The Emergence and Spread of Antimicrobial Resistance

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Abstract

Antibiotics are highly effective in improving human health. Since the early 1990s, antimicrobial medication resistance has increased dramatically. The tendency of bacteria to spread different antimicrobial resistance genes to vulnerable bacterial genera and species makes the emergence of bacterial antimicrobial resistance problematic. This rise in the frequency of bacterial. Antimicrobial resistance is a natural phenomenon that results from evolution. The use of antimicrobials for prophylaxis in food-producing animals has contributed significantly to the establishment of strains resistant to specific antimicrobials. Horizontal gene transfer can lead to the emergence of a resistant population in a specific compartment. Antibiotic treatment efficiency is heavily influenced by the social interactions among polymicrobial bacterial communities at the infection site. Currently, most studies focus on resistance emergence and propagation in monospecies circumstances. Our study identifies how interspecies interactions impact resistance evolution, distinguishing between the appearance of a resistant mutant and its spread across the population. Our data shows that taking into account bacteria's social behavior is crucial for designing successful antibiotic treatment techniques that minimize resistance development. The link between antimicrobial usage and resistance highlights the importance of designing treatment regimens to prevent resistance formation.

Keywords: Antimicrobial resistance, Emergence, Antibiotics, Antibiotic misuse, Pathogen evolution

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Introduction

The antimicrobial medications used in food-producing animals almost always lead to antimicrobial resistance in food-borne bacterial enteric infections. Such medications may be used medically, prophylactically, or to promote growth (feed supplements). Despite regulations aimed at regulating antimicrobial use in food-producing animals, non-typhoidal Salmonella enterica resistance has increased significantly in developed countries in recent years. The use of antimicrobial agents in medical practice has led to several publications on the issue of antibiotic resistance. Most papers mention the advent of bacteria resistant to various antimicrobial agents and their frequencies. Antibiotic resistance surveillance studies collect MIC values for various medications (Barathe et al., 2024). Resistance occurs when a patient receives adequate antimicrobial treatment for a specific infection, but fails to meet clinical or microbiological cure criteria. Clinical resistance is defined in microbiology laboratories using breakpoints. A clinical breakpoint is a minimum inhibitory concentration (MIC) value that distinguishes between isolates with a high likelihood of therapeutic success and those with a high likelihood of failure, based on clinical outcomes (Arnold et al., 2024).

The rate of AMR infections has increased so quickly and there are not many new antimicrobial drugs being developed to address this problem, AMR has become the biggest worldwide issue of the 21st century (Ahmed et al., 2024). The consequences of overusing or neglecting antibiotics in a range of situations, mainly in clinical treatment, as well as in agriculture, animal healthcare, and the food system, can be among the main reasons behind the current issue. A complex interplay of variables involved in the evolution and dissemination of resistance mechanisms leads to the establishment of antibiotic resistance. Antibiotic overuse in clinics has been thought to be the main factor contributing to the growth of fresh resistances. Antibiotic-resistant microorganisms, particularly those with multidrug resistance, have emerged as major problems in the fields of medical treatment, animal husbandry, the food business, and public health (Bogri et al., 2024).

The development of antibiotics is one of the most successful drug therapies in medical history. The antibiotics development has helped to manage and significantly lower rates of infectious disease-related deaths, which were historically the primary cause of death among humans. With AMR spreading so quickly, infection and fatality rates are constantly monitored. In the UK, the predicted AMR rate for infection was 65, 162 people identified in 2019, up from 61,946 in 2018. In contrast, the European Centre for Disease Prevention and Control (ECDC) has reported that the annual infection rate of antimicrobial resistance (AMR) in the EU alone has surpassed 670,000 instances (Bennani et al., 2020). Asia and Africa are considered to have the highest estimated death rates because of their enormous populations and the absence of laws relevant to AMR prevention. Previous studies have shown that in the worldwide burden of Diseases regions linked to or associated with AMR, Sub-Saharan Africa had the largest all-age death rate in 2019, whereas Australasia had the lowest incidence of AMR-associated mortality.

