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Review Article

Antimicrobial Resistance: Challenges And Future Prospects

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ABSTRACT

Antibiotic abuse and misuse across a range of industries contribute to the creation of resistant bacteria, which in turn causes antimicrobial resistance (AMR), a serious worldwide health concern. The discovery of penicillin marked the beginning of antimicrobial resistance (AMR), and the emergence of multidrug-resistant bacteria has presented serious problems for healthcare systems around the globe. A "Silent Pandemic" that may outnumber other causes of death by 2050 is being created by the overuse of antibiotics in agriculture, human health, and animal health. This adds to the spread of resistance genes. AMR affects both humans and animals, and treating illnesses can be difficult due to resistant microorganisms. Through a variety of processes, including biofilm formation and enzymatic alteration, microorganisms are able to resist the effects of antibiotics. Ineffective antibiotics endanger common medical operations and, if unregulated, could result in millions of fatalities every year. With losses estimated in the trillions of dollars and severe financial strains on agriculture and healthcare systems, AMR has a huge economic impact. Despite obstacles including algorithmic biases and data quality, artificial intelligence is being investigated as a tool to improve diagnoses and treatment approaches in order to battle AMR. Effectively addressing AMR requires a One Health strategy that takes environmental, animal, and human aspects into account. Enhancing surveillance systems, encouraging stewardship initiatives, and funding research and development for novel antibiotic alternatives are all part of this. International cooperation, education, and public awareness are crucial for preventing AMR and maintaining the effectiveness of medicines. Since they have prevented infectious diseases from taking millions of lives, antibiotics are among the most significant discoveries of the 20th century. Due to strong selection pressure brought on by the growing use and abuse of antibiotics throughout time, microbes have evolved acquired antimicrobial resistance (AMR) to numerous medications. Human-to-human contact, both within and outside of healthcare facilities, is the main way that AMR is acquired and transmitted.

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Through a variety of drug-resistance mechanisms, AMR is governed by a vast array of interrelated healthcare and agricultural factors. One of the main contributing factors to the development and spread of AMR has been the unchecked use of antibiotics in livestock feed.

INTRODUCTION

Antibiotic resistance, Artificial intelligence, Preventive strategies, Alternative therapies, One Health approach, Global surveillance, Antibiotic use, Veterinary medicine, MRSA, Klebsiella pneumoniae, Non-typhoidal Salmonella, Mycobaterium tuberculosis. Antibiotics are regarded as the most amazing medical advancement of the 20th century and are the "magic bullets" for combating bacteria [1]. Millions of lives are still saved from bacterial diseases thanks to the development of antibiotics, which has altered the paradigm of treatment. Antibiotics have undoubtedly been a boon to humanity; in addition to their medical applications, they have been used for decades in many developing and underdeveloped nations for a variety of objectives, such as animal husbandry and production as preventative measures. The widespread use of antibiotics, particularly in poor nations, gives bacteria plenty of chance to produce AMR, which can have serious repercussions, such as significantly increased morbidity and death. The prevalence and incidence of antibiotic-resistant bacterial illnesses have increased to unprecedented proportions in the twenty-first century, posing a latent pandemic danger to global public health and calling for immediate interventions. [2,3,4]

1. Antimicrobial Resistance Definition and History:

An Overview and Background Globally, there is growing concern about the problem of antimicrobial resistance (AMR), which poses a significant threat to the general health of the world's population. AMR refers to the ability of microorganisms, including bacteria, viruses, fungi, and parasites, to resist the harmful effects of medications that were once effective against them [5]. The effectiveness of antivirals, antibiotics, and other medications is compromised by this occurrence, which raises morbidity, mortality, and medical costs. Since combating AMR has become a critical global health priority, governments, medical professionals, academics, and the general public must act quickly and cooperatively [6].

