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The Escalating Challenge of Antibiotic Resistance: Current Approaches and Future Perspectives

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ABSTRACT

It is a very serious global health issue as it reduces the effectiveness of antibacterial drugs and also makes the treatment of infectious diseases quite challenging. Thus, this review highlights complex factors of antibiotic resistance that include the misuse and overuse of antibiotics both in health and agriculture sectors while reporting genetic mechanisms through which resistance develops. Several major antibiotic-resistant pathogens already identified include multidrug-resistant tuberculosis, methicillin-resistant Staphylococcus aureus, and carbapenem-resistant Enterobacteriaceae. These are the greatest public health threats, thus it is a great move to discuss some of these current approaches that will in turn help combat this crisis of antibiotic resistance including stewardship programs, developing new antimicrobials, as well as prevention through vaccinations. We further discuss the role of international health organizations, especially the World Health Organization, in coordinating efforts across the globe to contain the increasing menace of antimicrobial resistance through surveillance, research, and cooperative actions. Finally, we introduce new approaches which may change the face of the future of antibiotic resistance management: phage therapy, CRISPR technology, and use of antimicrobial peptides. This is a big step forward toward the goal but leaves many serious challenges open for the door: economic and regulatory ones related to developing new antibiotics, access imbalances concerning medications, and public knowledge and awareness lacunas. Ultimately, comprehensive, multi-institutional collaboration is what will get this job done: ensure antibiotics continue working well and continue protecting public health.

Key Words: *Antibiotic Resistance; Multidrug-Resistant Pathogens; Antimicrobial Stewardship; Phage Therapy*

1. Introduction

1.1 The Rise of Antibiotic Resistance: A Global Concern

Antibiotic resistance is one of the emerging public health issues and a threat to modern medicine. The phenomenon involves the process by which bacteria become tolerant to drugs meant to kill them, thus making regular treatments ineffective. Overuse of antibiotics in human medicine and agricultural practices has escalated this resistance, with the effects of resistant infections having multiplied across the globe. The World Health Organization says that antibiotic resistance has now grown to become one of the biggest emerging threats to global health, food security, and development, with millions already affected annually (World Health Organization, 2020).

1.2 Impact of Antibiotic Resistance on Public Health and Healthcare Systems

It can range from individual patient outcomes levels to exerting a burden on the health systems all over the world. It tends to take longer time in hospitals, is much more expensive medically, and is higher in mortality rates as compared to others. According to the CDC report, it states that an excess of 2.8 million antibiotic-resistant infections are annually found in the U.S., with about more than 35,000 deaths (Centers for Disease Control and Prevention, 2019). It is expected that by 2050, antibiotic-resistant infections may hit a global level of 10 million deaths per year over and above the cancer toll (O'Neill, 2016).

Similarly, with regard to economics, this is as challenging. As such, the most vulnerable are the poorest countries in terms of health care delivery; they do not have cash to fight antibiotic resistance infection (Ventola, 2015). Resurgence diseases that were under control- especially tuberculosis and pneumonia because of antibiotic resistance are amongst such complications in effective management of public health.

Impact	**Description**
Individual Patient Outcomes	Prolonged hospital stays, increased medical costs, and increased mortality
Healthcare Systems	Strained healthcare systems worldwide
Economic Burden	Higher medical costs, particularly for countries with limited healthcare infrastructure
Public Health	Resurgence of previously controlled diseases, such as tuberculosis and pneumonia

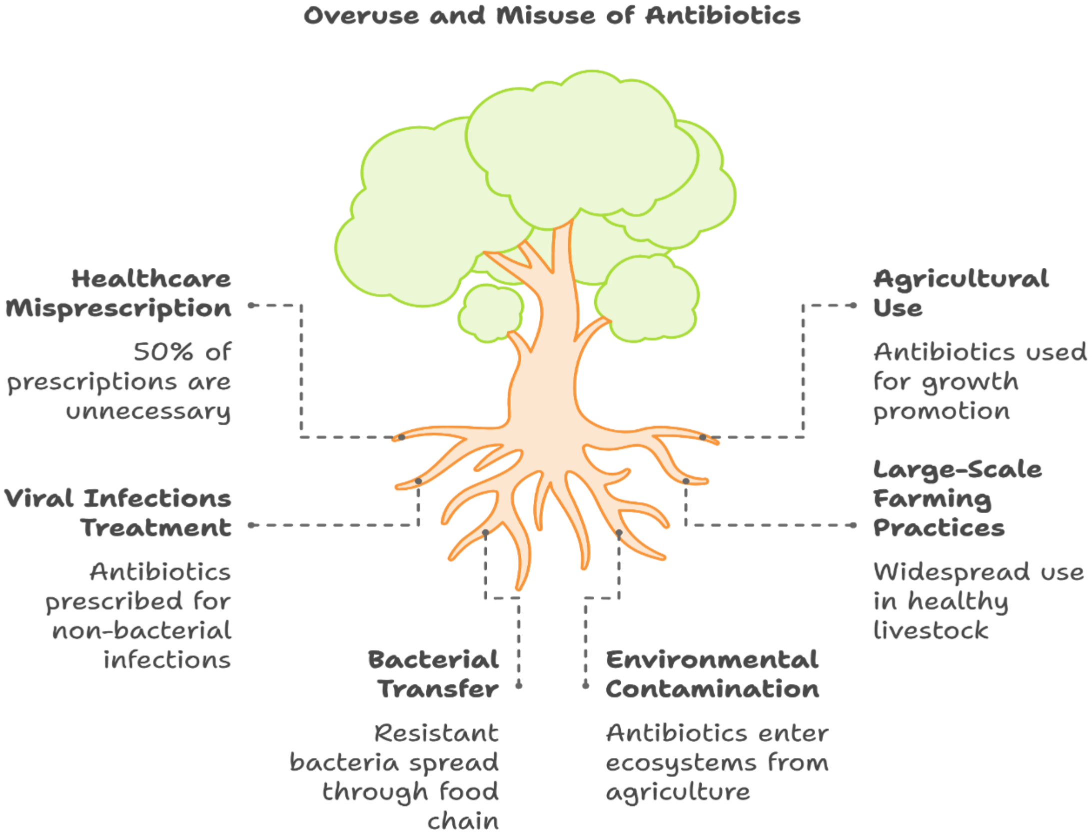
2. Causes and Mechanisms of Antibiotic Resistance