Raising public knowledge of the AMR outbreak as a preventative measure is one of the most successful strategies among the majority of these recently suggested measures; therefore, effective communication with all stakeholders is necessary. Examining the many existing global AMR management strategies is the goal of this review in order to help control it. The discovery of antimicrobials was one of the greatest pharmacological treatments in medical history. Previously the primary cause of mortality for humans, infectious illnesses have been managed and their death rates significantly reduced since the development of antimicrobials.

The average human lifespan has increased by 23 years after the first antibiotic was developed in 1910. In that regard, Sir Alexander Fleming's discovery of the antibiotic penicillin, which signaled the start of the "golden era" of antibiotics, was one of the most important medical advances of the 20th century (Endale et al., 2023). The mean lifespan of humans has increased by 23 years since the first antibiotic was created in 1910. In that sense, Sir Alexandra Fleming's discovery of the antibiotic penicillin, which signaled the start of the antibiotic golden age, was one of the most important medical advances of the 20th century. However, it was soon discovered that penicillinase, which was generated by antibiotic-resistant bacteria, rendered the antibiotic molecule inactive and made it clinically ineffective. This is important since penicillin and its related compounds are the primary class of antibiotics that are still used to treat infections in both people and animals.

A major global health concern that jeopardizes the efficacy of infection prevention and treatment is antimicrobial resistance (AMR), particularly bacterial AMR. Since bacterial AMR caused more than 5 million deaths in 2019 and is predicted to dramatically increase by 2050 if nothing is done, immediate action is required (Chokshi et al., 2019). For example, serious ocular and systemic infections were caused by a statewide outbreak of Pseudomonas aeruginosa in the USA that was largely carbapenem-resistant and associated with multidose artificial tears, which in turn led to fatalities. The COVID-19 pandemic also increased the use of antibiotics and sped up the development of pathogen resistance (Morrison et al., 2020). The unmet clinical need for AMR action is further supported by the worldwide emergence of AMR against several carbapenemases in many bacterial species, which is linked to increased mortality and possible biofilm formation.

Although there have been several excellent studies on AMR in the past, the majority of them have focused on particular aspects of AMR, such as the burden, dangers, and resistance mechanisms (Christaki et al., 2020). In light of the widespread impacts and quick development in this area, we sought to present a succinct overview of bacterial AMR, covering the epidemiology, resistance mechanisms, new non-antibiotic treatment modalities, and possible applications of artificial intelligence.

Sulfonamide was launched in 1937 as the first efficient antibacterial. Since then, the development of resistance has hampered their therapeutic application. Alexander Fleming, a renowned microbiologist, developed penicillin in 1928. However, before its use as a medicinal treatment, the enzyme that destroys it was identified. To inhibit cleavage by β-lactamases, penicillin was chemically modified to create methicillin. However, within three years after the introduction of methicillin, drug-resistant bacteria were discovered. Streptomycin was first used in 1944 to treat tuberculosis. It became clear that antibiotic resistance is genetically transmitted. Later, it was discovered that antibiotic resistance genes might be transmitted across bacterial pathogens via conjugation. Many other mechanisms, such as transformation and transduction, have been discovered in relation to antibiotic resistance. Many top publications have recently reviewed the area in light of numerous new findings. The sequence of antibiotics discovered and the rise of resistance is shown in Table 1.

