REVIEW

The superbug threat: unveiling the pandemic of antimicrobial resistance

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ABSTRACT

Antimicrobial resistance (AMR) is a major global threat to human, animal, and environmental health that is continuously evolving. The development, spread, and persistence of multidrug-resistant (MDR) bacteria, also known as "superbugs," is to blame. The effectiveness of an antimicrobial agent is harmed by the potential for tolerance or resistance to grow from the first time it is used. Antimicrobial agents used to treat bacterial, fungal, viral, and parasitic infections fall under this category. Several physiological and biochemical processes may be at play as this resistance grows. Antibiotics were discovered at a crucial point in human history, revolutionizing medicine and saving countless lives. Sadly, such "magic bullets" have been followed by pathogens that have developed resistance to them. Despite several proposals and measures over the last several decades, the environment has not kept up with microbes being increasingly immune to available drugs, a phenomenon known as antimicrobial resistance (AMR). Given the magnitude of the AMR crisis and the numerous areas of society impacted by its effects, solutions to the problem must be comprehensive and systematic. At this point, it is impossible to forecast the future scenario with certainty, but the regulation of AMR appears to be very difficult due to the scarcity of novel antibiotics. To solve this issue, multifaceted strategies should be used. Medical students, doctors, and pharmacists must receive ongoing and updated training. A component of research must be incorporated into AMR policy, as well as the pharmaceutical industry's encouragement to produce "superbug antibiotics." Gains in wellbeing are likely to be lost unless AMR is quickly tackled.

Keywords: Antimicrobial resistance, Antibiotic, inappropriate prescribing, superbug

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INTRODUCTION

Until the early nineteenth century, one in every two people died of infectious diseases before reaching the age of 20. Worldwide lifespan has now risen to 72 years and the discovery of antimicrobials has been one of the key drivers of this betterment of human health. Antimicrobials (also known as "antibiotics") suppress or hinder the growth of bacteria, parasites, viruses, and fungi [1]. Alexander Fleming is credited with isolating the first antibiotic from *Penicillium notatum* in 1928. The mass production of penicillin began in 1942, during World War II, and officially began the age of antibiotics. Antibiotics have since revolutionized medicine by allowing procedures that would have previously been

lethal, such as critical care medicine (such as the use of ventilators and catheters), cancer treatments, orthopedic surgery, organ transplantation, premature baby care, and autoimmune disorder treatment. Antibiotics are used in nearly all surgical procedures to avoid life-threatening postoperative complications. Antimicrobials are also widely used in toiletries, cleaning items for residential and commercial use, and agriculture, in addition to human healthcare. Antimicrobials, on the other hand, have proved to be a double-edged sword in recent years [2-4]. Antimicrobial resistance (AMR) has emerged as one of the most significant public health challenges of the twenty-first century, posing a threat to the successful prevention and treatment of an ever-widening spectrum of infections caused by bacteria, parasites, viruses, and fungi that are no longer susceptible to common antibiotics. Antibiotic resistance in bacteria makes the issue of AMR much more urgent. Bacteria that cause common or serious infections have established resistance to each new antibiotic that comes to market over several decades, to varying levels. Confronted with this fact, immediate action is needed to avert a looming global health emergency [5]. Microbes (bacteria, viruses, fungi, and parasites) evolve strategies to evade antimicrobials (antibiotics, antivirals, antifungals, and antiparasitics), rendering them ineffective. According to a recent WHO survey, our arsenal of successful antimicrobials is rapidly dwindling due to AMR [6]. Microbes, like all living things, are evolving to survive. AMR existed long before the discovery of the first antibiotic. AMR is most commonly caused by selective pressure imposed by antibiotic use, genetic mutations, or the acquisition of genetic material from a resistant bacterium through plasmid transfer [7]. AMR has been described as a global health problem with significant health, political, and economic consequences. Because of the advent of AMR, the advances made in modern medicine are in jeopardy. By 2050, global AMR deaths are projected to exceed 10 million each year [8]. This public health concern is gaining momentum around the world. Already many countries are dealing with the emergence of bacteria that are fully resistant to antibiotics, and countries are developing country-specific AMR action plans centered mostly on WHO's global AMR plan of action [9].

