CrossRef] [Google Scholar]

27. Martinez J.L. General principles of antibiotic resistance in bacteria. Drug Discov. Today. Technol. 2014;11:33–39. doi: 10.1016/j.ddtec.2014.02.001. [PubMed] [CrossRef] [Google Scholar]

28. Cox G., Wright G.D. Intrinsic antibiotic resistance: Mechanisms, origins, challenges, and solutions. Int. J. Med. Microbiol. IJMM. 2013;303:287–292. doi: 10.1016/j.ijmm.2013.02.009. [PubMed] [CrossRef] [Google Scholar]

29. Holmes A.H., Moore L.S., Sundsfjord A., Steinbakk M., Regmi S., Karkey A., Guerin P.J., Piddock L.J. Understanding the mechanisms and drivers of antimicrobial resistance. Lancet. 2016;387:176–187. doi: 10.1016/S0140-6736(15)00473-0. [PubMed] [CrossRef] [Google Scholar]

30. Munita J.M., Arias C.A. Mechanisms of Antibiotic Resistance. Microbiol. Spectr. 2016;4 doi: 10.1128/microbiolspec.VMBF-0016-2015. [PMC free article] [PubMed] [CrossRef] [Google Scholar]

31. Fernández L., Hancock R.E. Adaptive and mutational resistance: Role of porins and efflux pumps in drug resistance. Clin. Microbiol. Rev. 2012;25:661–681. doi: 10.1128/CMR.00043-12. [PMC free article] [PubMed] [CrossRef] [Google Scholar]

32. Rizi K.S., Ghazvini K., Noghondar M.K. Adaptive antibiotic resistance: Overview and perspectives. J. Infect. Dis. Ther. 2018;6:363. doi: 10.4172/2332-0877.1000363. [CrossRef] [Google Scholar]

33. Godijk N.G., Bootsma M.C.J., Bonten M.J.M. Transmission routes of antibiotic resistant bacteria: A systematic review. BMC Infect. Dis. 2022;22:482. doi: 10.1186/s12879-022-07360-z. [PMC free article] [PubMed] [CrossRef] [Google Scholar]

34. Krzemiński P., Markiewicz Z., Popowska M. Entry Routes of Antibiotics and Antimicrobial Resistance in the Environment. In: Hashmi M.Z., editor. Antibiotics and Antimicrobial Resistance Genes: Environmental Occurrence and Treatment Technologies. Springer International Publishing; Cham, Germany: 2020. pp. 1–26. [Google Scholar]

35. da Costa P.M., Loureiro L., Matos A.J. Transfer of multidrug-resistant bacteria between intermingled ecological niches: The interface between humans, animals, and the environment. Int. J. Environ. Res. Public Health. 2013;10:278–294. doi: 10.3390/ijerph10010278. [PMC free article] [PubMed] [CrossRef] [Google Scholar]

36. Landers T.F., Cohen B., Wittum T.E., Larson E.L. A review of antibiotic use in food animals: Perspective, policy, and potential. Public Health Rep. 2012;127:4–22. doi: 10.1177/003335491212700103. [PMC free article] [PubMed] [CrossRef] [Google Scholar]

37. Chancey S.T., Zähner D., Stephens D.S. Acquired inducible antimicrobial resistance in Gram-positive bacteria. Future Microbiol. 2012;7:959–978. doi: 10.2217/fmb.12.63. [PMC free article] [PubMed] [CrossRef] [Google Scholar]

38. Reygaert W.C. An overview of the antimicrobial resistance mechanisms of bacteria. AIMS Microbiol. 2018;4:482–501. doi: 10.3934/microbiol.2018.3.482. [PMC free article] [PubMed] [CrossRef] [Google Scholar]

39. Choi U., Lee C.R. Distinct Roles of Outer Membrane Porins in Antibiotic Resistance and Membrane Integrity in Escherichia coli. Front. Microbiol. 2019;10:953. doi: 10.3389/fmicb.2019.00953. [PMC free article] [PubMed] [CrossRef] [Google Scholar]

40. Ghai I., Ghai S. Understanding antibiotic resistance via outer membrane permeability. Infect. Drug Resist. 2018;11:523–530. doi: 10.2147/IDR.S156995. [PMC free article] [PubMed] [CrossRef] [Google Scholar]