Table 1: Timeline for Emergence of Antibiotics and Antibiotic resistance

Decennary	Emergence of Antibiotics	Development of Antibiotic resistant	References
2001-2010	Development of a wider range of fluoroquinolones, telithromycin, and tigecycline.	Vancomycin-resistant staphylococcal infections and the proliferation of metallo-B-lactamases (MBL) and extended-spectrum B-lactamases (ESBL) in Gram-negative bacteria.	(Zuckerman et al., 2009)
1991-2000	Development of oral extended spectrum cephalosporin	Vancomycin-resistant enterococci and multidrug-resistant Mycobacterium TB are emerging.	(Guay et al., 2000)
1981-1990	Amoxicillin, imipenem-cilastatin, cefotaxime, clavulanic acid, norfloxacin, and aztreonam were introduced.	Spread of Staphylococcus infections resistant to methicillin.	(Kumar et al., 2013)
1971-1980	Cefoxitin, cefaclor, and carbenicillin introduction	Infections resistant to ampicillin grow more common. Increasing prevalence of infections by opportunistic pathogens.	(Zaffiri et al., 2012)
1961-1970	Gentamicin, ampicillin, cephalothin, and amikacin were introduced.	Methicillin-resistant staphylococcal infections and pseudomonas infections resistant to gentamicin are emerging.	(Rubin et al., 2011)
1951-1960	Erythromycin, vancomycin, and methicillin introduction	Infections resistant to penicillin become clinically important.	(Levine et al., 2006)
1941-1950	Streptomycin, chloramphenicol, and chlortetracycline introduction	By 1950, penicillin was widely used in animals and was made accessible to the general populace.	(Singhal et al., 2023)
1930-1940	Presenting sulfonamide	The efficacy of penicillin in humans demonstrated; sulfonamides incorporated into animal feed.	(Gulçin et al., 2018)
1929	The discovery of penicillin	Several antibiotic resistances in pre-antibiotic strains in the Murray collection.	(Ligon et al., 2004)

2. Epidemiology

AMR is a major cause of death, accounting for roughly 9% of all fatalities worldwide. In 2019, an estimated 13.7 million deaths were attributed to infections, of which 1.27 million were directly caused by AMR-related infections, and 4.95 million were indirectly caused by these infections (Dadgostar et al., 2019). There were 28.0 AMR-associated fatalities per 100,000 people in Australia and 114.8 in western sub-Saharan Africa. One metagenomics investigation of urban sewage also revealed significant regional differences in AMR gene diversity and abundance. Extreme poverty is made worse in low- and middle-income countries (LMICs) by the effects of AMR-related illness or mortality. According to estimates, if the issue is not resolved, LMICs will lose more than 5% of their GDP by 2050 as a result of lower income from indirect healthcare expenditures, and the global GDP will drop by an estimated 3.8 percent year, or US$100 trillion (Bakkeren et al., 2020). Because of the high costs of lengthy hospital stays, expensive investigations or treatments, incapacity, and death have been expected to cost the United States $4.6 billion in 2017 (Puri et al., 2024). AMR will also result in a significant increase in healthcare spending.

AMR is a new challenge that necessitates a coordinated worldwide response. "One Health" acknowledges that human and animal health are directly related to their shared environment. The same germs, illnesses, and most importantly antibiotics that treat infectious diseases in both humans and animals can be found in both. Examples of antimicrobial agents that either prevent or eliminate the growth and multiplication of germs include antimicrobial agents, antifungals, antivirals, disinfectants, and food preservatives (Palma et al., 2020). Targeting bacterial infections and resistance, antibiotics are the most widely used antimicrobials. The 21st century has seen an extraordinary rise in antibiotic-resistant bacterial diseases, which presents a latent pandemic threat to public health worldwide. We must act immediately.

Any nation can have antibiotic resistance, and people of any age or gender can be affected. AMR is a serious threat to food security and global health. Many interrelated elements in agriculture and healthcare contribute to the spread of AMR. AMR is a complicated public health concern that can be impacted by several factors, including trade, finance, waste management, and pharmaceuticals (Akram et al., 2023). In order to promote growth and support antimicrobial stewardship measures in the care of Small domestic companion animals and food animals, these actions include passing legislation that forbids the use of particular antibiotics in agrifood systems. Such regulations could be challenging to execute, especially in poorer nations where the requirement for animals for food is always increasing (Abushaheen et al., 2020).