The word "superbugs" refers to bacteria that have increased morbidity and mortality as a result of elevated levels of antibiotic resistance [10]. These microbes have less treatment choices and are related to longer, more costly hospital stays. These superbugs have also developed increased virulence and transmissibility in some cases. *S. aureus* is one of the most well-known superbugs [3]. This multidrug-resistant microbe has long been a major cause of hospital-acquired infection, but MDR strains have recently spread into the general population. *Salmonella enterica* is another superbug, with several strains resistant to five antibiotics [10]. The advent of pathogens resistant to approximately all (and, in rare cases, all) antimicrobials, such as carbapenem-resistant *Klebsiella pneumonia*, is especially troubling. AMR is responsible for about 700,000 deaths each year, but as more "superbugs" arise, this figure is expected to grow to 10 million by 2050, at a cost of $100 trillion. As a result, experts believe that the rise of AMR is one of the most pressing issues in modern medicine [11-13]. These resistant microbes have fewer treatment choices, which are associated with a longer stay in the hospital

and higher costs. Super resistant strains have gained increased virulence as well as improved transmissibility in some cases [3]. Several bacterial human pathogens have developed into MDR forms as a result of erroneous antibiotic usage. MDR (Multiple Drug Resistance) in both the developing and developed worlds, Mycobacterium tuberculosis is a well-known example [14, 15].

HOW DO MICROBES ACQUIRE RESISTANCE?

Microorganisms have developed stringent mechanisms to evade the lethal effects of antimicrobial substances as a consequence of Darwinian selection. The majority of antibiotics are developed naturally by microbes such as saprophytic bacteria or environmental fungi, while others are modified synthetic antibiotics or fully synthetic antibiotics such as fluoroquinolones and sulphonamides [16]. Various species have developed protective mechanisms against them, including changes in the target site, drug entry or delivery inhibition, and enzyme activity that can destroy antimicrobials. As a result, antibiotic resistance could simply represent Darwinian competition from natural antimicrobial elements derived from microbes [17, 18]. The results of a functional meta-genomic study of soil microbes showed a wide range of genetic determinants linked to antibiotic resistance. While little is known about this factor of human pathogens, enzyme activity (β-lactamases) is an extraordinary example of a naturally occurring resistance mechanism that has an effect on human health [19, 20]. While few findings suggested a more complicated relationship, it is thought that various antimicrobial molecules formed by saprophytic bacteria inhibit the growth of other organisms present in that area, providing a mutual benefit in such environments. The concentration of antimicrobial substances in the soil, for example, tends to be much smaller, and may not be able to prevent the growth of neighboring bacteria [16, 17]. Second, evidence suggests that antimicrobial substances with sub-inhibitory doses have a major influence on microbial physiology and evolution, as well as acting as efficient signaling molecules that can induce host or microbial gene expression [20-22]. Another essential question is why only a small number of saprophytic bacteria develop carbapenems, a crucial broad-spectrum antibiotic. Several genes involved in carbapenem synthesis may also be involved in biofilm formation and quorum sensing. These results raise more questions about the antibiotics' unintended effects. Resistance does not only occur with natural antimicrobials; it also happens with synthetic antimicrobials [21].

Different factors which can contribute to AMR are listed below:

1. Overuse:

Sir Alexander Fleming sounded the issue about antibiotic overuse in 1945, predicting that the “public would demand [the drug]... then will begin a period... of abuses.” [4, 23]. ”Antibiotic overuse is obviously driving the development of antibiotic resistance [24, 25]. Antibiotic use has been related to the development and spread of antibiotic-resistant bacteria strains, according to epidemiological reports. Genes may be inherited from relatives or acquired from non-relatives on mobile genetic elements like plasmids in bacteria.

Antibiotic resistance can be passed down between bacteria species through horizontal gene transfer (HGT). Resistance may also arise naturally as a result of mutation. Drug-sensitive rivals are killed by antibiotics, allowing resistant bacteria to replicate as a result of natural selection. Antibiotics are overprescribed all over the world, despite warnings of overuse. Antibiotics are unrestricted in many other countries and are available without a prescription over the counter. Antibiotics are readily available, abundant, and inexpensive as a result of the lack of control, which encourages overuse. In countries where antibiotics are regulated, the ability to buy such drugs online has made them more affordable. [26].