41. Dutt Y., Dhiman R., Singh T., Vibhuti A., Gupta A., Pandey R.P., Raj V.S., Chang C.M., Priyadarshini A. The Association between Biofilm Formation and Antimicrobial Resistance with Possible Ingenious Bio-Remedial Approaches. Antibiotics. 2022;11:930. doi: 10.3390/antibiotics11070930. [PMC free article] [PubMed] [CrossRef] [Google Scholar]

42. Van Acker H., Van Dijck P., Coenye T. Molecular mechanisms of antimicrobial tolerance and resistance in bacterial and fungal biofilms. Trends Microbiol. 2014;22:326–333. doi: 10.1016/j.tim.2014.02.001. [PubMed] [CrossRef] [Google Scholar]

43. Ashley R.E., Dittmore A., McPherson S.A., Turnbough C.L., Jr., Neuman K.C., Osheroff N. Activities of gyrase and topoisomerase IV on positively supercoiled DNA. Nucleic Acids Res. 2017;45:9611–9624. doi: 10.1093/nar/gkx649. [PMC free article] [PubMed] [CrossRef] [Google Scholar]

44. Saha M., Sarkar A. Review on Multiple Facets of Drug Resistance: A Rising Challenge in the 21st Century. J. Xenobiotics. 2021;11:197–214. doi: 10.3390/jox11040013. [PMC free article] [PubMed] [CrossRef] [Google Scholar]

45. Foster T.J. Antibiotic resistance in Staphylococcus aureus. Current status and prospects. FEMS Microbiol. Rev. 2017;41:430–449. doi: 10.1093/femsre/fux007. [PubMed] [CrossRef] [Google Scholar]

46. Wendlandt S., Shen J., Kadlec K., Wang Y., Li B., Zhang W.J., Feßler A.T., Wu C., Schwarz S. Multidrug resistance genes in staphylococci from animals that confer resistance to critically and highly important antimicrobial agents in human medicine. Trends Microbiol. 2015;23:44–54. doi: 10.1016/j.tim.2014.10.002. [PubMed] [CrossRef] [Google Scholar]

47. Blair J.M., Webber M.A., Baylay A.J., Ogbolu D.O., Piddock L.J. Molecular mechanisms of antibiotic resistance. Nat. Reviews. Microbiol. 2015;13:42–51. doi: 10.1038/nrmicro3380. [PubMed] [CrossRef] [Google Scholar]

48. Nikaido H., Pagès J.M. Broad-specificity efflux pumps and their role in multidrug resistance of Gram-negative bacteria. FEMS Microbiol. Rev. 2012;36:340–363. doi: 10.1111/j.1574-6976.2011.00290.x. [PMC free article] [PubMed] [CrossRef] [Google Scholar]

49. Poole K. Efflux-mediated antimicrobial resistance. J. Antimicrob. Chemother. 2005;56:20–51. doi: 10.1093/jac/dki171. [PubMed] [CrossRef] [Google Scholar]

50. Blair J.M., Richmond G.E., Piddock L.J. Multidrug efflux pumps in Gram-negative bacteria and their role in antibiotic resistance. Future Microbiol. 2014;9:1165–1177. doi: 10.2217/fmb.14.66. [PubMed] [CrossRef] [Google Scholar]

51. Abushaheen M.A., Muzaheed, Fatani A.J., Alosaimi M., Mansy W., George M., Acharya S., Rathod S., Divakar D.D., Jhugroo C., et al. Antimicrobial resistance, mechanisms, and its clinical significance. Dis. A-Mon. DM. 2020;66:100971. doi: 10.1016/j.disamonth.2020.100971. [PubMed] [CrossRef] [Google Scholar]

52. Chaw P.S., Höpner J., Mikolajczyk R. The knowledge, attitude, and practice of health practitioners towards antibiotic prescribing and resistance in developing countries systematic review. J. Clin. Pharm. Ther. 2018;43:606–613. doi: 10.1111/jcpt.12730. [PubMed] [CrossRef] [Google Scholar]

53. Chokshi A., Sifri Z., Cennimo D., Horng H. Global Contributors to Antibiotic Resistance. J. Glob. Infect. Dis. 2019;11:36–42. doi: 10.4103/jgid.jgid\_110\_18. [PMC free article] [PubMed] [CrossRef] [Google Scholar]

54. Klein E.Y., Van Boeckel T.P., Martinez E.M., Pant S., Gandra S., Levin S.A., Goossens H., Laxminarayan R. Global increase and geographic convergence in antibiotic consumption between 2000 and 2015. Proc. Natl. Acad. Sci. USA. 2018;115:E3463–E3470. doi: 10.1073/pnas.1717295115. [PMC free article] [PubMed] [CrossRef] [Google Scholar]