2.1 Overuse and Misuse of Antibiotics in Healthcare and Agriculture

Some of the major reasons causing antibiotic resistance include over-prescription and misuse of antibiotics not only in the medical field but also in farming. More often than not, the healthcare practitioners end up prescribing antibiotics to those suffering from viral infections. These are infections that have no cure through the antibiotics, and it is calculated that about 50% of the antibiotics prescribed to the human are inappropriate or wrongly directed prescriptions (Centers for Disease Control and Prevention, 2020).

It accelerates the selection of resistant bacterial strains, some of which may multiply when the non-resistant ones are being removed. Use in agriculture In animal farming, antibiotics are administered not only for the treatment of infection in farm animals but also to stimulate their growth and used for preventing infection in the otherwise apparently healthy animal. Large scale farms more widely utilized.

Antibiotics in agriculture lead to the development of resistant bacteria, which can be passed from animals to humans through food chains or environmental contamination (Gouvêa, dos Santos, & Mellor, 2015). According to the Food and Agriculture Organization, one of the factors that have resulted in resistant bacteria is antibiotic use in agriculture, transferred along the food chain (FAO, 2016).



2.2 Genetic Mechanisms of Resistance: Mutations and Horizontal Gene Transfer

Bacteria can develop resistance to antibiotics through several genetic mechanisms, primarily via spontaneous mutations and horizontal gene transfer (HGT). Spontaneous mutations occur during bacterial replication and can sometimes lead to changes that confer resistance to antibiotics. These mutations might alter the antibiotic's target site or increase the bacterial cell's ability to expel the drug, rendering the treatment ineffective (Li, Plésiat, & Nikaido, 2015).

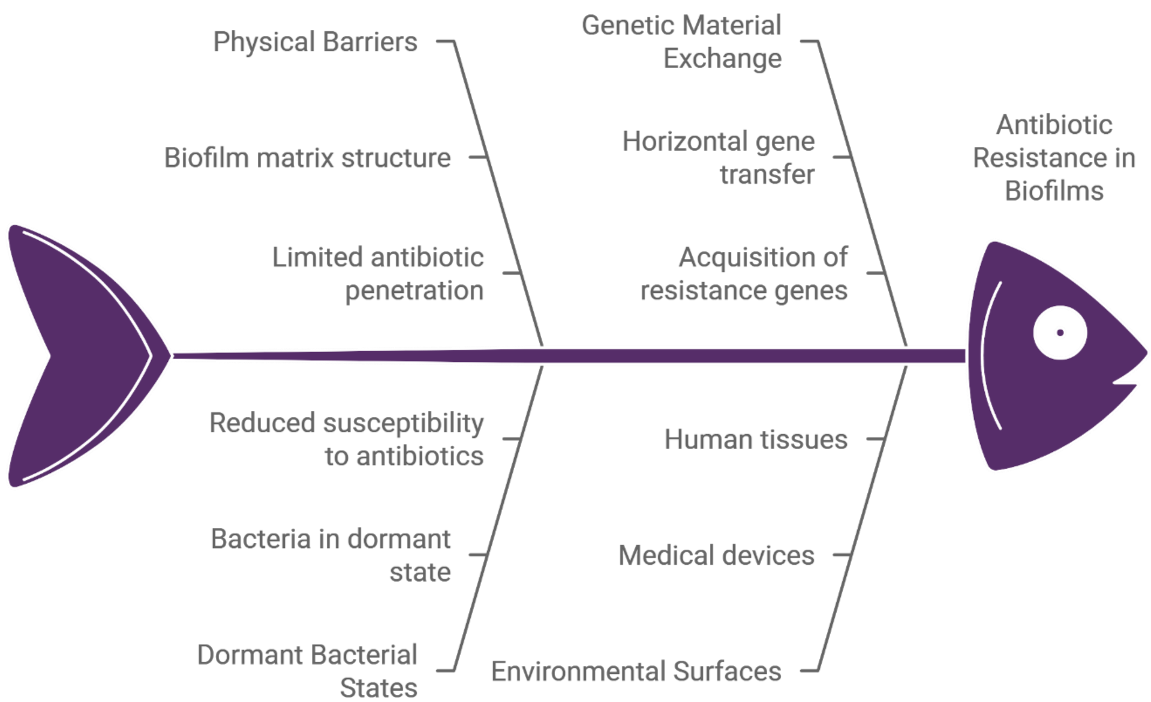
Horizontal gene transfer, however, plays a more significant role in the spread of resistance across bacterial populations. Through processes like transformation, transduction, and conjugation, bacteria can acquire resistance genes from other bacteria. Conjugation, often referred to as "bacterial mating," allows resistant genes to transfer directly from one bacterium to another, even across species. This mechanism has facilitated the rapid global dissemination of resistance genes, especially in hospital settings where resistant bacteria thrive (Davies & Davies, 2010).

2.3 The Role of Biofilms in Resistance Development

Biofilms, complex communities of bacteria embedded within a self-produced matrix, represent another major challenge in the fight against antibiotic resistance. Biofilms can form on various surfaces, including medical devices, human tissues, and environmental surfaces. The structure of biofilms offers bacteria a protective environment where they can thrive and become more resistant to antimicrobial treatments (Flemming & Wingender, 2010).