2. Mechanism Of Antimicrobial Resistance:

AMR mechanisms and the microorganisms involved AMR is caused by a number of factors, including natural selection, the overuse and abuse of antibiotics, inadequate access to clean water and sanitation, and shoddy and fake medications[7]. Self-medication, improper prescriptions, and insufficient treatment are just a few examples of antibiotic overuse and misuse. Resistance may develop in bacteria that survive a partial antibiotic course. AMR can also be caused by self-prescribing, using leftover antibiotics without a doctor's supervision, or prescribing medications for viral infections. Poor hygiene and inadequate sanitation contribute to the spread of infectious diseases, which increases the need for antibiotics and leads to the emergence of resistance. Lastly, poor-quality drugs can not have enough active ingredients or the right dosage, which could lead to ineffective treatment and the emergence of resistance. In order to resist the antibacterial effects of previously successful drugs used to cure ailments, microorganisms have evolved a variety of clever defense mechanisms. These defense mechanisms allow microbes to withstand the effects of antibiotics and other antimicrobial substances, which frequently prevent or kill them. Through structural changes and the use of clever metabolic pathways, bacteria and other parasites

exhibit amazing adaptation mechanisms that allow them to ignore or neutralize dangerous antimicrobial agents. [8,9]

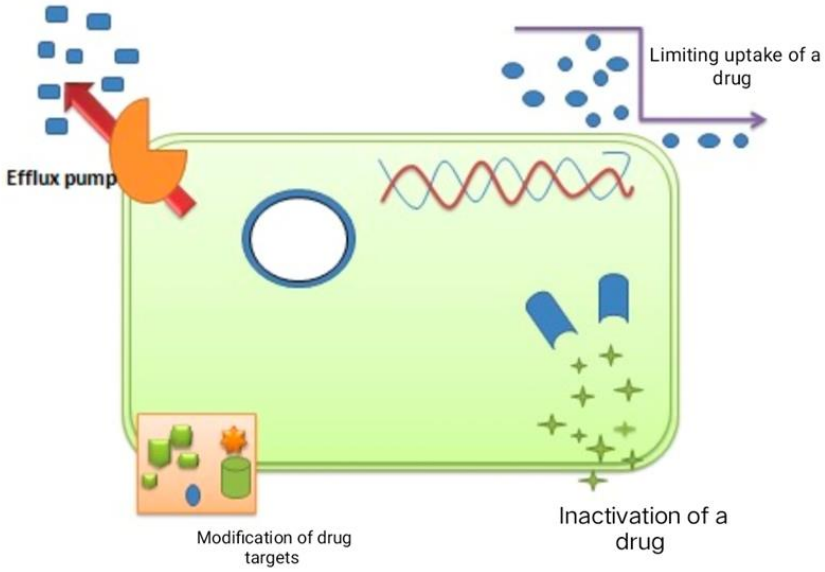

Figure 1. Different Mechanism of Drug Resistance

3. **Future Projections of Antimicrobial Resistance Burden and Associated Issues:** Research commissioned by the UK government shows that the outlook for the future is not promising. According to this study, disease resistance to antibiotics may be responsible for about 10 million fatalities per year by 2050 [10]. Infections and minor injuries could once again become life-threatening, and big treatments like hip replacements, chemotherapy, and organ transplants could become extremely dangerous. By 2050, AMR will have caused $100 trillion in economic losses [10]. The impact is projected to be greatest in low- and middle-income nations since the development of novel antimicrobial alternatives is not keeping up with the emergence of bacterial resistance. The availability of currently available, high-priced treatments is also hindered by a lack of resources.[11] There is a severe lack of global coordination, and fragmented containment efforts cannot keep up with the evolutionary capacity of harmful bacteria that are constantly exposed to the widespread use of antibiotics by humans in the environment, agriculture, and healthcare.[12]

4. **Challenges In Addressing Antimicrobial Resistance:**

The difficulties in dealing with AMR Addressing the advent of AMR poses difficult problems that cannot be easily solved. The extensive use of antibiotics in medicine and the economics of food animal production hinders efforts to lessen humanity's enormous use of these drugs [13]. Modern farming systems rely on the routine administration of antimicrobials to animals for infection prevention and growth promotion, while doctors frequently rely on empirical antibiotic prescribing to protect against bacterial infections due to the lack of rapid point-of-care diagnostics.

Despite awareness of the hazards of antibiotic resistance linked to overuse, antimicrobial stewardship programs in healthcare and updated animal husbandry rules are still not widely implemented [14].