A Chinese study claims that because mediated colistin resistance (MCR-1) can transfer from animal to human zoonosis, it poses a serious threat to antimicrobial resistance (AMR) (Friedman et al., 2016). It is believed that MCR-1 has been extensively dispersed across South Chinese food-producing animals. This investigation discovered that MCR-1 was present in isolates of *E. coli* from sources of animal and commercial meat. However, it was shown that a relatively low amount of MCR-1 was human-derived this difference in the frequency of MCR-1 in people and animals is probably the result of animal-to-human zoonotic transmission. Increasingly, individuals with bacteria resistant to other antibiotics are being treated with a last-resort antibiotic colistin, that still works. It was not often used to treat ailments because of its potentially dangerous adverse effects (Hernando-Amado et al., 2019). However, it can get harder to treat certain bacterial infections if colistin resistance develops quickly.

Lack of knowledge about antibiotics is also one of the primary causes of AMR. In 2017, Public Health England surveyed on antimicrobial awareness in the United Kingdom (Ferri et al., 2017). While 83% of participants agreed that antibiotics may be utilized for treating bacteria, 35% of participants believed they could also be utilized to treat viral diseases. The improvement in these ratings compared to the 2014 study identified that the people in the UK is now more knowledgeable and aware of antibiotics. In contrast, according to an Indian survey, 49% of participants thought that antibiotics could cure viral illnesses, while 45% of replies claimed that they take them to treat colds (Fouz et al., 2020). India was consequently said to have among the highest rates of viral disorders, particularly those caused by viruses that are sensitive to many medications. These findings suggest a connection between public knowledge and AMR.

The six leading causes (73%) of AMR-associated mortality in 2019, according to the 2022 Global Burden of Disease assessment, were *E. coli, Staphylococcus aureus, Klebsiella pneumoniae, Streptococcus pneumoniae, Acinetobacter baumannii, and P aeruginosa.* One Drug-resistant nosocomial infections are known to be caused by a distinct group of pathogens called ESKAPEE, which consists of Enterococcus species, *S. aureus, K. pneumoniae, A. baumannii, P. aeruginosa, Enterobacter species, and E. coli* (Huemer et al., 2020). These pathogens are included in WHO's list of priority bacterial infections for 2024. These infections have a wide range of resistance mechanisms that are acquired or innate that allow them to live or flourish in healthcare settings. In 2019, it was predicted that they caused over 330000 fatalities that were attributed to AMR (Ventola et al., 2015). However, the lack of general recommendations or protocols for testing for antibiotic susceptibility, the lack of data from 19 countries, the case-selection bias, and the lack of data in LMICs may confuse these figures (Huijbers et al., 2015). These factors underscore the need for future advancements. Furthermore, Mycobacterium tuberculosis, another significant WHO critical priority bacteria that cause drug-resistant tuberculosis, was responsible for around 1.3 million fatalities worldwide in 2022.

3. Mechanisms of Antimicrobial Resistance

Microorganisms can develop resistance through several mechanisms. Spontaneous mutations in microbial DNA can confer resistance by altering drug targets or metabolic pathways. Bacteria can acquire resistance genes from other organisms through transformation, transduction, or conjugation, allowing for the rapid dissemination of resistance traits (Singer et al., 2016). Many bacteria form biofilms, protective environments that enhance survival against antimicrobials and immune responses. The over-prescription of antibiotics in human medicine and their use in agriculture and livestock significantly contribute to the emergence of AMR.