Within biofilms, bacteria exhibit a higher tolerance to antibiotics due to several factors. First, the biofilm matrix can act as a physical barrier, limiting the penetration of antibiotics. Second, the bacteria within biofilms often enter a dormant state, which reduces their metabolic activity and makes them less susceptible to antibiotics that target actively growing cells. Finally, biofilms facilitate the exchange of genetic material, including antibiotic resistance genes, between bacterial cells, further enhancing the potential for resistance development (Hall & Mah, 2017).

Antibiotic Resistance in Biofilms



3. Major Antibiotic-Resistant Pathogens

3.1 Multidrug-Resistant Tuberculosis (MDR-TB)

Mycobacterium tuberculosis causes tuberculosis which is the main cause of deaths arising from infectious disease globally. Its variant has been the most difficult that has proved challenging in its prevention. Definition MDR-TB incorporates all the species of TB which have arisen due to at least isoniazid and rifampin (World Health Organization, 2021). Their usually emergence arises in case of treatment failure, or their non-completion through which they start surviving with becoming habituated to medication to overcome them.

MDR-TB is treated using drugs that are less potent and more toxic but take long time. In 2019, it was approximately 465 000 new cases of MDR/RR-TB globally where, while about 57% were cured, others faced prolonged illness and early deaths (World Health Organization, 2021). Further burden of MDR-TB is the heavy economic burdens in health care costs particularly for low- and middle-income countries where the TB epidemic is high.

3.2 Methicillin-Resistant Staphylococcus aureus (MRSA)

A another highly important antibiotic-resistant pathogen is methicillin-resistant Staphylococcus aureus, or MRSA. The pathogen became notorious in both the hospital and community settings. There is a very high percentage of resistance of MRSA to methicillin as well as other antibiotics given as treatment. Traditionally MRSA has been associated with HA-MRSA; but recently CA-MRSA becomes significant (Lee, 2013).

The spectrum of the disease ranges from simple cutaneous infections, like boils, to potentially fatal pneumonia or bloodstream infections and up to sepsis. CDC estimates more than 80,000 invasive MRSA cases annually in the United States, with around 11,000 deaths due to this condition (CDC, 2019). The morbidity level with restricted treatment options highlights the significance of infection vigilance and new antimicrobial therapies.

3.3 Carbapenem-Resistant Enterobacteriaceae (CRE)

he Enterobacteriaceae, now known as Carbapenem-resistant Enterobacteriaceae (CRE), have joined a family of Gram-negative bacteria that have managed to outwit the last-resort antibiotics-carbapenems. An infection with CRE is deemed ominous because the infections are difficult to treat owing to their resistance to nearly all antibiotics commercially available in the market, like carbapenems (Nordmann et al. 2011).

The presence of CRE infections is more dominant in hospitals and affects weaker conditions, such as the ICU or immunocompromised patients. This infection also has an alarming case fatality rate because, in patients infected through the bloodstream, it has been recorded to be 50% (CDC, 2019). This threat remains a public health concern for this pathogen because it spreads within the hospital and there are not many drugs to treat it.

3.4 Drug-Resistant Neisseria gonorrhoeae

Neisseria gonorrhoeae is the bacterium responsible for the disease gonorrhea, which has shown resistance to almost all the antibiotic classes used in treating the disease. It is one of the most frequent sexually transmitted infections globally, and drug-resistant N. gonorrhoeae has emerged as one of the major challenges to date. Resistance to both ceftriaxone and azithromycin, which are at present used as first-line drugs, has caused some serious concerns regarding the appearance of untreatable gonorrhea (Unemo & Shafer, 2014).

According to WHO, there are more than 80 million cases reported annually, most of which are caused by strains that have different levels of antibiotic resistance (WHO, 2020). If left unmanaged and untreated, infections cause severe complications such as pelvic inflammatory disease, infertility, and increased chances for HIV transmission. The recent appearance of drug-resistant N. This therefore calls for continuous observation and creation of new antibiotics or another way of treatment.

Pathogen	**Resistance Mechanism**	**Impact**
Multidrug-Resistant Tuberculosis (MDR-TB)	Resistance to isoniazid and rifampicin	Prolonged treatment, higher mortality, economic burden
Methicillin-Resistant Staphylococcus aureus (MRSA)	Resistance to methicillin and other beta-lactam antibiotics	Severe infections, high mortality, limited treatment options
Carbapenem-Resistant Enterobacteriaceae (CRE)	Resistance to carbapenems and other antibiotics	High mortality, limited treatment options, rapid spread in healthcare settings
Drug-Resistant Neisseria gonorrhoeae	Resistance to multiple antibiotics	Severe complications, increased risk of HIV transmission, limited treatment options

4. Current Strategies to Combat Antibiotic Resistance

Antibiotic resistance has emerged as one of the most significant threats to global public health. In response, a combination of medical, pharmaceutical, and public health interventions has been implemented to mitigate this crisis. These strategies aim to curb the misuse of antibiotics, promote the development of new drugs, and enhance infection control practices.

4.1 Rational Use of Antibiotics: Stewardship Programs

ASPs is an acronym for structured activities on the responsible use of antimicrobials in a healthcare facility. It means that such programs center on making antibiotic use as optimum as possible: treating an infection effectively with as few adverse effects of the infection as possible, among which overuse causes resistance (Dyar et al., 2017). In other words, ASPs involve giving the right antibiotic in the right dose for the right duration, which is what prevents overuse.

ASPs have been implemented in hospitals and clinics worldwide and have helped to limit the use of antibiotics. For instance, one study revealed that the use of antibiotics declined by 20% after an ASP was implemented in a hospital (Schuts et al., 2016). The programs also aim at educating health professionals on the dangers of over-prescription of antibiotics and the need for culture and sensitivity testing before commencing antibiotic treatment.