55. Van Boeckel T.P., Brower C., Gilbert M., Grenfell B.T., Levin S.A., Robinson T.P., Teillant A., Laxminarayan R. Global trends in antimicrobial use in food animals. Proc. Natl. Acad. Sci. USA. 2015;112:5649–5654. doi: 10.1073/pnas.1503141112. [PMC free article] [PubMed] [CrossRef] [Google Scholar]

56. CDC Antibiotic Use in the United States, 2022 Update: Progress and Opportunities. [(accessed on 10 November 2022)]; Available online: https://www.cdc.gov/antibiotic-use/stewardship-report/current.html

57. Michael C.A., Dominey-Howes D., Labbate M. The antimicrobial resistance crisis: Causes, consequences, and management. Front. Public Health. 2014;2:145. doi: 10.3389/fpubh.2014.00145. [PMC free article] [PubMed] [CrossRef] [Google Scholar]

58. Pulia M., Kern M., Schwei R.J., Shah M.N., Sampene E., Crnich C.J. Comparing appropriateness of antibiotics for nursing home residents by setting of prescription initiation: A cross-sectional analysis. Antimicrob. Resist. Infect. Control. 2018;7:74. doi: 10.1186/s13756-018-0364-7. [PMC free article] [PubMed] [CrossRef] [Google Scholar]

59. Woolhouse M., Waugh C., Perry M.R., Nair H. Global disease burden due to antibiotic resistance-state of the evidence. J. Glob. Health. 2016;6:010306. doi: 10.7189/jogh.06.010306. [PMC free article] [PubMed] [CrossRef] [Google Scholar]

60. CDC Antibiotic Resistance: A Global Threat. [(accessed on 10 November 2022)]; Available online: https://www.cdc.gov/drugresistance/solutions-initiative/stories/ar-global-threat.html

61. DiMasi J.A., Grabowski H.G., Hansen R.W. Innovation in the pharmaceutical industry: New estimates of R&D costs. J. Health Econ. 2016;47:20–33. doi: 10.1016/j.jhealeco.2016.01.012. [PubMed] [CrossRef] [Google Scholar]

62. Chang Q., Wang W., Regev-Yochay G., Lipsitch M., Hanage W.P. Antibiotics in agriculture and the risk to human health: How worried should we be? Evol. Appl. 2015;8:240–247. doi: 10.1111/eva.12185. [PMC free article] [PubMed] [CrossRef] [Google Scholar]

63. FAO Animal production. [(accessed on 12 November 2022)]. Available online: https://www.fao.org/antimicrobial-resistance/key-sectors/animal-production/en/

64. Castro-Sánchez E., Moore L.S., Husson F., Holmes A.H. What are the factors driving antimicrobial resistance? Perspectives from a public event in London, England. BMC Infect. Dis. 2016;16:465. doi: 10.1186/s12879-016-1810-x. [PMC free article] [PubMed] [CrossRef] [Google Scholar]

65. Frost I., Van Boeckel T.P., Pires J., Craig J., Laxminarayan R. Global geographic trends in antimicrobial resistance: The role of international travel. J. Travel Med. 2019;26:taz036. doi: 10.1093/jtm/taz036. [PubMed] [CrossRef] [Google Scholar]

66. Arcilla M.S., van Hattem J.M., Haverkate M.R., Bootsma M.C.J., van Genderen P.J.J., Goorhuis A., Grobusch M.P., Lashof A.M.O., Molhoek N., Schultsz C., et al. Import and spread of extended-spectrum β-lactamase-producing Enterobacteriaceae by international travelers (COMBAT study): A prospective, multicentre cohort study. Lancet. Infect. Dis. 2017;17:78–85. doi: 10.1016/S1473-3099(16)30319-X. [PubMed] [CrossRef] [Google Scholar]

67. McCubbin K.D., Anholt R.M., de Jong E., Ida J.A., Nóbrega D.B., Kastelic J.P., Conly J.M., Götte M., McAllister T.A., Orsel K., et al. Knowledge Gaps in the Understanding of Antimicrobial Resistance in Canada. Front. Public Health. 2021;9:726484. doi: 10.3389/fpubh.2021.726484. [PMC free article] [PubMed] [CrossRef] [Google Scholar]