2. Inappropriate Prescribing:

Antibiotics that are administered incorrectly lead to the spread of resistant bacteria. In 30 to 50 percent of cases, the treatment indication, agent option, or length of antibiotic therapy was inaccurate, according to studies [24, 27]. Just 7.6% of 17,435 patients diagnosed with community-acquired pneumonia (CAP) in the United States had a pathogen detected, according to one report. Using molecular diagnostic techniques (polymerase chain reaction [PCR] and semi quantitative PCR), researchers at the Karolinska Institute in Sweden were able to classify the probable pathogen in 89 percent of CAP patients [23]. Furthermore, it has been discovered that 30% to 60% of antibiotics administered in intensive care units (ICUs) are needless, inadequate, or suboptimal [27]. Antibiotics administered improperly have dubious clinical value and expose patients to antibiotic-related problems [28]. Antibiotic concentrations that are subinhibitory or subtherapeutic can facilitate the production of antibiotic resistance by promoting genetic changes such as gene expression changes, HGT, and mutagenesis. Greater mutagenesis and HGT encourage antibiotic resistance and spread, while changes in antibiotic-induced gene expression can increase virulence. Antibiotics at low doses have been shown to lead to strain diversification in organisms like *Pseudomonas aeruginosa*. Subinhibitory concentrations of piperacillin and/or tazobactam have also been shown to cause large proteomic changes in *Bacteroides fragilis* [29].

3. Extensive Agricultural Use:

Antibiotics are commonly used as growth supplements in livestock in both the developed and developing worlds [23, 24, 30]. Antibiotics are used in animals to stimulate growth and avoid infection, with an estimated 80 percent of antibiotics sold in the United States going to animals [4, 23, 31]. Antimicrobial treatment of livestock is said to boost the animals' overall health, resulting in higher outputs and a higher-quality material [32]. Antibiotics used in animals are consumed by humans through their food. The transfer of resistant bacteria from farm animals to humans was first recorded more than 35 years ago, when high rates of antibiotic resistance were discovered in both farm animals and farmers' intestinal flora. More recently, molecular detection methods have shown that bacteria resistant to antibiotics in farm animals make their way to consumers through food items [23]. This occurs as a result of the following events: 1) Antibiotics destroy or eliminate susceptible bacteria in food-producing animals, allowing

antibiotic-resistant bacteria to survive; 2) Resistant bacteria are spread through the food supply to humans; 3) these bacteria can cause infections in humans, which can lead to serious health problems [24]. Antibiotic use in agriculture has an effect on the microbiome in the ecosystem. Antibiotics provided to livestock are excreted in urine and stool to the degree that they are widely spread by manure, groundwater, and stream flow [23, 24]. Furthermore, in the western and southern United States, tetracycline and streptomycin are used as pesticides on fruit trees. While this application accounts for a small percentage of overall antibiotic use, the geographic distribution that results can be large. This practice often exposes microorganisms in the ecosystem to growth-inhibiting agents, modifying the ecology by increasing the proportion of sensitive and resistant microorganisms. Antibacterial agents used for hygienic or cleaning services can exacerbate the problem by limiting the production of environmental antigen immunities in both children and adults [32, 33]. As a result, immune system versatility could be harmed, potentially leading to an increase in morbidity and mortality from infections that aren't usually virulent [33].

HOW DO WE BEST PREVENT THE RISE OF "SUPERBUGS"?