4.2 Development of New Antibiotics and Alternative Therapies

This is critical since there will always be the emergence of new resistance that these constantly appearing bacteria are meeting. Yet, the pharmaceutical pipeline has been very slow for the discovery of new antibiotics. The main scientifically and regulatory-based challenges are facing but the financial rewards are pretty low too (Silver, 2011). This discovery of new antibiotics for drug-resistant bacteria is increasing still. These have recently been found, including an antibiotic, teixobactin that is said to function together with Gram-positive bacteria like MRSA and Mycobacterium tuberculosis. Ling et al., 2015.

Besides the conventional antibiotics, alternatives are slowly becoming an adjunct. There are bacteriophage therapy, antimicrobial peptides, and CRISPR-based techniques targeting bacterial DNA (Czaplewski et al., 2016). Among the promising measures against resistance, such measures may be used where these failed.

4.3 Vaccination as a Preventative Measure

Vaccination reduces the reliance on antibiotics because of protecting against bacterial infections. The vaccination of pneumococcal bacteria, for example Streptococcus pneumoniae as well as Hib has reduced infection number caused by these agents to a minimal level. With this reduction, therefore the use of antibiotics to kill these microorganisms has decreased dramatically (Jansen et al., 2018). Vaccination provides protection to an individual and helps in acquiring immunity at a herd level where the infection rate and by proxy the rate of developing resistance to the antibiotics would go down significantly.

WHO supports vaccination as a part of a global strategy against the further spread of antibiotic resistance: when vaccine-preventable diseases decline, so too does the aggregate demand for antibiotics, thus slowing down the rate of emergence (WHO, 2020).

4.4 Public Health Interventions and Infection Control Practices

Infection control practices should be successfully prevented from spreading resistant bacteria, particularly in health care facilities, as this is where the majority of antibiotic-resistant infections are linked with antibiotics. Public health interventions like hand hygiene sterilization of medical equipment and isolation of infected patients have been attributed to the prevention of spread of resistant pathogens (McLaws, 2015).

Public education campaigns on the use of antibiotics against misuse are on the rise. For example, WHO came up with a campaign known as "Antibiotics: Handle with Care" to target the use of antibiotics among both patients and health care practitioners (World Health Organization, 2015). Self-medication and the demand for antibiotics are part of reducing over-the-counter sales of antibiotics and are highly observed in low-resource environments.

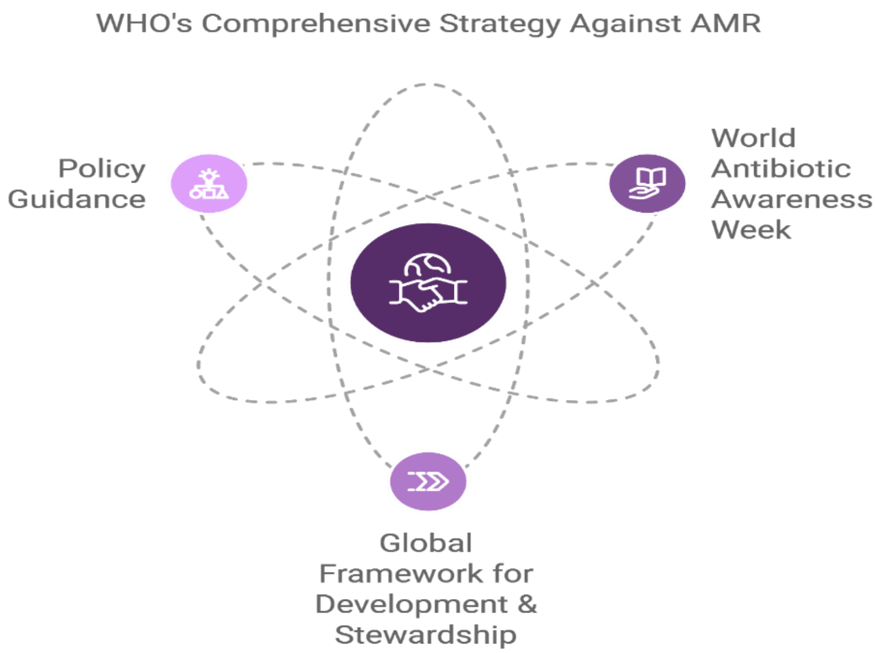
5. The Role of Global Health Organizations

Global health organizations will play a very crucial role in solving the crisis of antibiotic resistance. These international efforts are coordinated through policy-making, awareness campaigns, research initiatives, and surveillance programs in order to address the resistance. Such cooperation among them is required for standardized protocols in order to slow the spread of resistant pathogens.

5.1 World Health Organization (WHO) Initiatives

The World Health Organization is at the forefront in combating antibiotic resistance. In WHO, the purpose is awareness-raising, research, and policy development by member states on how to combat AMR. These include hosting the World Antibiotic Awareness Week, designed to be even more informative for public audiences and challenging best practices of health care providers, policy makers, and others (World Health Organization [WHO], 2020).

WHO has also devised the "Global Framework for Development & Stewardship to Combat Antimicrobial Resistance." This framework governs antibiotic use in countries, and they introduce newer drugs based on antimicrobial therapy (WHO, 2018). This strategy looks upon the prevention of misuse and excessive use of antibiotics and how their implementation impacts resistance prevention.



5.2 Global Action Plan on Antimicrobial Resistance

The WHO launched the Global Action Plan on Antimicrobial Resistance in 2015. This is an overarching strategy developed to respond to the growing problem of antibiotic resistance. It encompasses five key objectives, such as improving awareness and understanding of AMR, strengthening research and surveillance, reducing the incidence of infection, optimizing the use of antimicrobial agents, and fostering investment in new technologies and medicines (WHO, 2015). Encourage each country to develop a national action plan congruent with the global framework on tackling AMR.

Global Action Plan has been effective and able to emphasize the implementation of strategy on AMR from integration of human, animal and environmental health sectors due recognition of the "One Health" approach. In AMR, there is multiple causation that would result in the problem as that is not only associated with medical practice but also involves other sectors such as agriculture and veterinary practices, besides this, environmental management, it is a multi-dimensional field (Dar & Hasan, 2019).