68. Carter R.R., Sun J., Jump R.L. A Survey and Analysis of the American Public's Perceptions and Knowledge About Antibiotic Resistance. Open Forum Infect. Dis. 2016;3:ofw112. doi: 10.1093/ofid/ofw112. [PMC free article] [PubMed] [CrossRef] [Google Scholar]

69. WHO Antibiotic resistance. [(accessed on 12 November 2022)]. Available online: https://www.who.int/news-room/fact-sheets/detail/antibiotic-resistance

70. Lin T.Z., Jayasvasti I., Tiraphat S., Pengpid S., Jayasvasti M., Borriharn P. The Predictors Influencing the Rational Use of Antibiotics Among Public Sector: A Community-Based Survey in Thailand. Drug Healthc. Patient Saf. 2022;14:27–36. doi: 10.2147/DHPS.S339808. [PMC free article] [PubMed] [CrossRef] [Google Scholar]

71. Control A. Global Governance to Tackle Antimicrobial Resistance: The Way Forward. [(accessed on 4 June 2023)]. Available online: http://resistancecontrol.info/2019-3/armed-conflicts-and-antimicrobial-resistance-a-deadly-convergence/

72. Majumder M.A.A., Rahman S., Cohall D., Bharatha A., Singh K., Haque M., Gittens-St Hilaire M. Antimicrobial Stewardship: Fighting Antimicrobial Resistance and Protecting Global Public Health. Infect. Drug Resist. 2020;13:4713–4738. doi: 10.2147/IDR.S290835. [PMC free article] [PubMed] [CrossRef] [Google Scholar]

73. WHO Global Action Plan on Antibiotic Resistance. [(accessed on 12 November 2022)]. Available online: https://www.emro.who.int/health-topics/drug-resistance/global-action-plan.html

74. WHO Assessing Non-Prescription and Inappropriate Use of Antibiotics Report on Survey. [(accessed on 4 June 2023)]. Available online: https://apps.who.int/iris/bitstream/handle/10665/312306/9789289054089-eng.pdf?sequence=1&isAllowed=y

75. WHO Infection Prevention and Control. [(accessed on 12 November 2022)]. Available online: https://www.who.int/teams/integrated-health-services/infection-prevention-control

76. CDC Implementation of Antibiotic Stewardship Core Elements at Small and Critical Access Hospitals. [(accessed on 12 November 2022)]; Available online: https://www.cdc.gov/antibiotic-use/core-elements/small-critical.html

77. Pinto Ferreira J., Battaglia D., Dorado García A., Tempelman K., Bullon C., Motriuc N., Caudell M., Cahill S., Song J., LeJeune J. Achieving Antimicrobial Stewardship on the Global Scale: Challenges and Opportunities. Microorganisms. 2022;10:1599. doi: 10.3390/microorganisms10081599. [PMC free article] [PubMed] [CrossRef] [Google Scholar]

78. Aidara-Kane A., Angulo F.J., Conly J.M., Minato Y., Silbergeld E.K., McEwen S.A., Collignon P.J. World Health Organization (WHO) guidelines on the use of medically important antimicrobials in food-producing animals. Antimicrob. Resist. Infect. Control. 2018;7:7. doi: 10.1186/s13756-017-0294-9. [PMC free article] [PubMed] [CrossRef] [Google Scholar]

79. Mitchell J., Cooke P., Ahorlu C., Arjyal A., Baral S., Carter L., Dasgupta R., Fieroze F., Fonseca-Braga M., Huque R., et al. Community engagement: The key to tackling Antimicrobial Resistance (AMR) across a One Health context? Glob. Public Health. 2022;17:2647–2664. doi: 10.1080/17441692.2021.2003839. [PubMed] [CrossRef] [Google Scholar]

80. Othman L., Sleiman A., Abdel-Massih R.M. Antimicrobial Activity of Polyphenols and Alkaloids in Middle Eastern Plants. Front. Microbiol. 2019;10:911. doi: 10.3389/fmicb.2019.00911. [PMC free article] [PubMed] [CrossRef] [Google Scholar]

81. Al-Amin M.Y., Lahiry A., Ferdous R., Hasan M.K., Kader M.A., Alam A.K., Saud Z.A., Sadik M.G. Stephania japonica Ameliorates Scopolamine-Induced Memory Impairment in Mice through Inhibition of Acetylcholinesterase and Oxidative Stress. Adv. Pharmacol. Pharm. Sci. 2022;2022:8305271. doi: 10.1155/2022/8305271. [PMC free article] [PubMed] [CrossRef] [Google Scholar]