5. Timeline Of Major Antimicrobial Resistance Discoveries and Resistance:

When Paul Ehrlich discovered a synthetic prodrug called salvarsan and neosalvarsan in 1910 to treat syphilis brought on by Treponema pallidum, it signaled the beginning of the modern antibiotic era. Salvadorsan was eventually supplanted by prontosil, a sulfonamide prodrug that bacteriologist Gerhard Domagk had found. The first comprehensive assessment of soil bacteria and their capacity to produce chemicals with antibiotic activity was done in the 1930s by American scientist and microbiologist Selman Waksman. He discovered several antibiotics, including as streptomycin, a commonly used treatment for tuberculosis, from filamentous actinomycetes that live in the soil. He also described an antibiotic as "a compound made by a microbe to destroy other microbes. The golden age of antibiotic research began in 1928 when Scottish physician and microbiologist Sir Alexander Fleming isolated penicillin from a mold known as Penicillium rubens. This period of time lasted until the middle of the 1950s. The 1940s through the 1960s are considered the "Golden Age" of antibiotic discovery and the majority of the antibiotics currently in use were found during this time. Since then, the development of drug-resistant organisms has coincided with a slow downturn in the discovery of antibiotics. Antibiotic-resistant bacteria have been known about since the beginning of the antibiotic era [15].The first Staphylococcus strain that was resistant to penicillin was identified several years before to the drug's 1940 launch as a treatment. Surprisingly, a methicillin-resistant Staphylococcus strain was discovered in 1960, barely a year after methicillin was initially released in 1959 as the first semisynthetic penicillinase-resistant penicillin[16]. Unfortunately, vancomycin-resistant strains of coagulase-negative Staphylococci (CoNS) were reported in 1979, two decades after the glycopeptide vancomycin was first introduced in 1958 as a rescue medication for treating infections caused by methicillin-resistant Staphylococci. Ten years later, vancomycin-resistant Enterococcus (VRE) was also described. Vancomycin's effectiveness against S. aureus was later observed to have decreased; vancomycin-resistant Staphylococcus aureus (VRSA) and vancomycin-intermediate Staphylococcus aureus (VISA) were reported in 1997 and 2002, respectively. [17] A β-lactam antibiotic called cephalosporin was discovered in 1945 and used in clinical settings to treat cases of penicillin resistance. In 1964, since then, numerous generations of cephalosporins have been developed, the fifth of which is now on the market. Starting with gram-negative bacteria that produced extended beta-lactamases (ESBLs), it was quite effective. Up until recently, significant resistance had evolved in all cephalosporin generations up to the fourth generation. Another significant antibiotic that was found in 1950 and effectively treated a variety of common infections, including gastrointestinal disorders, is tetracycline. In 1959, ten years after its discovery, tetracycline was found to be ineffective against Shigella strains. After levofloxacin, a third-generation fluoroquinolone, was added to the list of medicines in 1996, reports of levofloxacin-resistant Pneumococcus surfaced in the same year [18]. The timeline of key antibiotics discoveries and their resistances is depicted below (Figure 1) [19].