5.3 International Collaboration in Surveillance and Research

International collaboration is an important tool for effective surveillance and research on antibiotic resistance. In this regard, surveillance systems follow the patterns of the spread of resistant pathogens and how policies reduce their effects. GLASS collects information on the trends of AMR in various nations and thus triggers timely interventions to looming threats (WHO, 2018).

Research efforts also reflect collaborations because global initiatives pool resources and expertise to develop new antimicrobial drugs and alternative therapies. For instance, the TATFAR and the JPIAMR contribute to international research collaboration on best practices (European Commission, 2017). These initiatives have contributed greatly to breakthroughs in understanding how AMR mechanisms work while driving the development of innovative diagnostic tools and treatments.

6. Novel Approaches and Future Directions

Antibiotic resistance has prompted scientists to discover new ways to combat the menace. These new approaches will either be strengthening already existing treatments or designing new treatments against the resistant bacteria. From biological therapies to advanced technologies, these new approaches promise a great future in the fight against antimicrobial resistance (AMR).

6.1 Phage Therapy: Targeting Resistant Bacteria

In another study, phage therapy represents using bacteriophages - viruses that selectively infect bacteria. Bacteriophages selectively destroy only bacteria, and a research has high hopes about the answer being found for diseases caused by MDR-producing bacteria. Unlike antibiotics that interfere simultaneously with pathogenic and the beneficial bacteria populations, there is a big potentiality of phage therapy acting almost selectively, diminishing the probability of disturbing microbiome populations in the organism (Kortright et al., 2019).

It has recently been shown that phages can co-evolve with bacteria, thereby avoiding resistance in the latter. Moreover, compassionate cases where traditional therapies had not worked well were well treated using phage therapy. However, there are still several issues that need to be solved; amongst which are resistance of phages and development of appropriate regulatory guidelines to permit safe clinical usage (Cisek et al., 2017).

6.2 CRISPR-Cas Systems for Precision Antibacterial Treatment

The discovery of CRISPR-Cas systems as part of the bacterial immune defense has made it possible to use this as a tool for precision antibacterial therapy. This gene-editing technology can be engineered to specifically target and cut bacterial DNA, either eliminating resistance genes or killing the pathogen directly. A benefit of CRISPR-Cas systems is that they are precise and enable selective targeting of resistant bacterial strains without harming the surrounding healthy microbiota (Gomaa et al., 2014).

Furthermore, scientists are researching the use of CRISPR-Cas as a delivery mechanism for the delivery of antimicrobial compound so that its utility would further increase in its clinical uses. However, before applying in clinics on a massive level, there are also various issues such as problems associated with the delivery, side effects, and some legal issues that need to be resolved (Bikard et al., 2014).

6.3 Use of Antimicrobial Peptides (AMPs) as Alternatives to Traditional Antibiotics

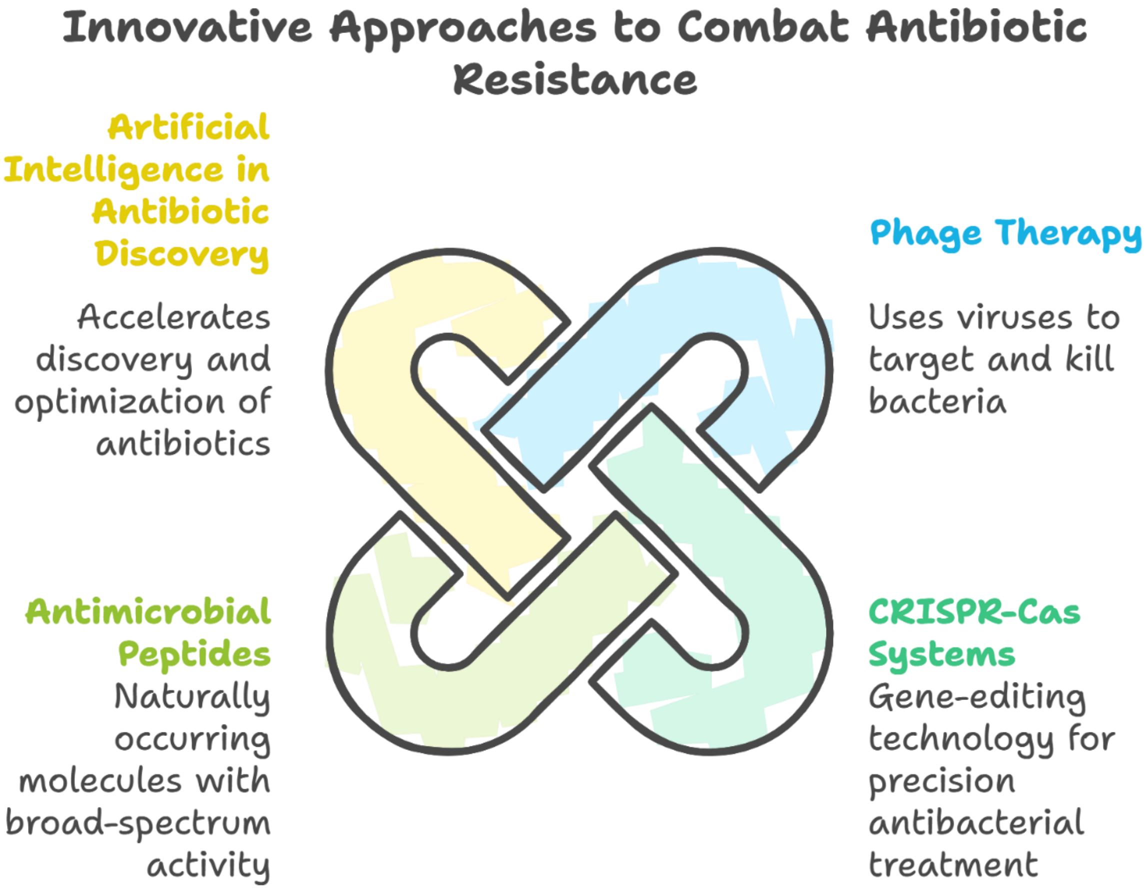
AMPs are endogenous molecules that have been shown to be a viable alternative to traditional antibiotics. AMPs are part of the innate immune system of many organisms and serve as a first line of defense against microbial infections. Their mechanisms of action include disrupting bacterial membranes, inhibiting cell wall synthesis, and targeting intracellular components (Mahlapuu et al., 2016).