It is believed that MCR-1 has been extensively dispersed across South Chinese food-producing animals. This investigation discovered that MCR-1 was present in isolates of *E. coli* from sources of animal and commercial meat. However, it was shown that a relatively low amount of MCR-1 was human-derived; this difference in MCR-1 prevalence between humans and animals is most likely the consequence of zoonotic transmission from animals to humans (Frieri et al., 2017). New transmission vectors are also discovered as new genes and resistance mechanisms develop. Recent studies on the intrinsic, naturally acquired, and external mechanisms by which bacteria pick up

AMR will be the main topic of this section. The topic of discussion will be how bacteria change the structures of antibiotic targets, make it harder for drugs to reach their targets, and change or render medications inactive (Jasovský et al., 2016). The decreased permeability of the bacterial membrane, which stops antibiotics from reaching their target, is the cause of Enterobacteriaceae's resistance to carbapenems. The purpose of antibiotics is to disrupt normal activity by binding to certain targets with high affinity. Antibiotic resistance can result from structural alterations that decrease an antibiotic's binding effectiveness without altering its action. Antibiotic resistance can also be achieved through post-translational alteration of target molecules as shown in Figure 1, which does not require a mutation in the corresponding genes (Klemm et al., 2018).

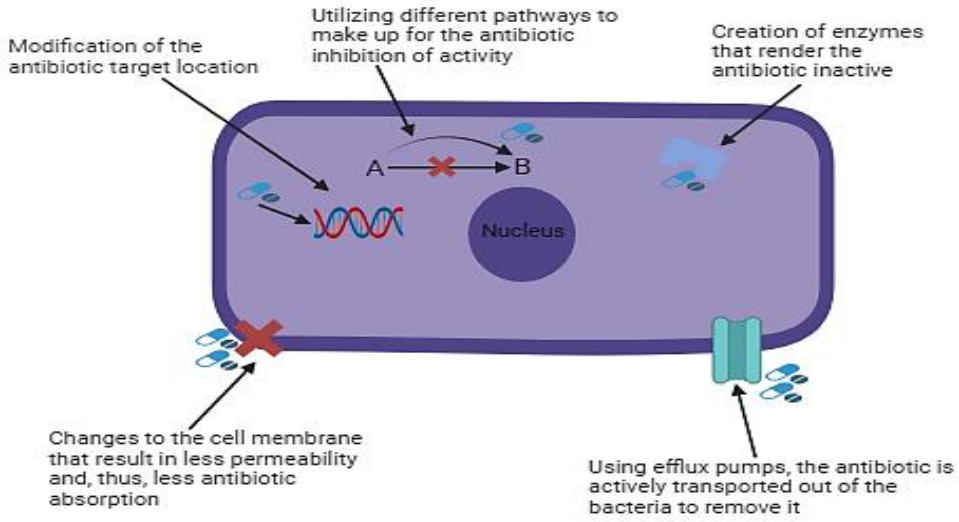

Fig. 1: Emergence of antibiotic resistance in bacterial cells

4. Impact of Antimicrobial Resistance on Public Health

Since human health is reliant on the health of animals, plants, and the environment, One Health places a strong emphasis on how ecosystems are interconnected. Through intimate animal-human contact, food, and water systems, and cultural and economic factors, AMR spreads both within and between ecosystems (Jeon et al., 2023). Controlling AMR requires an understanding of the complex interaction. WGS is being used to support One Health aspects of AMR, such as monitoring its spread through agriculture and food, enhancing surveillance for food-borne illnesses, and looking into outbreaks (Wu et al., 2024).

The public health of the world is seriously threatened by AMR emergence and spread in recent decades. The development of antibiotics is not keeping pace with the evolution of pathogens. Multi-sectoral activities at all levels of governmental and public health institutions will be necessary to address this threat. Genomic technologies are currently being used as a main weapon in the fight against AMR because recent developments have made them more widely available and reasonably priced. WGS has enhanced AMR surveillance by measuring regional and temporal variations in epidemiology and offering insight into its genesis and transmission (Robinson et al., 2016). In the twenty-first century, antimicrobial resistance (AMR), which impacts people, animals, and the environment, has grown to be a significant global concern. The overuse of antimicrobial agents in veterinary and medical, and agricultural industries may be the underlying cause of global AMR development (Wang et al., 2024).