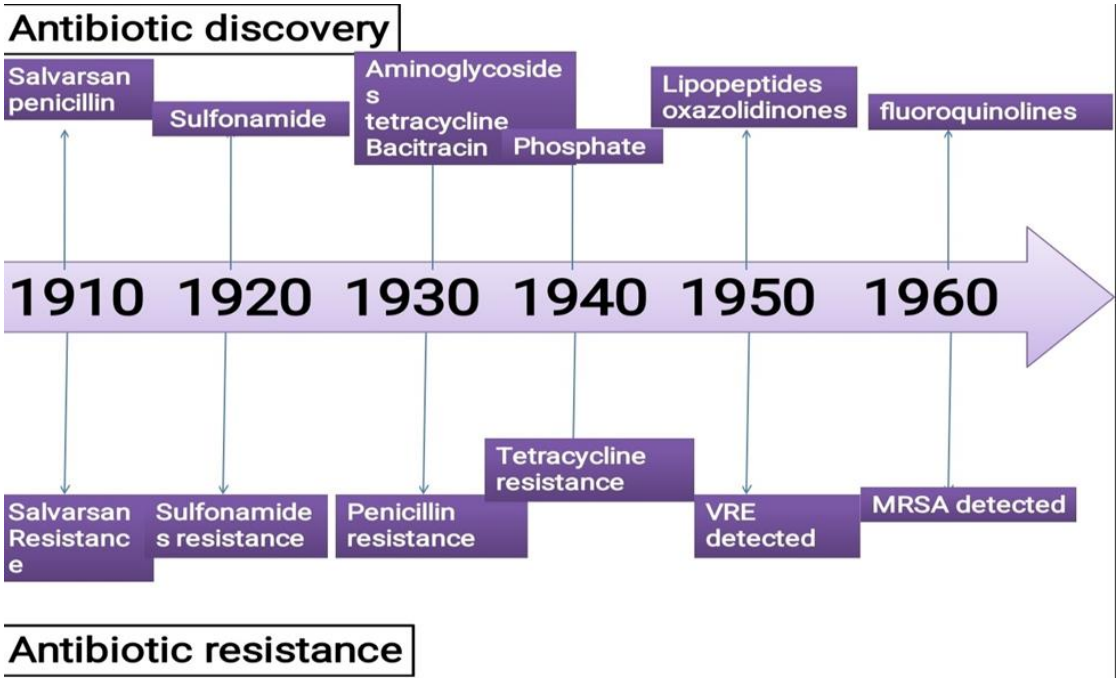

Figure 2. Timeline Of Discovery of Major Antibiotics and Antimicrobial Resistance

6. Basis Of Antimicrobial Resistance:

Antibiotic Resistance's Foundation A bacterial evolutionary response to the threat posed by therapeutic antibiotics is known as antibiotic resistance. Clinically speaking, when an antibiotic is first introduced, all targeted pathogens are still vulnerable to it; nevertheless, over time, bacteria become resistant to it. According to evolutionary theory, bacteria either (1) acquire foreign DNA by horizontal gene transfer (HGT) that codes for resistance determinants, or (2) undergo chromosomal gene alterations to adapt to the action of antibiotics. In order to produce antibiotic resistance, mutations primarily affect three different types of genes: those that encode the antibiotic's targets, transporters, and regulators that suppress the expression of transporters (such as multidrug efflux pumps and antibiotic-modifying enzymes). The idea that the antibiotic-resistance gene or genes that are passed on to human pathogenic bacteria by horizontal gene transfer (HGT) originate from commensal or ambient bacteria is intriguingly supported by evidence. [20] Numerous antibiotics are spontaneously produced by environmental microbes, as is widely known. They must also contain antibiotic-resistant genes to protect them from the effects of self-synthesized antibiotics; otherwise, their own antibiotics would have killed them. [21]

7. Mechanisms Of Drug Resistance:

In the same ecological niche, bacteria and antibiotics coexist, and bacteria build defenses against the negative effects of antibiotic compounds. Antibiotics must target four key components of bacterial cells: the cell wall, the cell membrane, protein synthesis, and nucleic acid production. Increasing active drug efflux, changing a drug target, inactivating a drug, and restricting drug uptake are the main causes of antimicrobial resistance. (Figure 3) [22,23]

8. Clinical Implications of Antimicrobial Resistance:

• Antimicrobial resistance hinders the successful treatment of microbial infections, including bacterial, fungal, and viral infections; [24]
• The emergence and spread of new resistant mechanisms threatens the scope of treatment for many common illnesses, including typhoid, flu, urinary tract infections, and upper respiratory tract infections, resulting in treatment failure, permanent disability, or even death;
• AMR will seriously jeopardize the success of cancer chemotherapy, transplantation surgery, and even minor dental procedures unless novel drugs are available;
• AMR infections require longer, more costly, and sometimes expensive alternative medications. [25,26]