Some of the key strengths of AMPs include a wide-spectrum activity profile with minimal risk of generating resistant pathogens. AMPs can show activities against nearly every known type of pathogen, even multi-drug resistant strains. But the pharmacological applications remain at experimental levels as production costs coupled with instability and toxicity persist to date (Hancock & Sahl, 2006).

6.4 Role of Artificial Intelligence in Antibiotic Discovery

Artificial intelligence (AI) is revolutionizing antibiotic discovery by speeding up the discovery of novel compounds. While traditional methods of discovering new antibiotics are slow and costly, AI models can quickly process large datasets and predict the potency of new molecules against resistant pathogens. For example, it has been used in screening millions of chemical compounds, and millions have already resulted in a new antibiotic discovered as halicin that was labeled a potent inhibitor of drug-resistant bacteria (Stokes et al., 2020).

AI also aids in the enhancement of already known antibiotics by showing modifications that might make it function better on resistant bacteria. Furthermore, AI is able to provide treatment plans personalized to the patient using predictions of resistance patterns in bacteria, making clinical outcomes better. However, AI discovery of new antibiotics only relies on full biological datasets and continuous interaction among biologists, data scientists, and clinicians (Yang et al., 2020).



7. Challenges in Implementing Global Solutions

The global nature of antibiotic resistance necessitates coordinated solutions. However, significant challenges impede progress in combating this growing threat. Economic, regulatory, access, and educational barriers continue to limit the effectiveness of global interventions. Addressing these obstacles is essential for a unified and sustainable response to antibiotic resistance.

7.1 Economic and Regulatory Barriers to New Antibiotic Development

The economic and regulatory factors also make it difficult for antibiotic innovation. The creation of a new antibiotic is a process that is very capital intensive with a low return over time. The high research cost, plus the little monetary gain, makes few pharmaceutical companies willing to venture into new research on new antibiotics. Antibiotics are said to be a costly expensive and time-consuming discovery because they hardly bring much gain since they are prescribed over short periods as compared to chronic drugs (O'Neill, 2016). Finally, resistance to new drugs can arise quite quickly, which could potentially be another reason to discourage investment.

Regulatory barriers also cause a delay in the approval of new antibiotics. It makes it difficult for smaller biotech companies to bring in new drugs to the market because of the strict requirements of clinical trials coupled with uncertainty about reimbursement policies (Renwick, Brogan, & Mossialos, 2016). The regulatory landscape has to change in a manner that creates incentives for innovative antibiotic development and ensures that these drugs are rapidly introduced into clinical practice.

7.2 Access to Antibiotics in Low- and Middle-Income Countries

While antibiotic resistance is a global issue, the burden of this issue is greater in LMICs where antibiotics are often in short supply or not controlled well. In most parts of the world, antibiotics are sold over the counter and therefore are frequently overused and misused leading to increased resistance (Laxminarayan et al., 2013). On the other hand, in other areas, antibiotics are unavailable or less accessible, and thus infections that could have been treated with antibiotics go unattended, leading to a higher rate of death and the proliferation of resistant organisms.

Antibiotic access in LMICs can be improved through an all-rounded strategy that would comprise of an improvement of healthcare infrastructure, effective regulation mechanisms, and access to affordable current and novel antibiotics. It is important to achieve cooperation and financing on the global level in addressing such access disparities (Okeke, 2014).

7.3 Public Awareness and Education Gaps

Public awareness and education are very key in the elimination of antibiotic-resistant infections, but still huge gaps persist both in areas. Many people remain oblivious of the risks associated with improper use of antibiotics, especially overuse, misuse, and the completion of prescribed treatments (WHO, 2020). Knowledge deficient among the public continues

leading to the continued misuse of antibiotics in both healthcare facilities and agriculture.
Health education programs of health care providers, agriculturists, and all members of society are therefore very essential to bring behavior change in antibiotic use. However, such practices are only achievable by continuous endeavors and funding. Governments and NGOs should engage with practicing health care workers to strengthen awareness and to educate members of the public on antibiotic use responsibility (Reddy et al., 2020).

8. Conclusion

Antibiotic resistance is an increasingly fast-moving global health threat, and thus collective actions must be taken now. This type of resistance mainly occurs due to the misuse of antibiotics in healthcare and overuse in agriculture coupled with genetic mechanisms and biofilm that enable resistant pathogens. The causes of antibiotic-resistant pathogens are multifactorial and widespread. Its examples include multi drug resistant organisms such as Methicillin-Resistant Staphylococcus aureus (MRSA) and Carbapenem-Resistant Enterobacteriaceae (CRE), and Multidrug-Resistant Tuberculosis or MDR-TB is another example.
Antibiotic resistance can be dealt with by current efforts like programs in antibiotic stewardship, new antibiotics and vaccines, alternative therapy treatments, vaccination, and campaigns towards public health efforts toward preventing infections. Most importantly, a lot of such effort seems to be stalled with obstacles such as economics, law, and regulatory practices regarding the development of a new antibiotic. This area is unfortunately either not in sufficient supply or uncontrolled in LMICs. Another gap is a dearth of public awareness and education on antibiotics.
Global health organizations, more especially the World Health Organization, have made big efforts by the Global Action Plan on Antimicrobial Resistance towards international cooperation. Yet for long-term sustainable successes, innovative approaches to research would include phage therapy, CRISPR-Cas systems, antimicrobial peptides (AMPs), as well as applications in artificial intelligence in drug discovery.
The way ahead needs to be multifaceted. Antibiotic resistance requires both scientific innovation and global action better regulation, public education, and a health-care system, particularly in resource-limited settings. Combating this growing threat requires the collaborative efforts of governments, researchers, pharmaceutical companies, and civil society. Only through comprehensive, global efforts may we hope to prevent antibiotic resistance from deteriorating modern medicine and public health.