Create a national antimicrobial resistance alliance with all main stakeholders as participants. To effectively prevent antimicrobial resistance, a collaborative approach between providers and consumers is needed. Policymakers, planners, physicians and prescribers, pharmacists and dispensers, institution managers, diagnostic and pharmacy industries, department of animal husbandry, and patients and the community are all key players on the provider hand. Global efforts to prevent and contain antimicrobial resistance should be implemented by a multi-sectoral national steering committee led by the chief medical officer and supported by advisory or expert groups [7, 10, 34]. Via designated national and regional reference centers, implement effective surveillance frameworks in the health and veterinary sectors to generate accurate epidemiological information, baseline data, trends in antimicrobial resistance, antimicrobial agent use, and economic and health effects. Encourage non-therapeutic use of antimicrobial agents as growth promoters in veterinary, agricultural, and fishery activities. Develop uniform standard treatment and infection control guidelines and ensure their implementation at all levels of health care and veterinary services through training, ongoing educational activities, the formation of functional drugs and therapeutic committees, and hospital infection control committees in health facilities, with a focus on established cost-effective interventions such as isolation [5, 34]. To control and encourage fair use of medicines and to ensure adequate patient treatment at all levels, appropriate steps must be taken to avoid the selling of antibiotics without a physician's prescription over the counter and to ensure continuous access to vital medicines of guaranteed quality in hospitals and communities. Vaccination policies can also be changed in order to reduce infection burdens even further. Conducting organizational research to gain a deeper understanding of the scientific and behavioral aspects of antimicrobial resistance prevention and control. In the national context, use the findings of these research studies or programs

to enhance policy and program progress [16, 34]. Productive collaborations with the pharmaceutical industry to ensure that current antimicrobials are adequately approved, promoted, and sold, as well as to facilitate the production of new drugs and vaccines. Community education and awareness initiative for various types of health care practitioners. To minimise disease burden, strengthen the communicable disease prevention programme and make infectious diseases a priority in medical education and health services [12, 14, 34]. Attempts to deal with resistance have embraced many different strategies which are listed in table below:

S. No.	Measures
1.	Increasing vaccine use to protect against multidrug-resistant bacteria (such as*Streptococcus pneumoniae*)[35, 36]
2.	Legitimizing laboratory sensitivity testing procedures, particularly for new resistance mechanisms that may not be detectable using current methods or for which accurate detection methods are expensive or time-consuming [35, 37-39]
3.	In order to avoid the clonal spread of drug-resistant pathogens in health-care environments, infection-control steps should be prioritized [35, 40]
4.	Analyzing data of resistance patterns and antimicrobial use in health care institutions [35, 41]
5.	Promoting the integration of antimicrobial resistance control as a focus of educational programmes for prescribers and other health care workers, health care managers and patients [35, 42]
6.	Lessening specific antimicrobial pressure by strengthening antimicrobial use strategies [35, 43, 44]
7.	Promoting the discovery of new antimicrobials to cover the gaps in treatment [35]

Specialists advise two main strategies for slowing the spread of AMR: reducing the number of infections and reducing antibiotic use [2].

PREVENTION

When a disease is stopped, less people need to be treated with medications. "The most relevant technology for fighting drug resistance is to avoid infections," says Prof. Willem van Schaik of the Institute of Microbiology and Infection at the University of Birmingham, one of the leading EU institutes researching AMR. This can be achieved by technologically simple solutions (e.g., healthcare staff washing their hands and isolating patients colonized by multidrug-resistant bacteria), but technological breakthroughs (e.g., UV air disinfection) are also encouraging. Vaccine-based methods to

tackle AMR are also of great importance, since prevention is often preferable to treatment." Many experts believe that better vaccine design, manufacturing, and delivery methods would likely become the key strategy for combating AMR in the future [1].Surveillance, in addition to vaccination, isolation, and good hygiene, is important. AMR genes are rapidly being tracked through the food chain using next-generation sequencing technology, which can sequence the entire genomes of microbes[45,46]. However, such monitoring has not yet been applied internationally, and most countries continue to classify specimens using older, less informative techniques. Many areas of the world, in fact, still lack sufficient (if any) surveillance methods. As a result, global strengthening and harmonization of AMR surveillance is required, as well as the implementation of agreed-upon regulations and techniques [5].