82. Foyzun T., Mahmud A.A., Ahammed M.S., Manik M.I.N., Hasan M.K., Islam K.M.M., Lopa S.S., Al-Amin M.Y., Biswas K., Afrin M.R., et al. Polyphenolics with Strong Antioxidant Activity from Acacia nilotica Ameliorate Some Biochemical Signs of Arsenic-Induced Neurotoxicity and Oxidative Stress in Mice. Molecules. 2022;27:1037. doi: 10.3390/molecules27031037. [PMC free article] [PubMed] [CrossRef] [Google Scholar]

83. Islam M.A., Zaman S., Biswas K., Al-Amin M.Y., Hasan M.K., Alam A., Tanaka T., Sadik G. Evaluation of cholinesterase inhibitory and antioxidant activity of Wedelia chinensis and isolation of apigenin as an active compound. BMC Complement. Med. Ther. 2021;21:204. doi: 10.1186/s12906-021-03373-4. [PMC free article] [PubMed] [CrossRef] [Google Scholar]

84. Mustafa S., Akbar M., Khan M.A., Sunita K., Parveen S., Pawar J.S., Massey S., Agarwal N.R., Husain S.A. Plant metabolite diosmin as the therapeutic agent in human diseases. Curr. Res. Pharmacol. Drug Discov. 2022;3:100122. doi: 10.1016/j.crphar.2022.100122. [PMC free article] [PubMed] [CrossRef] [Google Scholar]

85. Pawar J.S., Mustafa S., Ghosh I. Chrysin, and Capsaicin induces premature senescence and apoptosis via mitochondrial dysfunction and p53 elevation in Cervical cancer cells. Saudi J. Biol. Sci. 2022;29:3838–3847. doi: 10.1016/j.sjbs.2022.03.011. [PMC free article] [PubMed] [CrossRef] [Google Scholar]

86. Kundo N.K., Manik M.I.N., Biswas K., Khatun R., Al-Amin M.Y., Alam A., Tanaka T., Sadik G. Identification of Polyphenolics from Loranthus globosus as Potential Inhibitors of Cholinesterase and Oxidative Stress for Alzheimer's Disease Treatment. BioMed. Res. Int. 2021;2021:9154406. doi: 10.1155/2021/9154406. [PMC free article] [PubMed] [CrossRef] [Google Scholar]

87. Amaning Danquah C., Minkah P.A.B., Osei Duah Junior I., Amankwah K.B., Somuah S.O. Antimicrobial Compounds from Microorganisms. Antibiotics. 2022;11:285. doi: 10.3390/antibiotics11030285. [PMC free article] [PubMed] [CrossRef] [Google Scholar]

88. Brives C., Pourraz J. Phage therapy as a potential solution in the fight against AMR: Obstacles and possible futures. Palgrave Commun. 2020;6:100. doi: 10.1057/s41599-020-0478-4. [CrossRef] [Google Scholar]

89. Dickey S.W., Cheung G.Y.C., Otto M. Different drugs for bad bugs: Antivirulence strategies in the age of antibiotic resistance. Nat. Reviews. Drug Discov. 2017;16:457–471. doi: 10.1038/nrd.2017.23. [PubMed] [CrossRef] [Google Scholar]

90. WHO One Health Initiative. [(accessed on 29 June 2023)]. Available online: https://www.who.int/teams/one-health-initiative

91. CDC One Health Basics. [(accessed on 29 June 2023)]; Available online: https://www.cdc.gov/onehealth/basics/index.html

92. Van Camp P.J., Haslam D.B., Porollo A. Prediction of Antimicrobial Resistance in Gram-Negative Bacteria from Whole-Genome Sequencing Data. Front. Microbiol. 2020;11:1013. doi: 10.3389/fmicb.2020.01013. [PMC free article] [PubMed] [CrossRef] [Google Scholar]

93. Anderson M., Clift C., Schulze K., Sagan A., Nahrgang S., Ait Ouakrim D., Mossialos E. Averting the AMR Crisis: What Are the Avenues for Policy Action for Countries in Europe? European Observatory on Health Systems and Policies © World Health Organization 2019 (acting as the host organization for, and secretariat of, the European Observatory on Health Systems and Policies); Copenhagen, Denmark: 2019. European Observatory Policy Briefs. [PubMed] [Google Scholar]