9. References

1. World Health Organization. (2020). *Antimicrobial resistance*. https://www.who.int/news-room/fact-sheets/detail/antimicrobial-resistance
2. Centers for Disease Control and Prevention. (2019). *Antibiotic resistance threats in the United States, 2019*. U.S. Department of Health and Human Services, CDC. https://www.cdc.gov/drugresistance/pdf/threats-report/2019-ar-threats-report-508.pdf
3. O'Neill, J. (2016). *Tackling drug-resistant infections globally: Final report and recommendations*. Review on Antimicrobial Resistance. https://amr-review.org/Publications
4. Ventola, C. L. (2015). The antibiotic resistance crisis: Part 1: Causes and threats. *P&T: A Peer-Reviewed Journal for Formulary Management, 40*(4), 277–283. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4378521/
5. Centers for Disease Control and Prevention. (2020). *Antibiotic use in outpatient settings*. U.S. Department of Health and Human Services, CDC. https://www.cdc.gov/antibiotic-use/data/report.html
6. Gouvêa, R., dos Santos, F. F., & Mellor, K. (2015). The impact of antibiotic use in animal production on the emergence of antimicrobial resistance. *Journal of Veterinary Science & Medicine, 3*(1), 1–8. https://doi.org/10.13188/2325-4645.1000018
7. Food and Agriculture Organization. (2016). *The FAO action plan on antimicrobial resistance 2016–2020*. http://www.fao.org/3/i5996e/i5996e.pdf
8. Li, X. Z., Plésiat, P., & Nikaido, H. (2015). The challenge of efflux-mediated antibiotic resistance in Gram-negative bacteria. *Clinical Microbiology Reviews, 28*(2), 337–418. https://doi.org/10.1128/CMR.00117-14
9. Davies, J., & Davies, D. (2010). Origins and evolution of antibiotic resistance. *Microbiology and Molecular Biology Reviews, 74*(3), 417–433. https://doi.org/10.1128/MMBR.00016-10
10. Flemming, H. C., & Wingender, J. (2010). The biofilm matrix. *Nature Reviews Microbiology, 8*(9), 623–633. https://doi.org/10.1038/nrmicro2415
11. Hall, C. W., & Mah, T. F. (2017). Molecular mechanisms of biofilm-based antibiotic resistance and tolerance in pathogenic bacteria. *FEMS Microbiology Reviews, 41*(3), 276–301. https://doi.org/10.1093/femsre/fux010
12. World Health Organization. (2021). *Global tuberculosis report 2021*. https://www.who.int/publications/i/item/9789240037021
13. Lee, A. S., De Lencastre, H., Garau, J., Kluytmans, J., Malhotra-Kumar, S., Peschel, A., & Harbarth, S. (2018). Methicillin-resistant *Staphylococcus aureus*. *Nature Reviews Disease Primers, 4*(1), 18033. https://doi.org/10.1038/nrdp.2018.33
14. Nordmann, P., Naas, T., & Poirel, L. (2011). Global spread of carbapenemase-producing Enterobacteriaceae. *Emerging Infectious Diseases, 17*(10), 1791–1798. https://doi.org/10.3201/eid1710.110655
15. Centers for Disease Control and Prevention. (2019). *Antibiotic resistance threats in the United States, 2019*. U.S. Department of Health and Human Services, CDC. https://www.cdc.gov/drugresistance/pdf/threats-report/2019-ar-threats-report-508.pdf