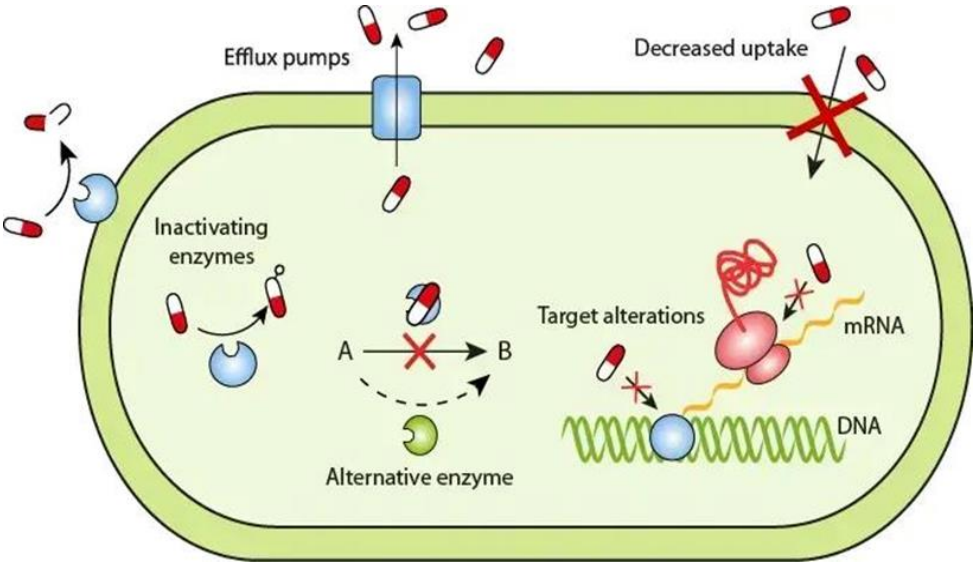

Figure 3: Drug Resistance Processes and Antibiotic Targets

9. Combat Antimicrobial Resistance: [29,30,31,32,]

Highlights of a few important national and international measures to combat AMR are described below and depicted in Figure 4. [27,28].

1. International Measures
2. National Strategies
3. Rational Use of Antibiotics
4. Infection Prevention and Control
5. Ban over the counter (OTC) Antibiotics
6. Antimicrobial Stewardship Program (ASP)
7. Use of Antibiotics in Animals
8. Development of New Drugs and Vaccines
9. Introduction of Checkpoints
10. Community Engagement
11. Alternatives to Antibiotics.
12. Phase therapy
13. Antivirulence Drugs
14. Bacteriocins
15. One Health antimicrobials resistance

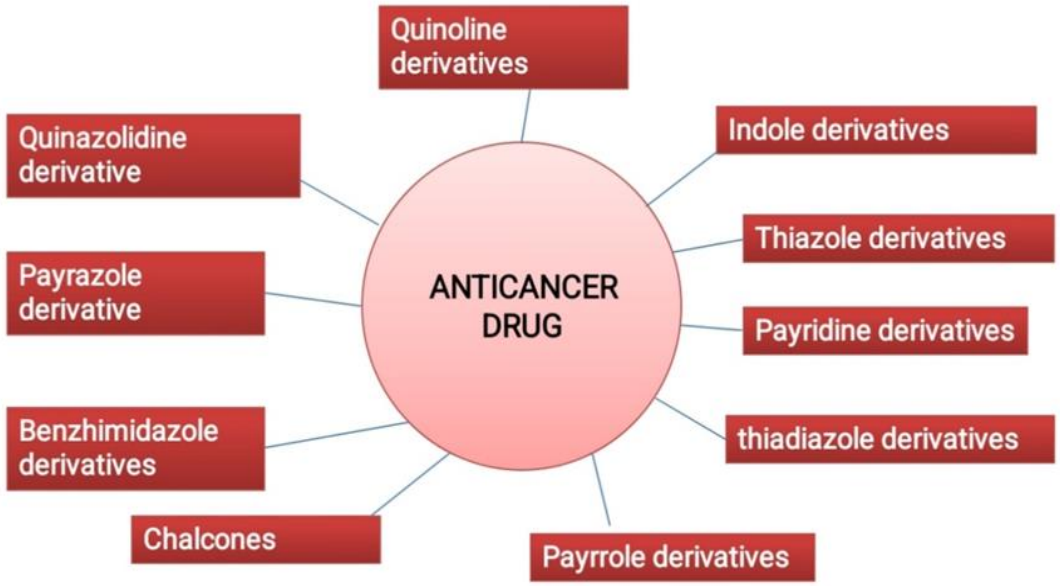

Figure 4. Major Interventions to Combat

CONCLUSION

Effective antimicrobial treatments, a cornerstone of contemporary medicine, are at danger due to bacteria's and other microorganisms' ability to quickly evolve resistance. Due to the enormous selective evolutionary pressure caused by humanity's widespread abuse of antibiotics in agriculture and healthcare, pathogenic bacteria have been able to evolve a variety of defense mechanisms against once-effective antimicrobials. We have entered a perilous post-antibiotic age as a result of antibiotic discovery falling behind the global spread of multidrug resistance. Important first actions include putting in place stewardship programs that restrict the use of antibiotics inappropriately and strengthen infection control. Nonetheless, the distinct "tragedy of the commons" of antibiotic resistance, which cuts beyond national boundaries and industry sectors, calls for legally obligatory international cooperation. We can stop the spread of resistance and protect biodiversity by implementing conservation policies, access equity, synchronized surveillance, and innovation financing under a one health framework.

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