The situation has been made worse by improper over-the-counter antibiotic sales, inadequate sanitation, and the release of non-metabolized antibiotics or their remains into the environment through industrial effluents and feces/manure (Morrison et al., 2020). These contributory factors and the environmental spread of AMR are closely related. Approximately 700,000 people die each year from infections with microbiological germs that are resistant to drugs. By 2050, it is predicted that the annual death rate will surpass the number of deaths from cancer by reaching 10 million deaths if a sufficient action plan is not implemented (Roca et al., 2015).

In both clinical and natural settings, improper or excessive use of antibiotics results in artificial selection pressure that is detrimental to the health of both humans and animals. Resistance in bacteria develops spontaneously. Genetic mutation Resistance can develop in two ways, either through the introduction of new resistance genes or through genetic exchange mechanisms (Marston et al., 2016). Through horizontal gene transfer, antibiotics are known to promote pathogen resistance mechanisms. Microbial resistance to carbapenems, polymyxins, and third-generation cephalosporins is rapidly increasing (Liu et al., 2020). Antimicrobial resistance (AMR) is considered a serious global concern by major global health agencies and surveillance systems (Ma et al., 2021).

Antibiotics and AMR genes are the primary causes of AMR, a worldwide issue, however, other significant issues include pollution and inadequate local sanitation. Poor hygiene and sanitation, the discharge of antibiotics that have not been metabolized into the surroundings through feces or manure, imprecise usage and inadequate regulations, ignorance that results in excessive or ineffective antibiotic use, and the application of antibiotics to cattle and poultry to encourage growth rather than infection control agents are the main causes of antibiotic resistance (Morehead et al., 2018). The pressure of genetic selection is increased by these circumstances that causing bacterial infections that are resistant to many drugs to appear in the community. There are several ways that AMR can spread among people, animals, and the environment (Tang et al., 2023). People and natural microbial ecosystems are under significant selective pressure from increased antibiotic use. Like other pharmaceutical products, antibiotics that are unused or expired are thrown away and

do not break down, which makes it possible for them to enter aquatic or groundwater systems while wastewater treatment is underway. By changing target sites or transferring genes horizontally, a relatively small quantity of these discarded antibiotics might provide selective pressure (Salam et al., 2023).

The microorganisms that cause these infections can also be found in livestock, and many prevalent diseases are resistant to first-line medications. Examining the relationship between farm usage of antibiotics and dangers to human health is a challenging task. Because of epidemiological concerns, A simple model for the generation of resistant infections does not adequately capture the evolutionary processes of AMR. It is yet unknown how much each antimicrobial medication contributes to the total burden of AMR (Murray et al., 2022).

Conclusion

Antimicrobial resistance is a complicated, multifaceted problem that necessitates concerted international action. Stakeholders may create effective strategies to counteract this pressing public health problem by comprehending the mechanisms of resistance and the factors that contribute to its establishment. AMR is a worldwide health issue that cannot be addressed just with stronger antimicrobial agents. WGS has shed light on AMR dynamics and the impact of random antibiotic use. The data is striking. Recognizing and understanding the complexity of the worldwide AMR epidemic is a crucial first step toward addressing it. The next steps will likely shape the future of infectious disease control. Genomics has identified trends in the formation and spread of AMR bacteria. While we cannot stop bacterial evolution, we can channel it. There is a clear correlation between antibiotic use and resistance development. Using suitable antibiotic regimens can help prevent or reduce the emergence of resistance. The MPC concept and MSW theory may help achieve this purpose, however, they have limits. Initially, they focused on mutational resistance rather than the acquisition of resistant genes. Resistance to antibiotics is an unavoidable aspect of microbial evolution. This underscores the importance of ARG surveillance as a critical component of future policymaking. WGS and metagenomics, along with advanced bioinformatics tools and databases, have expanded our knowledge in this area. The reliability of these approaches supports their use in regular diagnostics. Antibiotics can cause dysbiosis in the gut microbiota, leading to a variety of side effects. Monitoring AMR and using NGS technologies present unique technical problems and requirements for each domain. To address the growing AMR threat, ongoing education, surveillance, data analysis, and research are essential.

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