16. Unemo, M., & Shafer, W. M. (2014). Antibiotic resistance in *Neisseria gonorrhoeae*: Origin, evolution, and lessons learned for the future. *Annals of the New York Academy of Sciences, 1323*(1), 97–119. https://doi.org/10.1111/nyas.12471
17. World Health Organization. (2020). *Global priority list of antibiotic-resistant bacteria to guide research, discovery, and development of new antibiotics*. https://www.who.int/medicines/publications/WHO-PPL-Short_Summary_25Feb-ET_NM_WHO.pdf
18. Dyar, O. J., Huttner, B., Schouten, J., & Pulcini, C. (2017). What is antimicrobial stewardship? *Clinical Microbiology and Infection, 23*(11), 793-798. https://doi.org/10.1016/j.cmi.2017.08.026
19. Schuts, E. C., Hulscher, M. E., Mouton, J. W., Verduin, C. M., Stuart, J. W., Overdiek, H. W., ... & Prins, J. M. (2016). Current evidence on hospital antimicrobial stewardship objectives: A systematic review and meta-analysis. *The Lancet Infectious Diseases, 16*(7), 847-856. https://doi.org/10.1016/S1473-3099(16)00065-7
20. Silver, L. L. (2011). Challenges of antibacterial discovery. *Clinical Microbiology Reviews, 24*(1), 71-109. https://doi.org/10.1128/CMR.00030-10
21. Ling, L. L., Schneider, T., Peoples, A. J., Spoering, A. L., Engels, I., Conlon, B. P., ... & Lewis, K. (2015). A new antibiotic kills pathogens without detectable resistance. *Nature, 517*(7535), 455-459. https://doi.org/10.1038/nature14098
22. Czaplewski, L., Bax, R., Clokie, M., Dawson, M., Fairhead, H., Fischetti, V. A., ... & Rex, J. H. (2016). Alternatives to antibiotics—a pipeline portfolio review. *The Lancet Infectious Diseases, 16*(2), 239-251. https://doi.org/10.1016/S1473-3099(15)00466-1
23. Jansen, K. U., Knirsch, C., & Anderson, A. S. (2018). The role of vaccines in preventing bacterial antimicrobial resistance. *Nature Reviews Microbiology, 16*(4), 266-271. https://doi.org/10.1038/nrmicro.2017.153
24. World Health Organization. (2020). *Vaccines and antibiotic resistance: What you need to know*. https://www.who.int/news-room/fact-sheets/detail/vaccines-and-antibiotic-resistance
25. McLaws, M. L. (2015). The relationship between hand hygiene and health care-associated infection: It's complicated. *Infection and Drug Resistance, 8*, 7–18. https://doi.org/10.2147/IDR.S62704
26. World Health Organization. (2015). *Antibiotics: Handle with care* [Campaign]. https://www.who.int/campaigns/world-antibiotic-awareness-week/2015
27. World Health Organization. (2020). *World Antibiotic Awareness Week* [Campaign]. https://www.who.int/campaigns/world-antibiotic-awareness-week/2020
28. World Health Organization. (2018). *Global Antimicrobial Resistance Surveillance System (GLASS) report: Early implementation 2016-2017*. https://www.who.int/glass/resources/publications/early-implementation-report/en/
29. World Health Organization. (2015). *Global action plan on antimicrobial resistance*. https://www.who.int/publications/i/item/9789241509763
30. Dar, O. A., & Hasan, R. (2019). The global response to AMR: momentum, success, and critical gaps. *Antimicrobial Resistance & Infection Control, 8*, 70. https://doi.org/10.1186/s13756-019-0531-3
31. European Commission. (2017). *Transatlantic Taskforce on Antimicrobial Resistance (TATFAR)*. https://ec.europa.eu/health/antimicrobial-resistance/transatlantic-taskforce-tatfar_en
32. Kortright, K. E., Chan, B. K., Koff, J. L., & Turner, P. E. (2019). Phage therapy: A renewed approach to combat antibiotic-resistant bacteria. *Cell Host & Microbe, 25*(2), 219-232. https://doi.org/10.1016/j.chom.2019.01.014
33. Cisek, A. A., Dąbrowska, I., Gregorczyk, K. P., & Wyzewski, Z. (2017). Phage therapy in bacterial infections treatment: One hundred years after the discovery of bacteriophages. *Current Microbiology, 74*(2), 277-283. https://doi.org/10.1007/s00284-016-1166-x
34. Gomaa, A. A., Klumpe, H. E., Luo, M. L., Selle, K., Barrangou, R., & Beisel, C. L. (2014). Programmable removal of bacterial strains by use of genome-targeting CRISPR-Cas systems. *MBio, 5*(1), e00928-13. https://doi.org/10.1128/mBio.00928-13
35. Bikard, D., Euler, C. W., Jiang, W., Nussenzweig, P. M., & Marraffini, L. A. (2014). Exploiting CRISPR-Cas nucleases to produce sequence-specific antimicrobials. *Nature Biotechnology, 32*(11), 1146-1150. https://doi.org/10.1038/nbt.3043
36. Mahlapuu, M., Håkansson, J., Ringstad, L., & Björn, C. (2016). Antimicrobial peptides: An emerging category of therapeutic agents. *Frontiers in Cellular and Infection Microbiology, 6*, 194. https://doi.org/10.3389/fcimb.2016.00194
37. Hancock, R. E., & Sahl, H. G. (2006). Antimicrobial and host-defense peptides as new anti-infective therapeutic strategies. *Nature Biotechnology, 24*(12), 1551-1557. https://doi.org/10.1038/nbt1267
38. Stokes, J. M., Yang, K., Swanson, K., Jin, W., Cubillos-Ruiz, A., Donghia, N. M., ... & Collins, J. J. (2020). A deep learning approach to antibiotic discovery. *Cell, 180*(4), 688-702. https://doi.org/10.1016/j.cell.2020.01.021
39. Yang, K., Swanson, K., Jin, W., Coley, C., & Collins, J. (2020). AI for antibiotic discovery: Advances, challenges, and recommendations. *Nature Reviews Drug Discovery, 19*(1), 37-54. https://doi.org/10.1038/s41573-019-0050-4
40. O'Neill, J. (2016). Tackling drug-resistant infections globally: Final report and recommendations. *Review on Antimicrobial Resistance*. Retrieved from https://amr-review.org

41. Renwick, M. J., Brogan, D. M., & Mossialos, E. (2016). A systematic review and critical assessment of incentive strategies for discovery and development of novel antibiotics. *The Journal of Antibiotics, 69*(2), 73-88. https://doi.org/10.1038/ja.2015.98
42. Laxminarayan, R., Duse, A., Wattal, C., Zaidi, A. K. M., Wertheim, H. F. L., Sumpradit, N., ... & Cars, O. (2013). Antibiotic resistance—the need for global solutions. *The Lancet Infectious Diseases, 13*(12), 1057-1098. https://doi.org/10.1016/S1473-3099(13)70318-9
43. Okeke, I. N. (2014). Poverty and root causes of resistance in developing countries. *The Lancet Infectious Diseases, 4*(9), 564-566. https://doi.org/10.1016/S1473-3099(04)01110-2
44. World Health Organization (WHO). (2020). Antibiotic resistance. Retrieved from https://www.who.int/news-room/fact-sheets/detail/antibiotic-resistance
45. Reddy, P. S., Garg, R., Verma, M., Goyal, N., Chauhan, N., & Singh, G. (2020). Enhancing public awareness and engagement on antimicrobial resistance through participatory approaches in India. *Frontiers in Public Health, 8*, 124. https://doi.org/10.3389/fpubh.2020.00124