REDUCTION

Antibiotic drugs select for resistance for each dose administered. Antibiotic stewardship is important for ensuring that antibiotics are taken in the appropriate quantities for the duration of the treatment and only when absolutely necessary. Antibiotics were freely accessible in most parts of the world until recently. Even when not available over the counter, however, misuse is popular. In 2010, healthcare providers in the United States prescribed 258 million antibiotic courses (833 prescriptions per 1000 people). At least half of all antibiotic prescriptions are deemed useless [2, 5]. There is a need for more information initiatives aimed at both consumers and healthcare professionals. Antibiotics are often used to treat the common cold and flu, despite the fact that they are ineffective against both. As a result, prescription audits should become commonplace. Improved diagnostics that allow for rapid pathogen identification down to the strain level at the point of care will also aid healthcare providers in making better antibiotic treatment decisions. Interventions are also needed to stop antimicrobials from being misused in cleaning materials, agriculture, and other industries. Veterinary antibiotics account for up to 75% of the antibiotics used in certain countries [2, 47]. Antibiotics fight diseases in livestock and poultry, as well as as growth promoters or prophylactics in subtherapeutic doses to compensate for stressful and unsanitary conditions. Around 8 billion animals in the United States are treated with up to ten different antibiotics. Many of the same antimicrobial groups are used in human health, which is worrying. Another source of concern is that approximately 75% of all antibiotics provided to animals are not fully digested. Antibiotics leach into the water system after massive amounts of manure are sprayed onto fields. Animals, birds, and insects will spread the AMR bacteria that emerge. Consumers should mobilize for better animal husbandry to minimize the need for antimicrobials, and laws regulating the non-human use of antimicrobials should be placed in place and/or implemented more strictly [47-50].

HOW DO WE SLOW THE EVOLUTION OF ANTIMICROBIAL RESISTANCE?

To delay the evolution of antibiotic resistance, we must lower the likelihood that a resistance gene will first appear in a disease-

causing organism (via natural mutation or lateral gene transfer) and the intensity of the reproductive advantage imposed on that resistance by drug use. Antibiotic stewardship is one way to reduce the risk that resistance will develop first in a drug-sensitive pathogen population. Each dose of antibiotic drugs is chosen for resistance in harmless bacteria that naturally occur on or in us, which may be a potential source of lateral transfer of resistance genes to bacterial infections. The less we use antibiotics, the less of those genes will be present in us or in our climate, decreasing the risk of pathogens gaining resistance to them. As a consequence, it's important that people only use antibiotics when strictly essential [2]. In an ideal world, people can only use narrow-spectrum antibiotics, which target problematic bacteria with minimal side effects on beneficial or harmless bacteria that live on or in us. Antibiotics can only be used when absolutely necessary, according to the first rule of resistance management. The second rule is to choose the ones that trigger the least amount of resistance selection in nontarget species. Reduce the number of infections and reduce antibiotic usage in community and health care settings are two main ways to slow the spread [2, 51]. When an infection is avoided, fewer people may need to take antibiotics. Vaccines, hygiene, and sanitation, as well as isolation during infectivity, can also help to avoid infections. These measures can be difficult to enforce; even in hospitals, regular hand washing is difficult to implement. Antibiotic usage is limited, which delays the spread of resistance genes in pathogen populations. The question of whether or not to administer antibiotics poses a fascinating quandary. If we can kill any bacterium A in an individual with a drug B treatment (i.e., all are drug sensitive), we would be able to prevent any bacterium from developing resistance in the first place (dead bacteria cannot mutate or receive resistance genes by lateral transfer). If resistant bacteria are already present, however, the more actively we destroy drug-sensitive bacteria, the greater the evolutionary advantage we confer on any current, drug-resistant bacteria. When complete eradication is not possible, we can reduce the selection pressure for resistance evolution by reducing antibiotic use on a biological level (e.g., treating for fewer days) [2, 41, 52]. As a consequence, the dilemma arises: aggressive treatment may help prevent resistance from occurring in the first place, but at the expense of increasing selection in favour of any existing resistance [2, 53]. In the life sciences, balancing these competing forces for resistance management is a point of contention [2]. This biological uncertainty creates a nontrivial conundrum when it comes to influencing prescription behaviour, as it may send mixed messages about how long antibiotics should be taken. The best solution for managing resistance would most likely differ depending on the bacteria, medication, and clinical and epidemiological circumstances. As research progresses, the challenges of creating health messages and communicating them to physicians, patients, and the general public will become more complex [2, 53].

WHY DON'T WE JUST DISCOVER MORE NEW ANTIBIOTICS?

Since the 1980s, no new antibiotic classes have been found. A class of antibiotics is a group of antibiotics that function in a similar way – for example, by destroying bacteria or preventing them from multiplying –

and are effective against specific infections. Antibiotics that have been introduced to the market in the last three decades are combinations of previously discovered medicines. Finding and discovering truly new antibiotics is difficult: the science is complex, and the research and development process is time-consuming and costly, and it often fails. A new antibiotic will take ten years and cost over a billion dollars to create. Antibiotics are also less profitable than medications used to treat chronic diseases, which is particularly true when proper antibiotic stewardship is exercised. In fact, the cost of creating a new antibiotic is now likely to outweigh the benefits [11]. We are on the brink of not providing successful drugs for many common infectious diseases, due to a rise in antibiotic-resistant bacteria and a worryingly low rate of newly approved antibiotics for clinical use. Traditionally, the discovery of antibiotics has been crucial to surpassing resistance, and success is closely linked to systematic procedures—platforms—that have catalysed the golden age of the antibiotic, namely the Waksman Platform, followed by semi-synthesis platforms and fully synthetic antibiotics. Said platforms resulted in the major antibiotic classes: aminoglycosides, amphenicols, ansamycins, beta-lactams, lipopeptides, diaminopyrimidines, fosfomycins, imidazoles, macrolides, oxazolidinones, streptogramins, polymyxins, sulphonamides, glycopeptides, quinolones and tetracyclines. The target-based platform emerged during the genomics period, and it was widely regarded as a failure due to difficulties in translating drugs to the clinic. As a result, cell-based platforms were reinstated, and they remain critical in the fight against infectious diseases. Although the antibiotic pipeline is still lacking, especially in terms of new classes and mechanisms of action, there is a growing amount of knowledge on microbial metabolism available in the post-genomic age. The translation of this experience into new formats will potentially lead to the discovery of new and improved therapeutics, which will help us reclaim the fight against infectious diseases [54].

ARE THERE ANY ALTERNATIVES TO ANTIBIOTICS?

Over the last 70 years, antibiotics have saved countless lives and facilitated the advancement of modern medicine. However, it is clear that antibiotics' effectiveness may have been fleeting, and we now face a long-term, if not never-ending, challenge in developing new antibiotics to fight antibiotic-resistant bacteria. In order to combat bacterial infection, a more comprehensive approach is needed. Antibodies, probiotics, and vaccines in phase 2 and phase 3 trials are the most sophisticated techniques. This first wave of antibiotic alternatives would most likely be used as adjunctive or preventive therapies, implying that traditional antibiotics will still be needed [55]. CRISPR, antimicrobial peptides, and phage therapy are examples of other innovations, but they all face major obstacles in clinical application [10, 47, 56]. Pathogens could be targeted for neutralization rather than destruction, putting less selection pressure on resistance to develop. Alternatively, rather than targeting the microbe, the host may be targeted to modulate the immune response and the host environment in order to reduce the effects of infection without the use of antibiotics [4]. In conclusion, antimicrobial resistance can be addressed in a variety of

ways, including reducing antibiotic use through the use of alternative products. Since a number of unique and general approaches are required to both prevent and treat disease, no single alternative will be able to replace all antibiotic use. Immunotherapeutics, vaccinations, and gut microbiota modulation may all be viable options [57].

CONCLUSION

Antimicrobial resistance is a global epidemic and a public health emergency. Antibiotic misuse in the human, livestock, food, and agricultural sectors has led to the current situation. The fact that the discovery of new antibiotics is a brief rare occurrence adds to the concern about the rising prevalence of drug-resistant bacteria. Most antibiotic groups on the market today were discovered in the mid-to-late twentieth century. As a result, the arsenal of drugs available to combat resistant bacteria is small, and bacteria may be resistant to several drugs at the same time.The exploitation of antimicrobial agents, as well as the unavailability of newer drugs due to strict regulatory requirements as well as decreased financial incentives, has been blamed for the antimicrobial resistance crisis. Evolving microorganisms, resistance mechanisms, and antimicrobial agents must all be studied in order to slow the rate of resistance. Health-care environments, as well as the environment and agriculture industries, require multidisciplinary approaches. Probiotics, antibodies, and vaccinations are examples of progressive alternative treatments that have shown positive results in studies, implying that they may be used as preventive or adjunct therapies in the future.

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